Report on the Deliberation Results

February 28, 2019

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Biktarvy Combination Tablets
Non-proprietary Name	Bictegravir Sodium/Emtricitabine/Tenofovir Alafenamide Fumarate (JAN*)
Applicant	Gilead Sciences K.K.
Date of Application	December 14, 2018

Results of Deliberation

In its meeting held on February 22, 2019, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. The drug product is classified as a powerful drug.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.

2. The applicant is required to request the physician to provide the patient with sufficient information and obtain the patient's informed consent prior to the use of the product. In the informed consent process, the physician should explain that collection of further data on the efficacy and safety of the product is ongoing.

3. The applicant is required to submit the data from relevant clinical studies currently ongoing or being planned overseas and the results of analyses of thereof as soon as the studies are completed.

4. The applicant is required to conduct a post-marketing surveillance covering all patients treated with the product in Japan, as a general rule, until the end of the re-examination period, thereby collecting information on the use status (e.g., patient characteristics, efficacy and safety [including the efficacy and safety of the product in combination with other drugs], and drug-drug interaction data), reporting the results periodically, and submitting the results of the surveillance at the time of submission of the application for re-examination.

**Japanese Accepted Name (modified INN)*

Review Report

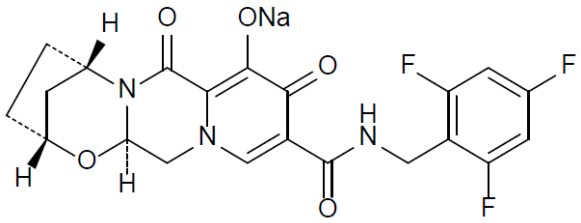
February 5, 2019
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Biktarvy Combination Tablets
Non-proprietary Name	Bictegravir Sodium/Emtricitabine/Tenofovir Alafenamide Fumarate
Applicant	Gilead Sciences K.K.
Date of Application	December 14, 2018
Dosage Form/Strength	Film-coated tablets: Each tablet contains 52.5 mg of bictegravir sodium (equivalent to 50 mg of bictegravir), 200 mg of emtricitabine, and 28 mg of tenofovir alafenamide fumarate (equivalent to 25 mg of tenofovir alafenamide)
Application Classification	Prescription drug, (1) Drug with a new active ingredient and (2) New combination drug

Chemical Structure

Bictegravir sodium

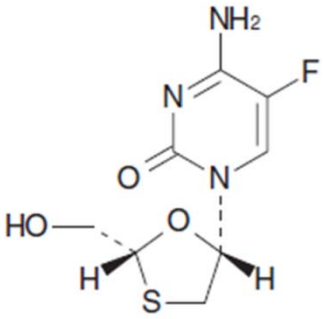


Molecular formula: $C_{21}H_{17}F_3N_3NaO_5$

Molecular weight: 471.36

Chemical name: Monosodium (2*R*,5*S*,13a*R*)-7,9-dioxo-10-{[(2,4,6-trifluorophenyl)methyl] 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

Emtricitabine

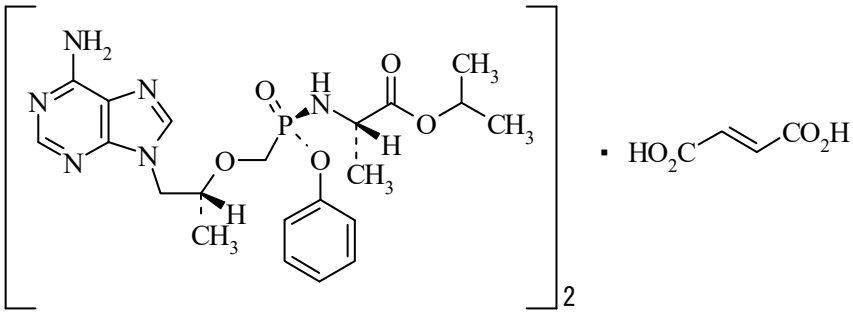


Molecular formula: $C_8H_{10}FN_3O_3S$

Molecular weight: 247.25

Chemical name: 4-Amino-5-fluoro-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl] pyrimidin-2(1*H*)-one

Tenofovir alafenamide fumarate



Molecular formula: $(C_{21}H_{29}N_6O_5P)_2 \cdot C_4H_4O_4$

Molecular weight: 1069.00

Chemical name: 1-Methylethyl *N*-[(*S*)-{[(1*R*)-2-(6-amino-9*H*-purin-9-yl)-1-methylethoxy] methyl}phenoxyphosphinoyl]-L-alaninate hemifumarate

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 424 of 2018 [*30 yaku*], PSEHB/PED Notification No. 1227-1 dated December 27, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare (MHLW) [Bictegravir sodium], Orphan Drug Designation No. 172 of 2004 [*16 yaku*], PFSB/ELD Notification No. 1013001 dated October 13, 2004, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW [Emtricitabine], and Orphan Drug Designation No. 368 of 2015 [*27 yaku*], PSEHB/ELD Notification No. 1119-1 dated November 19, 2015, by the Evaluation

and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW [Tenofovir alafenamide fumarate])

The product was eligible for prior assessment in accordance with the PMSB/ELD Notification No. 1015 dated November 12, 1998 (the product was approved on February 7, 2018 in the United State [US] and on June 25, 2018 in Europe). The prior assessment of the product application was conducted based on the application dossier submitted in the US and Europe.

Reviewing Office Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with human immunodeficiency virus type 1 (HIV)-1 infection, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

Indication

Human immunodeficiency virus type 1 (HIV-1) infection

Dosage and Administration

The usual adult dosage is 1 tablet (containing 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide) administered orally once daily.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.

2. The applicant is required to request the physician to provide the patient with sufficient information and obtain the patient's informed consent prior to the use of the product. In the informed consent process, the physician should explain that collection of further data on the efficacy and safety the product is ongoing.

3. The applicant is required to submit the data of relevant clinical study currently ongoing or being planned overseas and the results of analyses thereof as soon as the studies are completed.

4. The applicant is required to conduct a post-marketing surveillance covering all patients treated with the product in Japan, as a general rule, until the end of the re-examination period, thereby collecting information on the use status (e.g., patient characteristics, efficacy and safety [including the efficacy and safety of the product in combination with other drugs], and drug-drug interaction

data), reporting the results periodically, and submitting the results of the surveillance at the time of submission of the application for re-examination.

Attachment

Prior Assessment Report (1)

December 11, 2018

The following is an outline of the data submitted by the prior assessment requestor and the content of the prior assessment conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product for Prior Assessment

Intended Brand Name	Biktarvy Combination Tablets
Non-proprietary Name	Bictegravir Sodium/Emtricitabine/Tenofovir Alafenamide Fumarate
Prior Assessment Requestor	Gilead Sciences K.K.
Dosage Form/Strength	Film-coated tablets: Each tablet contains 52.5 mg of bictegravir sodium (equivalent to 50 mg of bictegravir), 200 mg of emtricitabine, and 28 mg of tenofovir alafenamide fumarate (equivalent to 25 mg of tenofovir alafenamide)
Intended Indication	Human immunodeficiency virus type 1 (HIV-1) infection

Intended Dosage and Administration

The usual adult dosage is 1 tablet (containing 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide) administered orally once daily, with or without food.

Date of Preparatory Meeting for Prior Assessment

August 10, 2018

Items Warranting Special Mention

The product is eligible for prior assessment in accordance with the PMSB/ELD Notification No. 1015 dated November 12, 1998 (the product was approved on February 7, 2018 in the US and on June 25, 2018 in Europe). The prior assessment of the present application is based on the application dossier submitted in the US and Europe.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

The treatment for human immunodeficiency virus (HIV) infection recommended in Japan is an anti-retroviral therapy consisting of the combination of 1 key drug (integrase strand-transfer inhibitor [INSTI], protease inhibitor [PI], or nonnucleoside reverse transcriptase inhibitor [NNRTI], with or without low-dose ritonavir) and 2 backbone drugs (nucleoside reverse transcriptase inhibitor [NRTI]) (according to the Practice Guideline for Treatment of HIV-infected Patients [Research Group for Study on How to Conquer HIV Infection and Complications, the HIV/AIDS Control Research Project funded by the FY 2017 Health, Labour and Welfare Policy Research Grants, March 2018 edition]).

Biktarvy is a fixed-dose combination (FDC) product containing, as its active ingredients, bictegravir (BIC) sodium, which is a novel INSTI discovered by Gilead Sciences, Inc. (US), and approved NRTIs emtricitabine (FTC) and tenofovir alafenamide (TAF) fumarate (hereinafter referred to as BIC/FTC/TAF FDC). The BIC/FTC/TAF FDC was developed by Gilead Sciences, Inc. (US).

FTC- or TAF-based anti-HIV drugs approved in Japan include Descovy Combination Tablets (FTC/TAF FDC), Odefsey Combination Tablets (rilpivirine [RPV]/FTC/TAF FDC), and Genvoya Combination Tablets (elvitegravir [EVG]/cobicistat [COBI]/FTC/TAF FDC).

Outside of Japan, 2 phase III studies of BIC/FTC/TAF FDC (Studies GS-US-380-1489 and GS-US-380-1490) in treatment-naïve adult patients with HIV-1 infection and 2 phase III studies of BIC/FTC/TAF FDC (Studies GS-US-380-1844 and GS-US-380-1878) in adult patients with HIV-1 infection who were virologically suppressed on anti-HIV therapy were conducted. On the basis of the results of these studies, BIC/FTC/TAF FDC was approved in the US in February 2018 and in Europe in June 2018.

2. Data Relating to Quality and Outline of the Prior Assessment Conducted by PMDA

The drug substances used are bictegravir sodium, emtricitabine, and tenofovir alafenamide fumarate. FTC is identical to the drug substance registered in the Drug Master File (DMF) (DMF registration number 229MF10061), and the manufacturing processes and controls are the same as those for the drug substance used in the manufacture of the approved drug products containing FTC. TAF fumarate is identical to the drug substance registered in DMF (DMF registration number 227MF10232), and the manufacturing processes and controls are the same as those for the drug substance used in the manufacture of "Vemlidy Tablets 25 mg," a drug for which the prior assessment requestor is the marketing authorization holder.

2.1 Drug substance (BIC sodium)

2.1.1 Characterization

BIC sodium is an off-white to yellow solid. The determined general properties of the drug substance include melting point, dissociation constant, partition coefficient, hygroscopicity, solubility, and crystalline polymorphism.

BIC sodium has 3 asymmetric centers, and its chemical structure has been elucidated by nuclear magnetic resonance spectrometry (^{1}H-, ^{13}C-, and ^{19}F-NMR), mass spectrometry, infrared

spectrophotometry, ultraviolet-visible spectrophotometry, elemental analysis, and single crystal X-ray diffractometry.

2.1.2 Manufacturing process

BIC sodium is synthesized using [redacted] and [redacted] as the starting materials.

The strategy for quality control has been developed based on the following investigations (Table 1):

- Identification of critical quality attributes
- Identification of critical process parameters, identification and optimization of critical steps

Table 1. Outline of the quality control strategy for the drug substance

Critical quality attributes	Controlling methods
[redacted]	[redacted], manufacturing process
[redacted]	[redacted], manufacturing process
[redacted]	[redacted], manufacturing process
[redacted]	[redacted], manufacturing process
[redacted]	[redacted], manufacturing process
Impurity ([redacted])	[redacted], manufacturing process
Impurity ([redacted])	[redacted], manufacturing process
Impurity ([redacted])	[redacted], manufacturing process
Impurity ([redacted])	Manufacturing process
Impurity ([redacted])	Manufacturing process
Impurity ([redacted])	Manufacturing process
[redacted]	[redacted], manufacturing process
[redacted]	Manufacturing process
[redacted]	[redacted], manufacturing process
[redacted]	Manufacturing process

The synthesis of [redacted][1)], the synthesis of [redacted][2)], the synthesis and isolation of [redacted][3)], the synthesis and isolation of [redacted], and the synthesis of [redacted] were identified as critical steps. [redacted], [redacted], [redacted], and [redacted] are identified as critical intermediates, and in-process control parameters and action limits have been established for the critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for BIC sodium include content, description, identification (infrared spectrophotometry and liquid chromatography), purity (clarity and color of solution, related substances [liquid chromatography], residual solvents and [redacted] impurities [gas chromatography], [redacted] [gas chromatography], [redacted] [gas chromatography], and [redacted] [liquid chromatography]), water content, sodium (liquid chromatography), and assay (liquid chromatography).

1) [redacted]

2) [redacted]

3) [redacted]

2.1.4 Stability of drug substance

Table 2 shows main stability studies conducted. Photostability testing showed that BIC sodium was photostable.

Table 2. Stability studies of the drug substance BIC sodium

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term testing	8 pilot batches	30°C	75% RH	Polyethylene bag (double-layered) + high-density polyethylene drum	18-36 months
Accelerated testing	8 pilot batches	40°C	75% RH		6 months

Based on the above, a retest period of 36 months has been proposed for the drug substance when stored at room temperature in a double-layered polyethylene bag placed in a high-density polyethylene drum, in accordance with the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term testing is planned to continue for up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is film-coated tablets, each containing 52.45 mg of BIC sodium (equivalent to 50 mg of BIC), 200°mg of FTC, and 28.04 mg of TAF fumarate (equivalent to 25 mg of TAF). Excipients contained in the drug product are microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and Opadry II brown ([redacted]).

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of the following steps: Production of [redacted] ([redacted] and [redacted]), production of [redacted] ([redacted] and [redacted]), tableting, film-coating, primary packaging, secondary packaging, labeling, test, and storage. Among these steps, production of [redacted] ([redacted] and [redacted]), production of [redacted] ([redacted] and [redacted]), [redacted], and [redacted] were identified as the critical steps. In-process control parameters and action limits have been established for [redacted], [redacted], and [redacted].

Based on the following investigations, the strategy for quality control was developed (Table 3):

- Identification of critical quality attributes
- Identification of in-process control and critical process parameters based on the quality risk assessment

Table 3. Outline of quality control strategy for the drug product

Critical quality attributes	Control method
[redacted]	[redacted], manufacturing process
[redacted]	[redacted], manufacturing process
[redacted]	[redacted], manufacturing process
[redacted]	[redacted], manufacturing process
[redacted]	[redacted], manufacturing process
[redacted]	[redacted], manufacturing process
[redacted]	[redacted]

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (ultraviolet and visible spectrophotometry and liquid chromatography), purity (related substances [liquid chromatography]), water content, uniformity of dosage units (content uniformity [liquid chromatography]), dissolution (liquid chromatography), microbial limit, and assay (liquid chromatography).

2.2.4 Stability of drug product

Table 4 shows the main stability studies conducted. Photostability testing showed that the drug product was photostable.

Table 4. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term testing	6 pilot batches	30°C	75% RH	High-density polyethylene bottle (with silica gel) + polypropylene cap + aluminum foil	12-24 months
Accelerated testing	6 pilot batches	40°C	75% RH		6 months

Based on the above, the shelf life of 36 months has been proposed for the drug product when filled together with silica gel in a high-density polyethylene bottle with a polypropylene cap, heat-sealed in aluminum foil, and stored at room temperature, in accordance with the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003). Long-term testing is planned to continue for up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the results of the reviews on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is controlled adequately.

3. Non-clinical Pharmacology and Outline of the Prior Assessment Conducted by PMDA

The prior assessment requestor submitted the results of primary pharmacodynamics studies, secondary pharmacodynamic studies, and safety pharmacology studies as the supporting data of the pharmacological action of BIC. The prior assessment requestor also submitted the results of pharmacodynamic drug interaction studies. The pharmacological actions of FTC and TAF have already been evaluated by PMDA at the review of Emtriva Capsules 200 mg and Genvoya Combination Tablets (Review Report of Emtriva Capsules 200 mg [dated February 8, 2005], Review Report of Genvoya Combination Tablets [dated May 19, 2016]).

3.1 Primary pharmacodynamics (BIC)

3.1.1 *In vitro* antiviral activity

3.1.1.1 Antiviral activity against laboratory strains (CTD 4.2.1.1.1 to 4.2.1.1.3 and 4.2.1.1.14)

The antiviral activity of BIC was investigated using human T lymphoblastoid cell lines, MT-2 and MT-4, infected with HIV-1 (IIIB strain). The mean 50% effective concentration (EC_{50}) was 1.5 and 2.4 nmol/L, respectively.

The antiviral activity of BIC was investigated using primary human CD4+ T lymphocytes and primary human monocyte-derived macrophages infected with HIV-1 (BaL strain). The mean EC_{50} was 1.5 and 6.6 nmol/L, respectively.

The antiviral activity of BIC was investigated using MT-2 cells infected with HIV-1 (IIIB strain) at a multiplicity of infection of 0.009, 0.03, 0.09, and 0.3. The mean EC_{50} was 0.44, 0.58, 1.21, and 2.86 nmol/L, respectively.

The antiviral activity of BIC was investigated using MT-4 cells infected with HIV-1 (IIIB strain). Protein-adjusted 95% effective concentration (EC_{95})[4)] was 361 nmol/L (162 ng/mL).

The effect of serum proteins on the antiviral activity of BIC was investigated using MT-2 cells infected with HIV-1 (IIIB strain). In the presence of human serum albumin (35 mg/mL) and α1-acid glycoprotein (1.5 mg/mL) or in the presence of human serum (100%), EC_{50} was 18.6 and 27.4 nmol/L, respectively, showing an approximately 20- and 74-fold increase, respectively.

3.1.1.2 Antiviral activity against clinical isolates (CTD 4.2.1.1.4 and 4.2.1.1.17)

The antiviral activity of BIC was investigated using primary human peripheral blood mononuclear cell (PBMC) infected with clinically isolated HIV-1 (subtypes A [2 strains], B [4 strains], C [2 strains], D [2 strains], E [2 strains], F [1 strain], G [1 strain], O [3 strains], and N [1 strain]), or with clinically isolated HIV-2 (1 strain). EC_{50} (range or individual value) was 0.74 to 1.71, 0.35 to 0.88, 0.15 to 1.4, 0.31 to 1.06, 0.28 to 0.8, 1.13, <0.05, <0.08 to 0.09, <0.08, and 1.11 nmol/L, respectively.

3.1.2 Mechanism of action (CTD 4.2.1.1.5, 4.2.1.1.6, and 4.2.1.1.18)

The inhibitory effect of BIC on HIV-1 integrase 3' processing and strand transfer was investigated by enzyme assay. The 50% inhibitory concentration (IC_{50}) for 3' processing and strand transfer was 241 and 7.5 nmol/L, respectively.

The inhibitory effect of BIC on the integration of HIV-1 DNA into chromosomal DNA was investigated by polymerase chain reaction (PCR) using MT-2 cells infected with HIV-1 (IIIB strain). BIC (28 nmol/L), dolutegravir (DTG) (31 nmol/L), efavirenz (EFV) (17 nmol/L), and darunavir (DRV) (57 nmol/L) inhibited the integration of HIV-1 DNA into MT-2 cell DNA by 99%, 98%, 92%, and 23%, respectively. In cells treated with BIC, DTG, EFV, and DRV (the same concentrations as above), the amount of viral DNA synthesized by reverse transcriptase was 0.9, 0.8, 0.2, and 0.9 times, respectively, that in dimethylsulfoxide (DMSO)-treated cells.

The binding affinity of BIC, DTG, raltegravir (RAL), and EVG to wild-type integrase-DNA complexes and to INSTI-resistance mutation (G140S + Q148H)-introduced integrase-DNA complexes was investigated. Table 5 shows their binding half-life and the dissociation half-life.

[4)] The efficacy of INSTIs, RAL and EVG, increases in patients whose trough plasma concentration remains above protein-adjusted EC_{95} (*J Acquir Immune Defic Syndr.* 2006;43:1-5, *J Acquir Immune Defic Syndr.* 2006;43:509-15).

Table 5. Binding half-life and dissociation half-life of the test drug to and from integrase-DNA complex

Test drug	Binding half-life (min)		Dissociation half-life (h)	
	Wild-type	G140S + Q148H	Wild-type	G140S + Q148H
BIC	35 ± 5	37 ± 4	38 ± 19	2.5 ± 0.07
DTG	36 ± 4	24 ± 5	16 ± 9	0.65 ± 0.2
RAL	24 ± 8	-	5.2 ± 0.6	-
EVG	15 ± 6	-	1.5 ± 0.2	-

Mean ± standard deviation (SD)
-, Not tested

3.1.3 Resistance profile

3.1.3.1 *In vitro* resistance development studies (CTD 4.2.1.1.10, 4.2.1.1.13, and 4.2.1.1.16)

MT-2 cells infected with HIV-1 (IIIB strain) and primary human CD4+ T-lymphocytes infected with HIV-1 (BaL strain) were cultured separately for 35 days in the presence of BIC (5991 nmol/L[5)]). No decrease in susceptibility of the virus to BIC was observed.

MT-2 cells infected with HIV-1 (IIIB and xxLAI strains) were cultured in the presence of BIC (with ascending BIC concentrations) to investigate fold-changes in the susceptibility of the viruses to BIC. Table 6 shows amino acid substitutions and fold-changes in susceptibility observed after resistance induction.

Table 6. Mutations in integrase region and fold-changes in susceptibility observed after resistance induction

Viral strain	Amino acid substitution	Fold-change in susceptibility[a)]	Days until mutation was detected
HIV-1 (IIIB)	R263R/K	1.7	47
	R263K	2.6-3.5	71
	R263K + M50I	5.0-7.9	156
HIV-1 (xxLAI)	T66I + S153F	-	79
	T66I + S153F + E152K + M154I + E157K	-	131
	S153F + S24G + M154I + E157K	-	191
	S153F + S24G + E152K	-	207

-, Not tested.
a) EC_{50} for mutant virus/EC_{50} for wild-type virus

3.1.3.2 Antiviral activity against mutant strains (CTD 4.2.1.1.9, 4.2.1.1.11 to 4.2.1.1.13, 4.2.1.1.15, and 4.2.1.1.16)

HIV-1 (HXB2 strain) with amino acid substitutions in the main integrase region (e.g., M50I, R263K, T66I, S153F) or in other integrase regions induced by BIC in the resistance development study [see Section 3.1.3.1] was subjected to a test for fold-changes in susceptibility to each test drug (Table 7).

5) Corresponds to C_{min} following administration of BIC to humans at the clinical dose.

Table 7. Antiviral activity of each test drug against strains with mutations in integrase region

Amino acid substitution	Fold-change in susceptibility[a)]			
	BIC	DTG	EVG	RAL
EC_{50} for wild-type virus	1.44 nmol/L	1.70 nmol/L	1.43 nmol/L	6.70 nmol/L
M50I	1.3	1.2	1.4	1.1
R263K	2.1	2.1	3.8	1.2
M50I + R263K	2.9	2.1	5.1	1.2
EC_{50} for wild-type virus	2.67 nmol/L	2.58 nmol/L	3.07 nmol/L	9.49 nmol/L
T66I	0.4	0.4	9.2	1.3
S153F	1.9	1.6	2.1	1.0
T66I + S153F	0.5	0.5	33	1.0
T66I + E138K + Q148K	44	26	>125	>179
EC_{50} for wild-type virus	1.6 nmol/L	1.4 nmol/L	2.4 nmol/L	9.4 nmol/L
E92Q	1.2	1.3	36	4.0
Y143R	1.1	1.4	6.1	45
Q148R	0.7	0.8	154	45
N155H	1.0	1.8	48	20
R263K	1.8	1.9	4.4	1.1
E138K + Q148K	8.8	10.1	1520	163
G140S + Q148R	2.0	4.8	369	262
E92Q + N155H	1.3	2.1	326	67
Q148R + N155H	4.5	3.5	921	232
EC_{50} for wild-type virus	1.53 nmol/L	1.57 nmol/L	1.79 nmol/L	8.03 nmol/L
T97A	0.6	0.6	3.8	1.6
T97S	0.8	0.7	2.1	1.1
T97I	0.5	0.6	1.8	1.0
T97V	0.4	0.6	2.9	1.5
M50I	1.0	1.1	1.5	1.2
G70R	0.9	1.1	2	1.2
V72I	1.0	1.0	1.8	1.2
L74I	0.9	1.0	1.7	1.1
L74M	0.7	0.7	1.7	1.2
A91E	0.7	0.7	1.1	0.8
G118R	3.4	6.1	4.9	6.2
S119G	0.8	0.9	1.5	1.1
S119P	0.9	0.9	1.9	1.0
S119R	1.1	1.1	2.1	1.3
S119T	0.9	1.0	1.6	1.3
F121Y	0.4	0.6	16	5.3
T122I	1.0	1.0	1.5	1.1
G163R	1.1	1.1	1.8	1.3
T97A + M50I	0.6	0.7	3.5	1.6
T97A + V72I	0.5	0.7	3.7	2.0
T97A + L74I	0.6	0.7	3.7	2.5
T97A + L74M	0.5	0.6	4.9	2.8
T97A + G118R	2.8	11	8.6	20
T97A + S119G	0.3	0.7	5.9	2.5
T97A + S119P	0.5	0.6	9.5	2.3
T97A + S119R	0.7	1.1	13	3.5
T97A + S119T	0.4	0.6	5.3	2
T97A + G163R	1.0	1.2	2.9	2.2
V72I + L74M	0.5	0.7	2.3	1.6
V72I + T122I	0.9	1.1	1.7	1.5
S119P + L74M	0.6	0.7	2.4	0.9
S119R + L74M	0.7	0.9	2.8	1.7
S119R + F121Y	0.7	1.1	74	14
T97A + S119G +L74M	0.4	0.5	8.9	3.6
T97A + S119P + L74M	0.5	0.6	17	4.4
T97A + S119R + L74M	0.6	0.8	18	4.2
T97A + S119R + G118R	0.5	0.6	4.1	2.6
T97A + S119T + L74M	0.5	0.5	7.8	3.2
T97A + V72I + L74M	0.5	0.6	4.9	3.3
T97A + S119R + V72I + L74M	0.6	0.9	26	4.8
S119R + V72I + L74M	0.8	0.9	4.0	1.9

Mean

a) EC_{50} for mutant virus/EC_{50} for wild-type virus

In addition, clinical isolates with INSTI-resistant mutation (17 and 47 strains) were subjected to a test for susceptibility to each test drug (Table 8).

Table 8. Antiviral activity against clinical isolates with INSTI-resistant mutations

Amino acid substitution	Number of strains tested	Fold-change in susceptibility[a)]			
		BIC	DTG	EVG	RAL
EC_{50} for wild-type virus		1.32 nmol/L	1.16 nmol/L	1.68 nmol/L	6.29 nmol/L
E92Q	8	0.9-1.5	1.2-1.9	25-57	2.0-5.1
Q148R	1	0.7	0.8	123	32
N155H	4	1.0-1.5	1.4-1.6	35-60	6.6-15
T66I + E157Q	1	0.2	0.3	22	1.6
Q148R + G140C	1	1.5	2.0	>208	24
N155H + G163R	1	1.0	1.4	35	15
T66I + T97A + E157Q	1	0.3	0.3	22	2.5
EC_{50} for wild-type virus		1.94 nmol/L	2.79 nmol/L	2.34 nmol/L	7.06 nmol/L
E92Q	2	1.19-1.30	1.58-1.73	60-61	6.70-18
T97A	1	0.66	0.88	10	1.78
Y143R	2	1.39	1.40-1.50	2.19-2.26	16-22
Y143C	1	1.49	1.76	4.24	14
N155H	1	1.42	2.07	>150	107
L68V + Y143C	1	0.54	0.54	1.90	4.06
L74I + F121Y	1	0.84	1.05	38	12
L74M + T97A	1	0.50	0.64	16	8.48
L74M + N155H	1	0.90	1.08	103	89
E92Q + E157E/Q	1	1.16	1.41	51	4.80
E92Q + N155H	1	1.72	3.49	>150	>143
T97A + F121Y	1	0.80	1.63	>150	112
T97A + Y143R	1	0.83	1.11	20	>143
T97A + Y143C	2	1.02-1.60	1.35-1.47	29-42	>143
T97A + N155H	1	0.99	1.51	95	53
G140A + Q148R	1	2.03	2.22	>150	88
G140S + Q148H	9	1.99-4.37	3.44-13	>150	>143
G140S + Q148R	2	3.01-7.05	6.15-17	>150	>143
Q148R + E138A	1	1.69	2.17	>150	43
Q148R + E138K	1	1.80	2.05	>150	54
N155H + E157E/Q	1	1.23	1.66	28	19
N155H + G163R	1	1.70	1.95	31	15
L68L/V + L74M + Y143R	1	0.59	0.74	26	>143
L74L/M + G140A + Q148R	1	5.38	8.81	>150	>143
L74M + G140C + Q148R	1	8.36	9.06	>150	>143
E92Q + N155H + G163R	1	2.02	4.12	>150	>143
T97A + G140S + Q148H	2	4.39-7.62	14-15	>150	>143
E138K + G140C + Q148R	1	5.32	8.58	>150	>143
E138K + G140S + Q148H	3	2.42-2.62	3.59-13	>141 to >150	>114 to >143
E138K + G140A + Q148K	1	19	63	>150	>143
G140S + Q148H + G163K	1	2.48	5.68	>150	>143
G140S + Q148H + E138A	1	7.23	10	>150	>143

Range (individual value in 1 strain)

a) EC_{50} for mutant virus/EC_{50} for wild-type virus

3.1.4 Antiviral activity against NRTI-, NNRTI-, or PI-resistant mutants (CTD 4.2.1.1.8)

The effect of amino acid substitutions[6)] associated with resistance to NRTI, NNRTI, or PI on the antiviral activity of BIC was investigated using MT-2 cells infected with HIV-1 (pLAI or HXB2 strains). In all mutant strains tested, the fold-change in susceptibility to BIC (EC_{50} for mutant virus to EC_{50} for wild-type virus) was <2.

3.2 Secondary pharmacodynamics (BIC)

3.2.1 Effect on non-HIV viruses (CTD 4.2.1.2.3)

The antiviral activity of BIC against hepatitis B virus (HBV), hepatitis C virus (HCV) (genotypes 1b and 2a), influenza virus (types A and B), human rhinovirus, and RS virus was investigated using cells infected with these viruses (Table 9).

6) NRTI resistance substitutions (K65R and M184V), thymidine analog resistance substitutions (M41L, D67N, K70R, L210W, T215F, and K219Q), NNRTI resistance substitutions (K103N, Y181C, Y188L, L100I + K103N, and K103N + Y181C), and PI resistance substitutions (I50V, I84V + L90M, I54V + V82S, and G48V + V82A + L90M)

Table 9. Antiviral activity against viruses other than HIV

Virus	EC_{50} (μmol/L)
HBV	>50
HCV genotype 1b	>44
HCV genotype 2a	>44
Influenza A virus PC/1/73	53.5
Influenza B virus LEE/40	37.2
Human rhinovirus 1A, 14, and 16	>50
RS virus	>50

Mean

3.2.2 *In vitro* cytotoxic activity (CTD 4.2.1.1.1, 4.2.1.1.3, and 4.2.1.2.2)

The cytotoxic activity of BIC against various human-derived cells was investigated (Table 10).

Table 10. Cytotoxic activity against various cells

Cell	CC_{50} (μmol/L)
MT-4 (human T-lymphoblastoid cells)	3.7
MT-2 (human T-lymphoblastoid cells)	10.3
CD4+ T lymphocytes	13.0
Monocyte-derived macrophages	29.8
PBMC (resting stage)	8.4
PBMC (active stage)	5.7
Huh-7 (human hepatocellular carcinoma-derived cells)	43.6
HepG2 (human hepatocellular carcinoma-derived cells)	34.6
PC-3 (human prostate cancer-derived cells)	>44
MRC-5 (human embryonic lung-derived fibroblasts)	>44
Primary human hepatocytes	>100

Mean

3.2.3 *In vitro* receptor-binding study (CTD 4.2.1.2.1)

The inhibitory activity of BIC was investigated by evaluating the binding of ligands to a panel of 68 targets such as neuroreceptors, ion channels, and nuclear receptors. BIC (10 μmol/L) did not inhibit ligand binding by >50%.

3.3 Safety pharmacology (BIC) (CTD 4.2.1.3.1 to 4.2.1.3.4)

The effect of BIC on the cardiovascular system, central nervous system, and respiratory system was evaluated (Table 11).

Table 11. Outline of safety pharmacology studies

Organ system	Test system	Evaluation items and methods	Dose or concentration	Route of administration	Findings
Cardiovascular	Human embryonic kidney-derived cells (3 samples/ concentration)	hERG current	0, 0.8, 7.1 μmol/L	*In vitro*	0.8 μmol/L: 1.0% inhibition 7.1 μmol/L: 10.3% inhibition
	Cynomolgus monkeys (4 males)	Telemetry	0, 30, 100, 1000 mg/kg[a)]	p.o.	None
Central nervous	Male rats (n = 8/group)	Irwin test	0, 10, 30, 100, 300 mg/kg[b)]	p.o.	None
Respiratory	Male rats (n = 8/group)	Plethysmography	0, 10, 30, 100, 300 mg/kg[b)]	p.o.	None

a) C_{max} (Day 1) following the administration of BIC 1000 mg/kg to male monkeys was 97.3 μg/mL [see Section 4.1.2], and the fraction unbound to monkey plasma protein was 0.31% [see Section 4.2.2].
b) C_{max} (Day 1) following the administration of BIC 300 mg/kg to male rats was 143 μg/mL [see Section 4.1.2], and the fraction unbound to rat plasma protein was 0.01% [see Section 4.2.2].

The prior assessment requestor's explanation:
BIC had no effect on the cardiovascular system, central nervous system, or respiratory system in the above studies, and therefore that BIC is unlikely to affect the cardiovascular system, central nervous system, or respiratory system in clinical use.[7)]

3.4 Pharmacodynamic drug interactions

3.4.1 Effect of co-administration of BIC, FTC, and TAF (CTD 4.2.1.4.7)

Using MT-2 cells infected with HIV-1 (xxLAI strain), the effect of co-administered BIC, FTC, and TAF on the virus was investigated by CalcuSyn program. Results showed a synergistic effect (combination index of 0.6).[8)]

3.4.2 Effect of BIC co-administered with other anti-HIV drugs (CTD 4.2.1.1.7)

Using MT-2 cells infected with HIV-1 (IIIB strain), the effect of BIC co-administered with other anti-HIV drugs (TAF, FTC, DRV, RAL, and EVG) was investigated. Table 12 shows the results.

Table 12. Effect of BIC co-administered with other anti-HIV drugs

Test drug	Volume [(μmol/L)^2%][a)]		Combination effect[b)]
	Synergy	Antagonism	
BIC + TAF	116 ± 27	−6.0 ± 5.8	Strong synergistic effect
BIC + FTC	123 ± 56	−4.4 ± 6.7	Strong synergistic effect
BIC + DRV	122 ± 41	−4.0 ± 10.4	Strong synergistic effect
BIC + RAL	15.6 ± 15.2	−10 ± 6.9	Additive effect
BIC + EVG	13.0 ± 8.7	−6.0 ± 6.1	Additive effect
BIC + BIC	7.3 ± 10.3	−15.1 ± 10.1	Additive effect

a) Calculated by MacSynergy TM II program based on the report of Prichard MN et al. (*Antiviral Res.* 1990;14:181-205 and *Antimicrob Agents Chemother.* 1993;37:540-5).
b) Values in "Volume ([μmol/L]^2%)" were defined as follows:
≤−100: strong antagonistic effect
≥−100 and <−50: weak antagonistic effect
≥−50 and <50: additive effect
≥50 and <100: weak synergistic effect
≥100: strong synergistic effect

3.4.3 Effect of sofosbuvir co-administered with BIC, FTC, or TAF (CTD 4.2.1.4.1)

Using MT-4 cells infected with HIV-1 (IIIB strain), the effect of sofosbuvir (HCV NS5B polymerase inhibitor) on the antiviral activity of BIC, FTC, and TAF was investigated. Sofosbuvir (0.64-2.56 μmol/L) had no effect on the EC_{50} of BIC, FTC, or TAF.

3.R Outline of the prior assessment conducted by PMDA

On the basis of the submitted data and on the results of the following reviews, PMDA has concluded that there is no particular problem currently from the point of view of non-clinical pharmacology.

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7 Estimated plasma C_{max} after administration of BIC/FTC/TAF FDC at the clinical dose to patients with HIV-1 infection is 6.15 μg/mL [see Section 6.2.6.1]. The fraction unbound to human plasma protein is 0.25% [see Section 4.1.2].

8) Combination index was defined as follows:
<0.1: very strong synergistic effect
≥0.1 and ≤0.3: strong synergistic effect
>0.3 and ≤0.7: synergistic effect
>0.7 and ≤0.85: moderate synergistic effect
>0.85 and ≤0.9: weak synergistic effect
>0.9 and ≤1.1: additive effect
>1.1 and ≤1.2: weak antagonistic effect
>1.2 and ≤1.45: moderate antagonistic effect
>1.45 and ≤3.3: antagonistic effect
>3.3 and ≤10: strong antagonistic effect
>10: very strong antagonistic effect

3.R.1 Antiviral activity of BIC and resistance

On the basis of the submitted data, PMDA considers that BIC has antiviral activity against HIV-1 [see Section 3.1.1]. *In vitro* studies showed ≥2-fold decrease in susceptibility to BIC in most of the strains with single mutants (G118R, R263K), double mutants including the single mutants, or double mutants including E138, G140, and Q148 mutants, among the strains with amino acid substitutions in the integrase region [see Section 3.1.3]. In contrast, susceptibility to BIC was maintained in most of the mutant strains showing decreased susceptibility to EVG or RAL [see Section 3.1.3]. Post-marketing information on mutations associated with resistance to BIC should be collected continuously, and any new findings should be communicated appropriately to healthcare professionals. The efficacy of BIC/FTC/TAF FDC in patients with HIV-1 infection is described in Section 7.R.1.3.

4. Non-clinical Pharmacokinetics and Outline of the Prior Assessment Conducted by PMDA

BIC (^{14}C-labeled or non-labeled) was administered to mice, rats, rabbits, dogs, and monkeys to investigate the pharmacokinetics (PK) of BIC in these animals. Biological samples obtained from humans and animals were analyzed to investigate the binding of BIC to plasma proteins, drug-metabolizing enzymes, and drug transporters. The PK of FTC and TAF has already been evaluated by PMDA at the time of the review of applications for Emtriva Capsules 200 mg and Genvoya Combination Tablets (Review Report of Emtriva Capsules 200 mg [dated February 8, 2005], Review Report of Genvoya Combination Tablets [dated May 19, 2016]).

The prior assessment requestor explained that the PK of the individual components (BIC, FTC, and TAF) co-administered was not investigated in the non-clinical studies, for the following reasons: (1) Since the main metabolic and excretion pathways of BIC, FTC, and TAF as the active ingredients are different from one another, co-administration of BIC, FTC, and TAF is unlikely to cause pharmacokinetic interactions among these components; and (2) investigation of the PK of the individual components following co-administration of BIC, FTC, and TAF in clinical studies did not show any clinically significant pharmacokinetic interactions [see Section 6.2.1.2].

Plasma BIC concentration was determined by the liquid chromatography-ultraviolet (LC-UV) method (lower limit of quantitation [LLOQ], 0.4 μg/mL in mice, 4 nmol/L or 0.2 or 0.4 μg/mL in rats, 0.4 μmol/L or 0.2 μg/mL in monkeys) and by LC-MS/MS (LLOQ, 1000 ng/mL in mice, 4 nmol/L or 1000 ng/mL in rats, 4 nmol/L in dogs, 4 nmol/L or 1000 ng/mL in rabbits, 4 nmol/L or 1000 ng/mL in monkeys). Radioactivity levels in plasma, urine, bile, and feces were determined by a liquid scintillation counter, and tissue radioactivity levels were determined by quantitative whole-body autoradiography.

PK parameters are expressed in mean values unless specified otherwise.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.1 to 4.2.2.2.3, 4.2.2.2.6, 4.2.2.2.8 to 4.2.2.2.10, and 4.2.2.2.12)

BIC (0.5 or 1.0 mg/kg) was administered to 3 each of male rats, dogs, and monkeys orally as a single dose or intravenously continuously for 30 minutes under fasted conditions. The bioavailability (BA) of BIC in male rats, dogs, and monkeys was 49.8%, 41.8%, and 73.8%, respectively. BIC (0.5 or 1.0 mg/kg) was administered orally in a single dose to 3 each of male rats, dogs, and monkeys. The $t_{1/2}$ of plasma BIC in male rats, dogs, and monkeys was 25.7, 4.3, and 3.3 hours, respectively. Table 13 shows PK parameters following single oral administration of BIC to mice, rats, rabbits, and monkeys under fed conditions.

Table 13. PK parameters in animals following single oral administration of BIC

Animal species	Dose (mg/kg)	Number of animals	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (μg·h/mL)
Mouse	30	3 males/time point	59.3	0.5	660
		3 females/time point	71.8	2	745
	100	3 males/time point	97.9	1	1257
		3 females/time point	108	8	1509
	300	3 males/time point	116	4	2106
		3 females/time point	127	8	2173
	1000	3 males/time point	135	0.5	2568
		3 females/time point	163	2	3197
	1500	3 males/time point	123	4	2155
		3 females/time point	164	2	2366
Rat	10	3 males	31.1 ± 6.0	2.7 ± 1.2	471 ± 142
	30	3 males	54.3 ± 5.8	2.3 ± 1.5	849 ± 66
	100	3 males	104 ± 30	4.8 ± 3.9	1625 ± 826
	300	3 males	120 ± 23	10.7 ± 11.7	2205 ± 248
	1000	3 males	115 ± 14	1.7 ± 0.6	1931 ± 109
Rat	30	3 males	55.3 ± 6.0	3.67 ± 3.79	926 ± 209
	100	3 males	102 ± 17	5.00 ± 3.61	1896 ± 331
	300	3 males	129 ± 9	6.00 ± 2.00	2436 ± 481
Rabbit	100	3 females	4.38 ± 0.21	1.67 ± 0.58	23.3 ± 1.9
	300	3 females	6.41 ± 1.73	2.00 ± 0.00	69.7 ± 6.9
	1000	3 females	9.76 ± 3.49	16.7 ± 12.7	171 ± 64
Monkey	30	3 males	18.7 ± 4.0	2.67 ± 1.15	171 ± 73
	100	3 males	42.1 ± 10.3	2.67 ± 1.15	348 ± 51
	1000	3 males	80.9 ± 25.6	5.33 ± 1.15	1056 ± 339

Mean ± SD

4.1.2 Repeated-dose studies (CTD 4.2.3.2.3 to 4.2.3.2.5 and 4.2.3.5.2.5)

Table 14 shows PK parameters following repeated oral administration of BIC to mice, rats, rabbits, and monkeys.

In all animal species tested, increases in the C_{max} and AUC of BIC were less than dose-proportional within the dose range investigated. Repeated administration did not cause clear accumulation of BIC in mice and monkeys, whereas in rats (at BIC 5 mg/kg) and rabbits, the repeated administration caused an increase in the exposure. No clear sex difference was observed in mice or monkeys, whereas in rats, C_{max} and AUC of BIC were higher in females than in males.

Table 14. PK parameters in animals following repeated oral administration of BIC

Animal species	Dose (mg/kg/day)	Sampling time point	Number of animals	Feeding	C_{max} (μg/mL)		t_{max} (h)		$AUC_{0\text{-}24h}$ (μg·h/mL)	
					Male	Female	Male	Female	Male	Female
Mouse	30	Day 1	3/sex/time point	Fed	65.3	50.0	4.00	4.00	679	610
		Week 4	3/sex/time point	Fed	62.5	55.1	0.500	4.00	606	652
	100	Day 1	3/sex/time point	Fed	97.4	121	1.00	4.00	1310	1280
		Week 4	3/sex/time point	Fed	90.0	108	0.500	4.00	1030	1330
	1000	Day 1	3/sex/time point	Fed	141	158	8.00	4.00	2590	2390
		Week 4	3/sex/time point	Fed	146	175	0.500	4.00	2230	2420
Rat	5	Day 1	3/sex/time point	Fed	19.4	22.9	2.00	1.00	341	436
		Week 26	3/sex/time point	Fed	28.8	70.0	0.500	4.00	457	1290
	30	Day 1	3/sex/time point	Fed	82.4	113	2.00	1.00	1420	1870
		Week 26	3/sex/time point	Fed	76.9	169	2.00	2.00	1010	2910
	300	Day 1	3/sex/time point	Fed	143	185	1.00	1.00	2380	3530
		Week 26	3/sex/time point	Fed	100	213	2.00	0.500	1830	4680
Rabbit, pregnant	100	Day 1	3 females	Fed	-	3.41 ± 0.87	-	3.33 ± 1.15	-	17.0 ± 9.00
		Day 13	3 females	Fed	-	3.96 ± 0.32	-	4.00 ± 0	-	38.5 ± 9.30
	300	Day 1	3 females	Fed	-	4.08 ± 0.38	-	10.7 ± 11.5	-	62.5 ± 29.2
		Day 13	3 females	Fed	-	4.05 ± 0.46	-	2.75 ± 2.17	-	60.3 ± 9.79
	1000	Day 1	3 females	Fed	-	9.62 ± 1.44	-	17.3 ± 11.5	-	146 ± 32.7
		Day 13	3 females	Fed	-	11.0 ± 1.11	-	3.33 ± 4.04	-	138 ± 25.8
Monkey	30	Day 1	7/sex	Fasted	40.1 ± 11.6	24.6 ± 4.89	2.29 ± 0.756	2.86 ± 1.07	280 ± 33.3	243 ± 65.5
		Week 39	7/sex	Fasted	28.3 ± 2.44	24.4 ± 7.80	2.25 ± 1.26	2.50 ± 1.00	248 ± 75.1	253 ± 84.3
	200	Day 1	7/sex	Fasted	43.4 ± 4.97	55.1 ± 6.49	3.43 ± 1.90	4.86 ± 1.07	514 ± 119	797 ± 123
		Week 39	7/sex	Fasted	67.8 ± 7.91	70.4 ± 12.1	2.00 ± 0	3.00 ± 2.00	595 ± 112	823 ± 219
	1000	Day 1	9/sex	Fasted	97.3 ± 23.6	111 ± 18.3	5.78 ± 0.667	5.33 ± 1.00	1450 ± 326	1520 ± 234
		Week 39	9/sex	Fasted	104 ± 33.4	109 ± 10.7	4.67 ± 1.63	4.67 ± 1.63	1450 ± 512	1750 ± 294

Mean ± SD
-, Not tested.

4.1.3 *In vitro* membrane permeability (CTD 4.2.2.2.7)

Membrane permeability of BIC was investigated in human colon adenocarcinoma-derived Caco-2 cells. Following the incubation of the cells with BIC (10 or 88 μmol/L), the apparent permeability coefficient from the apical surface (A) to the basolateral surface (B) ($P_{appA\rightarrow B}$) was 6.2 and 14.8 × 10^{-6} cm/sec, respectively, and the apparent permeability coefficient from B to A ($P_{app\ B\rightarrow A}$) was 27.2 and 22.6 × 10^{-6} cm/s, respectively, with the ratio of $P_{app\ B\rightarrow A}$ to $P_{appA\rightarrow B}$ (efflux ratio) being 4.4 and 1.5, respectively.

4.2 Distribution

4.2.1 Tissue distribution (CTD 4.2.2.3.1)

^{14}C-labeled BIC (2 mg/kg) was administered orally in a single dose to albino rats (n = 1 male/time point) and to pigmented rats (n = 1 male/time point). In both animal strains, the radioactivity was distributed in all tissues[9)] except for the lens within 0.25 to 1 hour post-dose, reaching the highest level

9) Radioactivity levels were measured in the following tissues from albino and pigmented rats:
Adrenals, arterial wall, bile, blood, bone, bone marrow, cerebellum, cerebrum, brain choroid plexus, medulla oblongata, olfactory lobe, bulbourethral gland, cecum, diaphragm, epididymis, esophagus, extra-orbital lacrimal gland, lens, uvea, vitreous fluid, eye, fascia, fat (abdominal), brown fat, Harderian gland, intraorbital lacrimal gland, renal cortex, renal medulla, kidney, large intestine, liver, lung, lymph nodes, muscles, cardiac muscles, nasal concha, pancreas, periosteum, pituitary gland, preputial glands, prostate gland, salivary gland, seminal vesicle, skin (non-pigmented site), small intestine, spinal cord, spleen, stomach, gastric mucosa, gastric wall, testis, thymus, thyroid gland, urinary bladder, urine [skin (pigmented site) also was investigated in pigmented rats])

in most of the tissues within 1 to 4 hours post-dose. After reaching the highest level, the radioactivity level tended to decrease over time, but the radioactivity was still detectable in most of the tissues even at 168 hours post-dose. Tissue radioactivity levels were high in the lung, bile, small intestine, etc., but were lower in all tissues than in blood at almost all sampling time points. No clear difference was observed in the radioactivity levels between pigmented and non-pigmented sites of the skin, based on which the prior assessment requestor explained that BIC and its metabolites have only low affinity to melanin-containing tissues.

4.2.2 Plasma protein binding and distribution in blood cells (CTD 4.2.2.3.2 to 4.2.2.3.5)

BIC (at the final concentration of 2 μmol/L) was added to rat, dog, monkey (cynomolgus and rhesus), and human plasma samples, and the plasma protein binding of BIC was investigated by equilibrium dialysis. The binding rates in rat, dog, cynomolgus monkey, rhesus monkey, and human plasma samples were 99.99%, 98.76%, 99.69%, 99.68%, and 99.75%, respectively.

M20, the main metabolite of BIC, (at the final concentration of 2 μmol/L) was added to rat, monkey, and human plasma samples, and the plasma protein binding of the metabolite was investigated by equilibrium dialysis. The binding rates in rat, monkey, and human plasma samples were 99.99%, 99.86%, and 99.87%, respectively.

BIC (at the final concentration of 3 μmol/L) was added to human liver microsomes, and the binding of BIC to microsomal proteins was investigated by equilibrium dialysis. The percentage of fraction of unbound BIC was 86.3%.

BIC (at the final concentration of 0.5 μmol/L) was added to the whole blood samples of rats, dogs, monkeys (cynomolgus and rhesus monkeys), and humans. The blood cell-to-plasma concentration ratio of BIC was 0.05, 0.17, 0.14, 0.11, and 0.19, respectively, and the blood-to-plasma concentration ratio of BIC was 0.58, 0.60, 0.65, 0.62, and 0.64, respectively.

4.3 Metabolism[10)]

4.3.1 Postulated metabolic pathway

Figure 1 shows the main metabolic pathways of BIC postulated from the results of studies in Sections 4.3.2, 4.3.3, and 6.2.1.1.

[10)] Metabolites described in this section are as shown in Figure 1 and in the following:
M305, N-dealkylated BIC; M465b, hydroxyl BIC; M10, cysteine-glycine conjugate of desfluoro-hydroxy BIC; M12, glucuronate conjugate of hydroxyl BIC; M15, glucuronate conjugate of BIC; M16, glucuronate conjugate of desfluoro-hydroxy BIC; M18, hydroxyl BIC-1; M19, desfluoro-hydroxy BIC-1; M28, desfluoro-hydroxy BIC-4; M30, cysteine conjugate of desfluoro-hydroxy BIC; M32, cysteine-glycine conjugate of desfluoro-hydroxy BIC; M35, glucuronate conjugate 2 of hydroxyl BIC; M37, cysteine conjugate-3 of desfluoro-hydroxy BIC; M38, dihydroxy BIC; M39, BIC glucoside; M42, hydroxyl BIC-5; and M58, BIC glucuronate conjugate

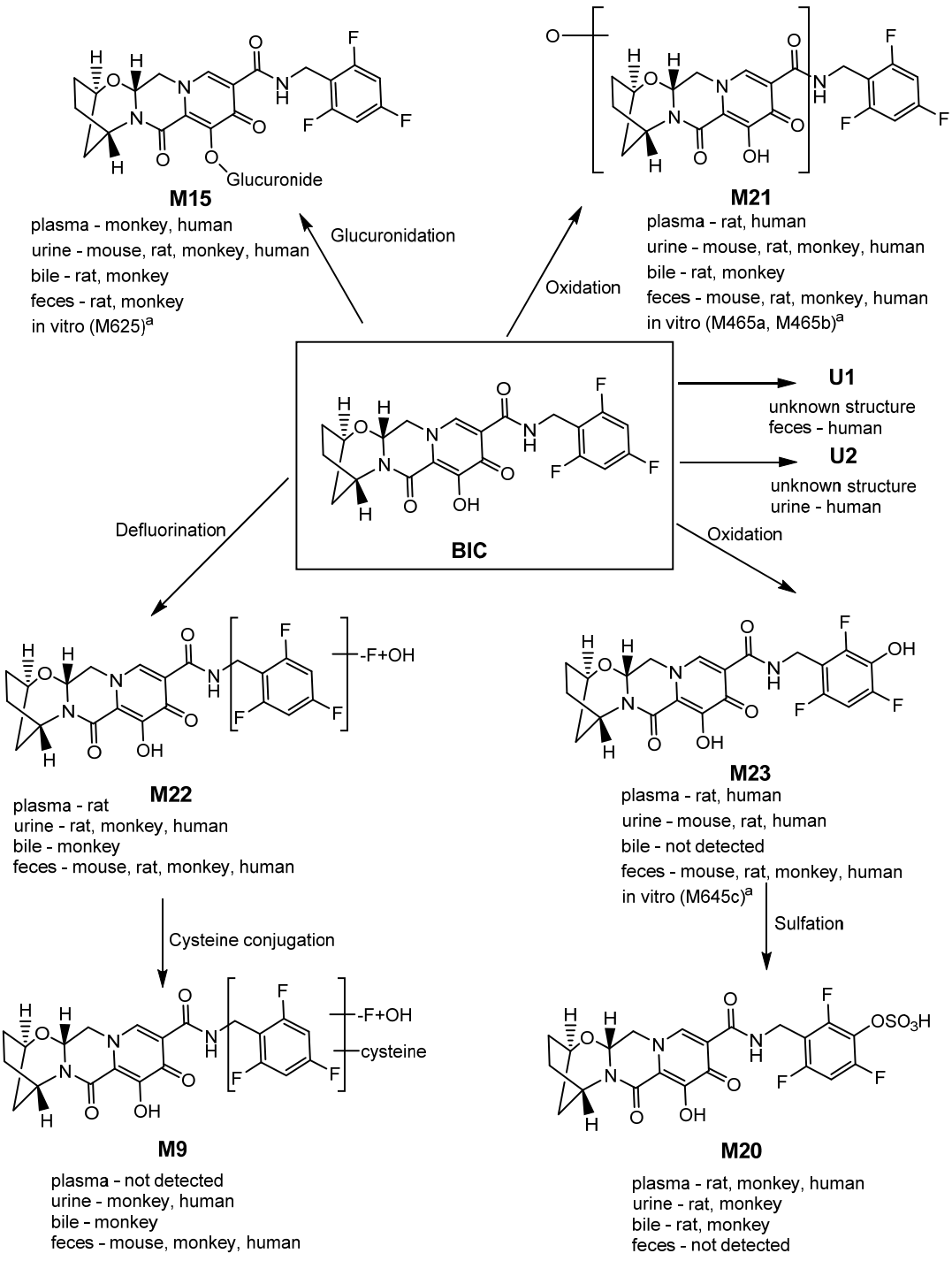

Figure 1. Postulated main metabolic pathways of BIC (cited from Figure 15 of CTD 2.6.4)

Postulated metabolic pathways of metabolites in humans that were excreted in an amount exceeding 1% of the administered radioactivity or that with AUC of plasma radioactivity exceeding 1% of total radioactivity

4.3.2 *In vitro* metabolism (CTD 4.2.2.4.2, 4.2.2.4.4, and 4.2.2.4.5)

^{14}C-labeled BIC (at the final concentration of 20 μmol/L) was added to hepatocytes of rats, dogs, monkeys, and humans, and the cells were incubated for 4 hours at 37°C. Unchanged BIC was mainly detected in all animal species, accounting for 91.5%, 78.7%, 52.4%, and 93.9% of the total

radioactivity in rats, dogs, monkeys, and humans, respectively. M15, M305, and M465b[11] were the main metabolites detected.

^{3}H-labeled BIC (at the final concentration of 2 μmol/L) was added to the system expressing a human cytochrome P450 (CYP) isoform (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP3A5) and the system was incubated at 37°C for 45 minutes. BIC was metabolized by CYP3A4 and CYP3A5.

BIC (at the final concentration of 5 μmol/L) was added to the system expressing a human UDP glucuronosyltransferase (UGT) isoform (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, or UGT2B17), and the system was incubated at 37°C for 60 minutes. BIC was metabolized mainly by UGT1A1.

4.3.3 *In vivo* metabolism (CTD 4.2.2.4.1, 4.2.2.4.6, and 4.2.2.4.7)

^{14}C-labeled BIC (2 mg/kg) was administered orally in a single dose to male mice (n = 4). In the first 48 hours post-dose, unchanged BIC was mainly detected in the plasma (accounting for 95.5% of total radioactivity in plasma), with M12 and other metabolites being detected as well. In the urine collected up to 24 hours post-dose, unchanged BIC, M15, and M21, all accounting for <1% of the administered radioactivity, were detected. In feces collected up to 48 hours post-dose, unchanged BIC (accounting for 64.4% of the administered radioactivity) was mainly detected, together with metabolites M9, M21/M22, M23, and M28.

^{14}C-labeled BIC (2 mg/kg) was administered orally in a single dose to bile-duct cannulated (n = 3) or non-cannulated (n = 18[12]) male rats to investigate metabolites in plasma, bile, urine, and feces. In the non-cannulated rats, unchanged BIC (accounting for 76.5% of plasma radioactivity) was mainly detected in the plasma up to 168 hours post-dose, together with metabolites M12, M20, M21/M22, M23, M26, etc. In the urine collected up to 48 hours post-dose, minute amounts of unchanged BIC, M21, M23, etc., were detected. In feces collected up to 168 hours post-dose, unchanged BIC (accounting for 23.9% of the administered radioactivity) was mainly detected, together with metabolites M7, M21/22, M23, M28, etc. In the bile duct-cannulated rats, M15 (accounting for 12.7% of the administered radioactivity) was mainly detected in the bile collected up to 168 hours post-dose, together with unchanged BIC, M9, M10, M16, M18/M19, etc.

^{14}C-labeled BIC (1 mg/kg) was administered orally in a single dose to bile-duct cannulated or non-cannulated (n = 3 each) male monkeys to investigate metabolites in plasma, bile, urine, and feces. In the non-cannulated monkeys, unchanged BIC (accounting for 80.2% of plasma radioactivity) was mainly detected in the plasma up to 72 hours post-dose, together with M35, M38, M42, etc. In urine collected up to 48 hours post-dose, M42 (accounting for 6.15% of the administered radioactivity), M15 (3.84%), and M35 (3.40%) were mainly detected together with M20/M21/M22, etc. The amount of unchanged BIC detected was <0.5% of the administered radioactivity. In feces collected up to 96

[11] M465b detected in the *in vitro* study is a regioisomer of M465a. As a result of an analysis by high-resolution mass spectrometry, M465b and M465a were found to be identical to M21 and M25, respectively, detected in *in vivo* studies, but their exact pathways are unknown.

[12] Fifteen animals (n = 3/time point) were used for the investigation of plasma metabolites, and 3 animals for the investigation of metabolites in urine, feces, and bile.

hours post-dose, unchanged BIC (accounting for 10.7% of the administered radioactivity), M21/M22 (9.05%), and M23/M42 (10.5%) were mainly detected. In the bile-duct cannulated monkeys, M9 (10.9% of the administered radioactivity), M20/M21/M22 (8.09%), and M15 (6.14%) were mainly detected in the bile collected up to 48 hours post-dose. M30, M32, M37/M38, M39, and M42 were also detected. The amount of unchanged BIC was <0.5% of the administered radioactivity.

4.4 Excretion

4.4.1 Biliary, urinary, and fecal excretion (CTD 4.2.2.3.1, 4.2.2.5.2, and 4.2.2.5.3)

^{14}C-labeled BIC (2 mg/kg) was administered orally in a single dose to male mice (n = 4). In the first 168 hours post-dose, 3.55% and 98.5% of the administered radioactivity were recovered in the urine and feces, respectively.

^{14}C-labeled BIC (2 mg/kg) was administered orally in a single dose to bile-duct cannulated male rats (n = 3). In the first 168 hours post-dose, 34.1%, 7.48%, and 42.4% of the administered radioactivity were recovered in the bile, urine, and feces, respectively.

^{14}C-labeled BIC (1 mg/kg) was administered orally in a single dose to bile-duct cannulated male monkeys (n = 3). In the first 168 hours post-dose, 39.7%, 15.2%, and 20.3% of the administered radioactivity were recovered in the bile, urine, and feces, respectively.

The prior assessment requestor explained that the above results suggest that BIC is excreted mainly in feces through the bile.

4.4.2 Excretion in milk

Study data related to BIC excretion in milk were not submitted.

The prior assessment requestor's explanation about BIC excretion in milk:
In a repeated oral dose toxicity study in which BIC (2-300 mg/kg) was administered to pregnant rats from Gestation Day 6 to Lactation Day 20 (CTD 4.2.3.5.3.1), BIC was detected in the plasma of newborn rats on Lactation Day 10 (day 10 postpartum), suggesting the excretion of BIC in milk.

Taking account of the observation that FTC and TAF, an active ingredient, and tenofovir (TFV), the active metabolite of TAF, are both excreted in human milk, together with the above findings, a precautionary statement will be provided to avoid breast-feeding during treatment with BIC/FTC/TAF.

4.5 Pharmacokinetic interactions

4.5.1 Inhibition of drug-metabolizing enzymes (CTD 4.2.2.6.7 to 4.2.2.6.8, and 4.2.2.6.10)

The inhibitory activity of BIC (0.4-100 μmol/L) against metabolism of the substrates[13)] of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) was investigated using human liver microsomes. BIC did not cause clear inhibition to the metabolism of any of the substrates of CYP isoforms investigated.

[13)] CYP1A2, phenacetin; CYP2B6, bupropion, CYP2C8, paclitaxel; CYP2C9, tolbutamide; CYP2C19, *S*-mephenytoin; CYP2D6, dextromethorphan; CYP3A, midazolam and testosterone

The time-dependent inhibitory activity of BIC (0.2-200 μmol/L) against the metabolism of the substrates[14] of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) was investigated using human liver microsomes. BIC inhibited the metabolism of midazolam, a substrate of CYP3A, in a time-dependent manner (inhibitor concentration at 50% of maximum inhibition rate [K_i] >100 μmol/L).

The inhibitory activity of BIC (0.01-300 μmol/L) against metabolism of β-estradiol, a substrate of UGT1A1, was investigated using human liver microsomes. BIC inhibited the metabolism of the substrate of UGT1A1 (IC_{50} 176 μmol/L).

Based on the above results and on the estimated steady-state plasma C_{max} of BIC (6146 ng/mL [13.7 μmol/L]) in patients with HIV-1 infection receiving BIC at the clinical dose [see Section 6.2.6.1], the prior assessment requestor explained that BIC is unlikely to inhibit metabolic enzymes for human exposure after administration of BIC/FTC/TAF FDC at the clinical dose.

4.5.2 Induction of drug-metabolizing enzymes and drug transporters (CTD 4.2.2.6.9)

Induction of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP3A4), UGT1A1, and P-glycoprotein (P-gp) by BIC (1-60 μmol/L) in human hepatocytes was investigated using the expression level of messenger RNA (mRNA) of each metabolic enzyme and the transporter as the index. BIC induced CYP2B6 and CYP3A4 (EC_{50}; 102.8 and 19.1 μmol/L, respectively). BIC at the maximum concentration tested (60 μmol/L) increased the expression level of P-gp mRNA (5.76-fold increase compared with the level without BIC).

The induction of CYP isoforms (CYP1A2, CYP2B6, or CYP3A) by BIC (1-60 μmol/L) in human hepatocytes was investigated based on the enzyme activity to metabolize the substrates[15] of the CYP isoforms. BIC increased the enzyme activity of CYP3A (by 1.19-2.57 fold).

The above results of the *in vitro* studies suggested that BIC induces CYP2B6, CYP3A4, and P-gp. However, taking account of the estimated steady-state plasma C_{max} of BIC (6146 ng/mL [13.7 μmol/L]) in patients with HIV-1 infection receiving BIC at the clinical dose [see Section 6.2.6.1] and other findings, the prior assessment requestor explained that BIC is unlikely to induce CYP2B6 in humans when administered at the clinical dose.

4.5.3 Potential of BIC as a substrate of drug transporters (CTD 4.2.2.6.3 and 4.2.2.6.4)

Transport of BIC was investigated using MDCKII cells expressing human P-gp or breast cancer resistance protein (BCRP). The efflux ratio of BIC was 7.5 and 6.5, respectively. In the presence of a P-gp inhibitor (cyclosporin A, the final concentration of 10 μmol/L) or a BCRP inhibitor (Kol34, the final concentration of 10 μmol/L), the efflux ratio of BIC decreased to 2.4 and 2.0, respectively.

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[14] CYP1A2, ethoxyresorufin; CYP2B6, bupropion; CYP2C8, paclitaxel; CYP2C9, diclofenac; CYP2C19, *S*-mephenytoin; CYP2D6, dextromethorphan; CYP3A, midazolam and testosterone

[15] CYP1A2, phenacetin; CYP2B6, bupropion; CYP3A, midazolam

Transport of BIC (at the final concentration of 1 μmol/L) was investigated using CHO cells expressing human organic anion transporting polypeptide (OATP)1B1 or OATP1B3. BIC uptake activity did not clearly differ between OATP1B1- or OATP1B3-expressing cells and non-expressing cells.

The prior assessment requestor explained that the above results suggest that BIC serves as a substrate for P-gp and BCRP.

4.5.4 Inhibition of drug transporters (CTD 4.2.2.6.1, 4.2.2.6.2, 4.2.2.6.5, and 4.2.2.6.11)

The inhibitory effect of BIC[16)] on the transport of substrates[17)] of transporters was investigated using the following cells: (1) MDCKII cells expressing human P-gp, BCRP, or organic cation transporter (OCT)2; (2) CHO cells expressing human organic anion transporter (OAT)1, OCT1, OCT2, OATP1B1, OATP1B3, or multidrug and toxin extrusion protein (MATE)1; (3) Flp-In 293 cells expressing human OAT3; and (4) membrane vesicles prepared from sf9 cells expressing human bile salt export pump (BSEP). BIC inhibited the transport of the substrates of OAT3, OCT2, and MATE1 (IC_{50} 55, 0.42, and 8.0 μmol/L, respectively). BIC also inhibited the transport of the substrates of P-gp, BCRP, OCT1, and BSEP by 20%, 6%, 13%, and 46%, respectively, at the maximum concentration tested (80 or 100 μmol/L).

The above *in vitro* studies suggested the possibility that BIC inhibits the transport of the substrates of OAT3, OCT1, OCT2, MATE1, P-gp, BCRP, and BSEP. Based on these results, whether clinical drug interaction studies should be conducted for evaluating the inhibitory effect of BIC on these transporters was assessed according to the draft guidance of the US regulatory agency for conducting clinical drug interaction studies (Guidance for Industry: Drug Interaction Studies-Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. DRAFT GUIDANCE, 2012). The prior assessment requestor determined that it was unnecessary to conduct clinical drug interaction studies on OAT3, OCT1, and MATE1. The prior assessment requestor also assessed the necessity of such studies based on the "Publication of 'Guidelines on drug interaction studies for drug development and appropriate provision of information (Final Draft)'" (Administrative Notice dated July 8, 2014), and explained that the results were the same as those obtained from the assessment based on the US draft guidance for conducting clinical drug interactions.

4.R Outline of the prior assessment conducted by PMDA

On the basis of the submitted data and on the results of the following reviews, PMDA has concluded that there is no particular problem currently from the point of view of non-clinical PK.

4.R.1 Placental transfer

PMDA asked the prior assessment requestor to explain the reasons for not investigating the placental transfer of BIC.

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16) Effect of BIC was studied at the following final concentrations:
P-gp and BCRP, 0.33 to 80 μmol/L; OATP1B1 and OATP1B3, 0.109 to 80 μmol/L; OCT2 and MATE1, 0.014 to 10 μmol/L; OAT1, OAT3, OCT1, and BSEP; 0.14 to 100 μmol/L

17) P-gp, calcein AM; BCRP, pheophorbide A; OATP1B1 and OATP1B3, Fluo 3; OCT1, OCT2 and MATE1, ^{14}C-tetraethylammonium chloride; OAT1, ^{3}H-*p*-aminohippuric acid; OAT3, ^{3}H-estrone-3-sulfate; BSEP, ^{3}H-taurocholate

The explanation of the prior assessment requestor:
No non-clinical study on the placental transfer of BIC was conducted because BIC was shown not to have any effect on the reproduction or development in reproductive and developmental toxicity studies [see Section 5.5].

TFV, the active metabolite of TAF which is an active ingredient, has been shown to cross the placenta in non-clinical studies. Therefore, a precautionary statement will be included in the package insert requiring careful administration in pregnant women. A foreign clinical study is being planned to evaluate the PK (including placental transfer) of the individual components, efficacy, and safety in patients with HIV-1 infection in the second and third trimester of pregnancy, during treatment with BIC/FTC/TAF.

PMDA accepted the explanation of the prior assessment requestor. If placental transfer of BIC is confirmed in the clinical study being planned, etc., the finding should be provided to healthcare professionals without delay.

5. Toxicity and Outline of the Prior Assessment Conducted by PMDA

The prior assessment requestor submitted the data from the following toxicology studies of BIC: Single-dose toxicity studies, repeated-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other toxicity studies (skin sensitization study, phototoxicity study, and study on impurities). Toxicity of FTC and TAF has already been evaluated by PMDA at the review of Emtriva Capsules 200 mg and Genvoya Combination Tablets (Review Report of Emtriva Capsules 200 mg [dated February 8, 2005], Review Report of Genvoya Combination Tablets [dated May 19, 2016]). No toxicity data on concomitant use of BIC, FTC, and TAF were submitted.

5.1 Single-dose toxicity

Acute toxicity of BIC was evaluated in single-dose toxicity studies[18)] in mice, rats, and monkeys (Table 15). No death or acute toxicity was observed. The approximate lethal dose was determined to be >1500 mg/kg in mice and >1000 mg/kg in rats and monkeys. In the 4-week repeated-dose toxicity study in mice (CTD 4.2.3.2.5), no death or acute toxicity was observed after the initial dose. The approximate lethal dose was determined to be >1000 mg/kg.

The prior assessment requestor explained that co-administration of BIC, FTC, and TAF is unlikely to cause a new acute toxicity, in light of the above results and the observation that neither FTC nor TAF caused acute toxicity.

[18)] A study conducted with the investigation of non-clinical PK of BIC as the primary objective

Table 15. Summary of single-dose toxicity studies of BIC

Test system	Route of administration	BIC dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female mice (Wild-Type rasH2 Tg[a)])	p.o.	30, 100, 300, 1000, 1500	None	>1500	4.2.2.2.12
Male rats (Wistar)	p.o.	10, 30, 100, 300, 1000	None	>1000	4.2.2.2.6
Male cynomolgus monkeys	p.o.	30, 100, 1000	None	>1000	4.2.2.2.9

a) 001178-W (Wild-Type) CByB6F1-Tg (HRAS) 2Jic

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies of BIC were conducted in mice, rats, and monkeys (Table 16). The no observed adverse effect level (NOAEL) of BIC was determined to be 1000 mg/kg/day in mice (4 weeks), 300 mg/kg/day in rats (26 weeks), and 200 mg/kg/day in monkeys (39 weeks). The $AUC_{0\text{-}24h}$ of BIC at the NOAEL was determined to be 2330 μg·h/mL in mice, 1830 μg·h/mL in male rats, 4680 μg·h/mL in female rats, and 709 μg·h/mL in monkeys. The exposures to BIC in mice, male rats, female rats, and monkeys were approximately 23 times, 18 times, 46 times, and 7 times, respectively, the human AUC_{tau} of BIC (102 μg·h/mL, see Section 6.2.6.1) after administration of BIC at the clinical dose. Main toxicity findings included elevated liver deviation enzyme activity in blood, bile duct hyperplasia, hepatocytomegaly, and neutrophil infiltration.

The main systemic toxicity of FTC was decreased red blood cell count in rats and monkeys, and main systemic toxicities of TAF were disorders of kidney and bone in rats and disorders of kidney, bone, and the cardiovascular system (QT prolongation) in dogs. Thus, systemic toxicities of BIC, FTC, and TAF do not overlap each other, suggesting that co-administration of the 3 drugs is unlikely to augment each toxicity. Also, administration of BIC/FTC/TAF FDC at the clinical dose is unlikely to affect the exposure to the individual components. Based on the above, the prior assessment requestor explained that there is little significance to conduct a repeated-dose toxicity study of co-administration of BIC, FTC, and TAF.

Table 16. Summary of repeated-dose toxicity studies of BIC

Test system	Route of administration	Duration of dosing	BIC dose (mg/kg)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female mice (Wild-Type rasH2 Tg[a])	p.o.	4 weeks (once daily)	0,[b] 30, 100, 1000	None	1000	4.2.3.2.5
Male and female rats (Wistar)	p.o.	2 weeks (once daily)	0,[b] 10, 30, 100, 300	None	300	4.2.3.2.1
Male and female rats (Wistar)	p.o.	26 weeks (once daily) + 4-week recovery period	0,[b] 5, 30, 300	None	300	4.2.3.2.3
Male and female cynomolgus monkeys	p.o.	2 weeks (once daily)	0,[b] 30, 100, 1000	1000: Decreased CYP1A activity (male)	1000	4.2.3.2.2
Male and female cynomolgus monkeys	p.o.	39 weeks (once daily) + 4-week recovery period	0,[b] 30, 200, 1000	1000: Increased ALT activity, bile duct hyperplasia, hepatocytomegaly (male and female), hepatic discoloration/surface roughness, hepatic regenerative hyperplasia, hepatic neutrophilic infiltration (male) Recovery group: 1000: Bile duct hyperplasia (male and female), hepatocytomegaly, hepatic lymphocytic infiltration (male) with reversible tendency	200	4.2.3.2.4

a) 001178-W (Wild-Type) CByB6F1-Tg (HRAS) 2Jic
b) Vehicle: Reverse osmosis water containing 0.5% (w/w) hydroxypropylmethylcellulose and 0.1% (w/w) polysorbate 20

5.3 Genotoxicity

The following genotoxicity studies were conducted on BIC: *In vitro* bacterial reverse mutation assay (Ames test) and chromosomal aberration assay using human primary lymphocytes (chromosomal aberration assay), and an *in vivo* micronucleus assay using rat bone marrow (rodent micronucleus assay) (Table 17). In the rodent micronucleus assay, $AUC_{0\text{-}24h}$ of BIC (Day 14 of administration) in rats at the maximum dose (300 mg/kg/day) was 2970 μg·h/mL, which was approximately 29 times the human AUC_{tau} of BIC (102 μg·h/mL, see Section 6.2.6.1) after administration of BIC/FTC/TAF FDC at the clinical dose.

Based on the above results, together with the findings that neither FTC nor TAF has genotoxicity, the prior assessment requestor explained that concomitant use of BIC, FTC, and TAF is unlikely to cause genotoxicity.

Table 17. Summary of genotoxicity studies on BIC

Test		Test system	Metabolic activation (treatment)	BIC concentration or dose	Results	Attached document CTD
In vitro	Ames test	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537	S9−/+	0,[a] 5, 16, 50, 160, 500, 1600, 5000 μg/plate	Negative	4.2.3.3.1.1
		Escherichia coli: WP2*uvr*A	S9−/+			
	Chromosomal aberration assay in mammalian cells	Human primary cultured lymphocytes	S9− (3 hours)	0,[a] 84, 172, 245 μg/mL	Negative	4.2.3.3.1.2
			S9− (24 hours)	0,[a] 9.89, 20.2, 28.8 μg/mL		
			S9+ (3 hours)	0,[a] 120, 172, 245 μg/mL		
In vivo	Micronucleus assay in rodents	Bone marrow of male and female rats (Wistar)		0,[b] 10, 30, 100, 300 mg/kg/day (p.o. for 2 weeks)	Negative	4.2.3.3.2.1

a) Vehicle: DMSO
b) Vehicle: Reverse osmosis water containing 0.5% (w/w) hydroxypropylmethylcellulose and 0.1% (w/w) polysorbate 20

5.4 Carcinogenicity

Carcinogenicity studies on BIC were conducted in rasH2 transgenic (rasH2 Tg) mice (26 weeks) and rats (2 years). No carcinogenicity was observed (Table 18).

The $AUC_{0\text{-}24h}$ of BIC (at Week 26) at the non-carcinogenic dose for mice (100 mg/kg/day in males, 300 mg/kg/day in females) was 1560 μg･h/mL in males and 2340 μg･h/mL in females. The exposures to BIC in males and females were approximately 15 times and 23 times, respectively, the human AUC_{tau} of BIC (102 μg･h/mL) after administration of BIC/FTC/TAF FDC at the clinical dose. The $AUC_{0\text{-}24h}$ of BIC (Week 52) at the non-carcinogenic dose for rats (300 mg/kg/day) was 2170 μg･h/mL in males and 4200 μg･h/mL in females. The exposures to BIC in males and females were approximately 21 times and 41 times, respectively, the human AUC_{tau} of BIC (102 μg･h/mL) after administration of BIC/FTC/TAF FDC at the clinical dose.

Based on the above results, together with the findings that neither FTC nor TAF has carcinogenicity, the prior assessment requestor explained that there is little significance to conduct a carcinogenicity study of co-administration of BIC, FTC, and TAF.

Table 18. Summary of carcinogenicity studies on BIC

Test system	Route of administration	Duration of dosing	Main lesions	Sex	BIC dose (mg/kg/day)				Non-carcinogenic dose (mg/kg/day)	Attached document CTD
					0[a]	5 (male), 10 (female)	15 (male), 30 (female)	100 (male), 300 (female)		
				N	25/sex	25/sex	25/sex	25/sex		
Male and female mice (rasH2 Tg)	p.o.	26 weeks (once daily)	Neoplastic lesion						100 (male) 300 (female)	4.2.3.4.2.1
			Haemangioma/ angiosarcoma[b]	M	1	2	4	3		
				F	1	3	7	2		
			Thymoma/ thymoma malignant	M	0	0	0	0		
				F	4	2	1	6		
			Non-neoplastic lesion							
				Male and female	No toxicity findings					

Test system	Route of administration	Duration of dosing	Main lesion	Sex	BIC dose (mg/kg/day)					Non-carcinogenic dose (mg/kg/day)	Attached document CTD
					0[c]	0[a]	2	10	300		
				N	55/sex	55/sex	55/sex	55/sex	55/sex		
Male and female rats (Wistar)	p.o.	104 weeks (once daily)	Neoplastic lesion							300	4.2.3.4.1.1
			Prostate gland Adenocarcinoma	M	0	0	0	1	2		
				F	-	-	-	-	-		
			Skin/subcutaneous tissue Basalioma	M	1	0	3	0	1		
				F	0	0	0	0	0		
			Skin/subcutaneous tissue Haemangioma	M	0	0	1	2	1		
				F	0	0	0	0	0		
			Skin/subcutaneous tissue Undifferentiated adenocarcinoma	M	0	0	0	2	0		
				F	1	0	0	0	0		
			Skin/subcutaneous tissue Schwannoma malignant	M	1	0	0	0	2		
				F	0	0	0	0	0		
			Adrenal cortex Adenoma/ adenocarcinoma	M	4	0	2	4	3		
				F	2	2	1	3	5		
			Brain Glioma/ oligodendroglioma	M	1	0	2	0	0		
				F	0	0	2	0	0		
			Uterine cervix/ uterus/vagina Schwannoma malignant	M	-	-	-	-	-		
				F	0	0	1	1	2		
			Non-neoplastic lesion								
				Male and female	No toxicity findings						

-, Not tested.
a) Vehicle: Reverse osmosis water containing 0.5% (w/w) hydroxypropylmethylcellulose and 0.1% (w/w) polysorbate 20
b) Sites of onset: Heart, kidney, preputial gland and spleen (male); spleen, urinary bladder, uterus and vagina (female)
c) Reverse osmosis water

5.5 Reproductive and developmental toxicity

The following reproductive and developmental toxicity studies on BIC were conducted: A study of fertility and early embryonic development to implantation in male and female rats, studies of embryo-fetal development in rats and rabbits, and a study of effects on pre- and postnatal development, including maternal function, in rats. No reproductive toxicity was observed (Table 19). Embryonal death was observed in the study of embryo-fetal development in rabbits, but the death was considered to be a change secondary to the general toxicity in the maternal animal.

The $AUC_{0\text{-}24h}$ of BIC at the NOAEL for fertility and early embryonic development (300 mg/kg) in rats was 2970 μg·h/mL (CTD 4.2.3.3.2.1), which was approximately 29 times the human AUC_{tau} of BIC (102 μg·h/mL) after administration of BIC/FTC/TAF FDC at the clinical dose. The $AUC_{0\text{-}24h}$ of BIC at the NOAEL for embryo-fetal development (300 mg/kg) in rats and rabbits was 3650 μg·h/mL in rats

(CTD 4.2.3.5.2.1) and 60.3 μg·h/mL in rabbits (CTD 4.2.3.5.2.5). The exposures to BIC in rats and rabbits were approximately 36 times and 0.59 times, respectively, the human AUC_{tau} of BIC (102 μg·h/mL) after administration of BIC/FTC/TAF FDC at the clinical dose. The $AUC_{0\text{-}24h}$ of BIC on Lactation Day 10 at the NOAEL (300 mg/kg) for pre- and postnatal development, including maternal function, was 3100 μg·h/mL in the maternal animals. The BIC exposure in the maternal animals was approximately 30 times the human AUC_{tau} of BIC (102 μg·h/mL) after administration of BIC/FTC/TAF FDC at the clinical dose.

The above results and the findings of reproductive toxicity studies of FTC and TAF show that reproductive toxicity of BIC, FTC, and TAF does not overlap each other, suggesting that co-administration of BIC, FTC, and TAF is unlikely to increase the individual toxicity. The prior assessment requestor explained that, judging from the above results, there is little significance to conduct a reproductive toxicity study of co-administration of BIC, FTC, and TAF.

Table 19. Summary of reproductive toxicity studies on BIC

Study	Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Fertility and early embryonic development to implantation	Male and female rats (SD)	p.o.	Male: 28 days prior to mating and throughout mating period (once daily) Female: 14 days prior to mating, during mating period and through Gestation Day 7 (once daily)	0,[a] 5, 30, 300	None	Parental animals (General toxicity): 300 (Fertility): 300 Early embryonal development: 300	4.2.3.5.1.1
Embryo-fetal development	Female rats (SD)	p.o.	Gestation Days 7-17 (once daily) Cesarean section: Gestation Day 21	0,[a] 5, 30, 300	None	Maternal animals (General toxicity): 300 Embryo-fetal development: 300	4.2.3.5.2.3
	Female rabbits (NZW)	p.o.	Gestation Days 7-19 (once daily) Cesarean section: Gestation Day 29	0,[b] 100, 300, 1000	Parental animals: 1000: Reduced amount of feces, right brown/yellow feces, emaciation, coldness, abortion, decreased body weight/food consumption Fetuses: 1000: Decreased body weight, increased number of resorption/increased rate of post implantation losses	Maternal animals (General toxicity): 300 Embryo-fetal development: 300	4.2.3.5.2.4
Pre- and postnatal development, including maternal function	Female rats (SD)	p.o.	Maternal animals: Gestation Day 6 to Lactation Day 20 (once daily)	0,[a] 2, 10, 300	None	Maternal animals (General toxicity): 300 Development of F1 offspring: 300 Development of F2 offspring: 300	4.2.3.5.3.1

a) Vehicle: Reverse osmosis water containing 0.5% (w/w) hydroxypropylmethylcellulose and 0.1% (w/w) polysorbate 20
b) Vehicle: Reverse osmosis water containing 0.5% (w/w) hydroxypropylmethylcellulose and 0.5% (w/w) polysorbate 20

5.6 Local tolerance

As an eye irritation study of BIC, a bovine corneal opacity and permeability (BCOP) test was conducted using isolated bovine cornea. BIC was considered to be a moderately irritating substance.

Also, a skin corrosion and irritation test of BIC was conducted using the *in vitro* model. No corrosivity was observed but moderate irritation was elicited by 20% solution (Table 20).

Table 20. Summary of local tolerance studies on BIC

Study	Test system	Testing method	Main findings	Attached document CTD
BCOP	Isolated bovine cornea	20% suspension was applied, and permeability was assessed after 90 minutes, and opacity after 4 hours.	Irritation score 27.58 Considered to be moderately irritating.	4.2.3.6.5
Skin corrosivity	EpiDerm™	25 mg was applied and cell viability was assessed after 3 and 60 minutes.	Cell viability: 76% (after 3 minutes), 94% (after 60 minutes) Considered not to be irritating.	4.2.3.6.3
Skin irritation	EpiDerm™ SIT (EPI-200)	25 mg was applied and cell viability was assessed after 60 minutes	Cell viability: 91.6% Considered not to be irritating	4.2.3.6.4

5.7 Other studies

5.7.1 Skin sensitization

A local lymph node assay (LLNA) of BIC was conducted in mice. No skin sensitization was observed (Table 21).

Table 21. Summary of skin sensitization study on BIC

Study	Test system	Testing method	Main findings	Attached document CTD
LLNA	Female mice (CBA/Ca)	BIC (10%, 25%, or 50% solution), positive control (25% v/v hexyl cinnamaldehyde), or vehicle control (propylene glycol) was applied to the back of both auricles QD for 3 days.	None	4.2.3.7.1.1

5.7.2 Phototoxicity

Phototoxicity of BIC was investigated in an *in vitro* phototoxicity study using mouse fibroblasts and in a repeated oral dose phototoxicity study on the eye and skin of pigmented rats. BIC was shown to be phototoxic in the *in vitro* phototoxicity study but negative in the repeated oral dose phototoxicity study, from which it was determined that phototoxicity of BIC is unlikely to pose any safety concerns (Table 22).

Table 22. Summary of phototoxicity studies on BIC

Study	Test system	Testing method	Main findings	Attached document CTD
Phototoxicity study	Mouse fibroblasts (BALB/c 3T3)	0,[a] 0.178, 0.316, 0.562, 1.00, 1.78, 3.16, 5.62, 10 µg/mL Exposed to UV-A (5 J/cm^2) and UV-B (20 mJ/cm^2) radiation	Phototoxic (phototoxicity index: test 1, >1.853; test 2, >1.916; mean photo effect: test 1, 0.124; test 2, 0.184)	4.2.3.6.1
	Female pigmented rats (Long-Evans)	Animals received BIC (0,[b] 2, 10, 300 mg/kg) QD orally for 3 days. Immediately after dosing, the animals were exposed to UV-A (10.05-10.78 J/cm^2) and UV-B (141-152 mJ/cm^2) radiation for 41-44 minutes.	Not phototoxic	4.2.3.6.2

a) Vehicle: Dulbecco's phosphate buffered saline containing 1% DMSO, Ca^{2+}, and Mg^{2+} (DPBS/DMSO)
b) Vehicle: Reverse osmosis water containing 0.5% (w/w) hydroxypropylmethylcellulose and 0.1% (w/w) polysorbate 20

5.7.3 Evaluation of the toxicity of impurities

The Ames test was conducted on GS-001, GS-002, and GS-003, which are impurities derived from the starting materials in the manufacturing process of BIC. The test results were all negative for the impurities (Table 23). In order to evaluate the safety of potential in-process impurities in BIC, a 4-week repeated oral dose toxicity study in rats was conducted on GS-004 prepared by spiking BIC with the in-process impurities. No toxicity was observed (Table 24).

Table 23. Summary of Ames test on impurities

Test substance	Test system	Metabolic activation	Concentration (μg/plate)	Results	Attached document CTD
GS-001	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvr*A	S9−/+	0,[a] 5.00, 16.0, 50.0, 160, 500, 1600, 5000	Negative	4.2.3.7.6.1
GS-002 GS-003	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvr*A	S9−/+	0,[a] 5.00, 16.0, 50.0, 160, 500, 1600, 5000	Negative	4.2.3.7.6.3

a) Vehicle, DMSO

Table 24. Summary of repeated-dose toxicity study on the potential in-process impurity (GS-004) of BIC

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Female rats (Wistar)	p.o.	28 days (once daily)	0[a] GS-004: 100, 300 BIC: 300	None	300	4.2.3.7.6.2

a) Vehicle, Reverse osmosis water containing 0.5% (w/w) hydroxypropylmethylcellulose and 0.1% (w/w) polysorbate 20

5.R Outline of the review conducted by PMDA

On the basis of the submitted data and on the results of the following reviews, PMDA has concluded that clinical use of BIC/FTC/TAF FDC does not cause any particular problem from a toxicological point of view.

5.R.1 Hepatotoxicity of BIC

PMDA asked the prior assessment requestor to explain whether the proliferative lesion of the bile duct observed in monkeys following repeated administration of BIC is relevant to humans.

The explanation of the prior assessment requestor:
The toxicity finding on the bile duct of monkeys is unlikely to be relevant to humans, judging from the following observations:

- Bile duct hyperplasia observed in animals receiving 39-week repeated dose of BIC (1000 mg/kg/day) tended to be reversible after a recovery period, suggesting that the bile duct lesion is unlikely to progress to tumor.

- There is a certain safety margin between the exposure to BIC ($AUC_{0\text{-}24h}$, 709 μg·h/mL) in the 1000 mg/kg/day animals developing bile duct hyperplasia and the human exposure to BIC (AUC_{tau}, 102 μg·h/mL) after administration of BIC/FTC/TAF FDC at the clinical dose [see Section 6.2.6.1].

- In the phase III studies in which BIC/FTC/TAF FDC was administered (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878), laboratory tests did not detect any clinically significant changes related to liver disorder.

PMDA accepted the explanation of the prior assessment requestor, taking account of the observation that no BIC-related neoplastic hepatic lesion was observed in the carcinogenicity study in rodents.

5.R.2 Evaluation of toxicity in concomitant use of BIC, FTC, and TAF

Since no toxicity data in the concomitant use of BIC, FTC, and TAF were submitted, PMDA asked the prior assessment requestor to explain the effect of the concomitant use on toxicity and to delineate the incidences of adverse events that were observed in humans treated with BIC, FTC, and TAF in combination or with BIC/FTC/TAF FDC and were unpredictable from the results of non-clinical safety studies.

The explanation of the prior assessment requestor:
Co-administration of BIC, FTC, and TAF to humans is unlikely to pose any safety problems, judging from the following observations:

- In the non-clinical safety studies administering BIC, FTC, or TAF alone, the toxicity did not overlap each other, suggesting that co-administration of the 3 drugs is unlikely to evoke new toxicities.

- There is a sufficient safety margin between the exposure to the individual components at the NOAEL in non-clinical safety studies and the exposure in humans receiving BIC/FTC/TAF FDC at the clinical dose.

- In the clinical study investigating the PK following co-administration of BIC and FTC/TAF FDC (Study GS-US-141-1218), no marked effect of co-administration was observed in the PK of any of the components [see Section 6.2.1.2].

- In the clinical studies in which BIC/FTC/TAF FDC was used or the clinical studies in which BIC, FTC, and TAF were co-administered, there were no adverse events unpredictable from the findings in the non-clinical safety studies in which the individual components were administered alone.

PMDA accepted the explanation of the prior assessment requestor.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Prior Assessment Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The prior assessment requestor submitted results of a relative BA study and a food effect study as data of biopharmaceutical studies.

The Formulations 1 to 3[19] were used in the clinical development of BIC/FTC/TAF FDC. During the foreign phase III studies (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878), the drug product used was changed from Formulation 2 to 3, and Formulation 3 was chosen as the to-be-marketed formulation.

- Formulation 1: Film-coated tablets containing BIC 75 mg, FTC 200 mg, and TAF 25 mg
- Formulation 2: Film-coated tablets containing BIC 50 mg, FTC 200 mg, and TAF 25 mg
- Formulation 3: Film-coated tablets identical to Formulation 2, except for a change[20] in the amount of the lubricants (magnesium stearate and microcrystalline cellulose)

BIC, FTC, TAF, TFV, and FTC concentrations in human plasma and BIC concentration in human urine were measured by liquid chromatography/tandem mass spectrometry (LLOQ: BIC, 1 or 20 ng/mL [in plasma], 1 ng/mL [in urine]; FTC, 5 ng/mL; TAF, 1 ng/mL; TFV, 0.3 ng/mL), and radioactivity concentration in human plasma, urine, and feces was measured by a liquid scintillation counter.

6.1.1 Study of relative BA and food effect (Reference CTD 5.3.1.2.1, Study GS-US-141-1233 [[redacted] to [redacted]])

A study was conducted in non-Japanese healthy subjects consisting of the following 2 cohorts (28 subjects per cohort for PK evaluation):

- In Cohort 1, a three-treatment, three-period, crossover design was used to investigate the PK of the individual components in subjects receiving a single oral dose of the BIC 75-mg tablet plus the FTC/TAF (200/25 mg) FDC tablet under fasted conditions, Formulation 1 (BIC/FTC/TAF 75/200/25 mg FDC) under fasted conditions, or Formulation 1 after a high-fat meal (approximately 800 kcal with fat accounting for approximately 50% of total calorie).

- In Cohort 2, a four-treatment, four-period, crossover design was used to investigate the PK of individual components in subjects receiving a single oral dose of the BIC 75-mg tablet plus the FTC/TAF (200/25 mg) FDC tablet under fasted conditions, Formulation 2 (BIC/FTC/TAF 50/200/25 mg FDC) under fasted conditions, Formulation 2 after a moderate-fat meal (approximately 600 kcal with fat accounting for approximately 27% of total calorie), or Formulation 2 after a high-fat meal (approximately 800 kcal with fat accounting for approximately 50% of total calorie).

Table 25 shows the comparison of plasma PK parameters of BIC, FTC, and TAF after co-administration of the BIC 75-mg tablet plus the FTC/TAF FDC tablet and those after administration of Formulation 1 or 2 under fasted conditions.

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[19] Formulations used mainly in the clinical studies:
Formulation 1 in Study GS-US-141-1233, Formulation 2 in Study GS-US-141-1233, and Formulation 3 in Studies GS-US-141-1489, GS-US-141-1490, GS-US-380-1844, and GS-US-380-1878

[20] The BIC/FTC/TAF FDC is a two-layered tablet consisting of a layer containing BIC and a layer containing FTC/TAF. The formulation was modified to improve the adhesiveness of the two layers.

Table 25. Least squares geometric mean ratio of PK parameters after administration of Formulation 1 or 2 to those after co-administration of BIC plus FTC/TAF FDC

Analyte	No. of subjects	Least squares geometric mean ratio [90% CI]		
		C_{max}	AUC_{inf}	AUC_{last}
Formulation 1 (BIC/FTC/TAF 75/200/25 mg) vs. BIC (75 mg) + FTC/TAF (200/25 mg), under fasted conditions				
BIC	28	1.31 [1.20, 1.42]	1.27 [1.18, 1.36]	1.27 [1.18, 1.36]
FTC	28	1.05 [0.98, 1.13]	1.02 [0.99, 1.04]	1.02 [1.00, 1.04]
TAF	28	0.95 [0.80, 1.14]	0.92 [0.82, 1.02]	0.92 [0.82, 1.02]
Formulation 2 (BIC/FTC/TAF 50/200/25 mg) vs. BIC (75 mg) + FTC/TAF (200/25 mg), under fasted conditions				
BIC	27	0.78 [0.73, 0.83]	0.79 [0.73, 0.84]	0.78 [0.73, 0.84]
FTC	27	1.02 [0.94, 1.12]	0.97 [0.94, 0.99]	0.97 [0.94, 0.99]
TAF	27	0.84 [0.68, 1.05]	0.85 [0.75, 0.97]	0.85 [0.75, 0.97]

Table 26 shows plasma PK parameters of BIC, FTC, and TAF after single oral administration of Formulation 2 (BIC/FTC/TAF 50/200/25 mg FDC) under fasted conditions, after a moderate-fat meal (approximately 600 kcal, with fat accounting for approximately 27% of total calorie), or after a high-fat meal (approximately 800 kcal, with fat accounting for approximately 50% of total calorie).

Table 26. Effect of food on PK parameters

Analyte	Dietary conditions	No. of subjects	C_{max} (ng/mL)	t_{max}[a)] (h)	$t_{1/2}$[a)] (h)	AUC_{inf} (ng·h/mL)	Least squares geometric mean ratio [90% CI] (fed/fasted)	
							C_{max}	AUC_{inf}
BIC	Under fasted conditions	27	5228 (16.9)	2.0 [0.5, 6.0]	18.9 [12.6, 24.8]	112,620 (21.9)	-	-
	After moderate-fat meal	27	6280 (18.3)	3.0 [1.0, 4.0]	19.3 [13.7, 24.8]	140,198 (23.6)	1.20 [1.13, 1.28]	1.24 [1.16, 1.33]
	After high-fat meal	27	5936 (18.3)	4.0 [1.0, 6.0]	19.1 [13.5, 25.8]	140,032 (21.8)	1.13 [1.06, 1.20]	1.24 [1.16, 1.33]
FTC	Under fasted conditions	27	2220 (30.1)	1.5 [0.5, 4.0]	19.1 [10.1, 41.0]	10,874 (13.6)	-	-
	After moderate-fat meal	27	1999 (18.4)	2.0 [1.0, 4.0]	19.5 [13.2, 32.8]	10,973 (9.5)	0.92 [0.84, 1.00]	1.01 [0.99, 1.04]
	After high-fat meal	27	1881 (24.2)	2.0 [1.0, 6.0]	22.6 [10.7, 45.9]	10,467 (11.9)	0.86 [0.78, 0.93]	0.96 [0.94, 0.99]
TAF	Under fasted conditions	28	249.2 (51.6)	0.5 [0.5, 2.0]	0.3 [0.2, 0.6]	208.8 (46.3)	-	-
	After moderate-fat meal	27	251.1 (66.7)	1.5 [0.5, 4.0]	0.4 [0.3, 0.6]	293.1 (40.9)	0.99 [0.79, 1.24]	1.48 [1.30, 1.68]
	After high-fat meal	27	236.6 (65.1)	2.0 [0.5, 4.0]	0.6 [0.3, 2.3]	318.4 (32.8)	0.92 [0.73, 1.14]	1.67 [1.47, 1.89]

Mean (CV%)
a) Median [range]

6.2 Clinical pharmacology

The prior assessment requestor submitted the data of PK after administration of single-agent BIC or the BIC/FTC/TAF FDC, or after co-administration of BIC plus FTC/TAF FDC, in the form of results from the following studies: Studies in healthy subjects (PK studies in healthy subjects, PK studies in subjects with renal impairment or with hepatic impairment, pharmacokinetic interaction studies, a

QT/corrected QT interval (QTc) study, etc.), studies in patients with HIV-1 infection, population pharmacokinetics (PPK) analysis, etc.

In vitro studies using human biomaterials are described in Sections 4.2.2, 4.3.2, 4.5 on non-clinical pharmacokinetics.

PK parameters are expressed in mean unless specified otherwise.

6.2.1 Studies in healthy subjects

6.2.1.1 Mass balance study (Reference CTD 5.3.3.1.2, Study GS-US-141-1481 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A single dose of BIC (100 mg, included ^{14}C-labeled BIC) was administered orally to healthy non-Japanese subjects (8 for PK evaluation), and mass balance was investigated. In the first 120 hours post-dose, 35.0% and 60.3% of the administered radioactivity were excreted in the urine and feces, respectively. In the plasma samples collected up to 72 hours post-dose, unchanged BIC was mainly detected (accounting for 67.9% of total radioactivity in plasma), and M15 and M20 (8.6% and 20.1%, respectively) were detected as the main metabolites. In the urine samples collected up to 96 hours post-dose, M15/M58 (21.4% of the administered radioactivity) was mainly detected, together with a slight amount of unchanged BIC (3.6%). In the feces collected up to 144 hours post-dose, unchanged BIC (30.6%) was mainly detected, and metabolites detected included M9, M21/M22, and M23 (13.0%, 8.1%, and 3.6%, respectively).

6.2.1.2 Phase I study (Reference CTD 5.3.3.1.1, Study GS-US-141-1218 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A single dose of BIC (5, 25, 50, 100, 300, or 600 mg) was administered orally to healthy non-Japanese subjects (36 subjects for PK evaluation) under fasted conditions. Table 27 shows PK parameters of BIC observed.

Table 27. PK parameters following single oral administration of BIC to healthy subjects

Dose (mg)	No. of subjects	C_{max} (ng/mL)	t_{max}[a)] (h)	$t_{1/2}$[a)] (h)	AUC_{inf} (ng·h/mL)
5	6	691.2 (22.1)	1.3 [0.5, 3.0]	18.5 [14.2, 20.5]	13,060 (25.1)
25	6	1618 (26.7)	2.0 [1.0, 4.0]	18.1 [15.3, 20.3]	35,718 (21.3)
50	6	3965 (40.1)	3.0 [1.5, 4.0]	16.7 [15.2, 21.1]	78,400 (29.7)
100	6	6998 (36.1)	2.3 [1.0, 4.0]	18.9 [16.6, 27.6]	163,028 (24.3)
300	6	14,605 (27.1)	3.5 [1.5, 6.0]	18.1 [12.0, 21.2]	355,917 (32.9)
600	6	20,050 (7.5)	3.5 [2.0, 6.0]	17.9 [16.1, 20.0]	454,447 (19.9)

Mean (CV%)
a) Median [range]

BIC (5, 25, 50, 100, or 300 mg) was administered orally QD to healthy non-Japanese subjects (30 subjects for PK evaluation) under fasted conditions, and the PK of BIC on Days 1 and 7 was investigated. Table 28 shows the results.

Table 28. PK parameters following multiple oral administration of BIC to healthy subjects

Dose (mg)	Sampling time point	No. of subjects	C_{max} (ng/mL)	t_{max}[a)] (h)	C_{24h} or C_{tau} (ng/mL)	$AUC_{0\text{-}24h}$ or AUC_{tau} (ng·h/mL)	Accumulation ratio of AUC
5	Day 1	6	709.7 (9.5)	1.5 [1.0, 1.5]	231.8 (10.7)	9034 (8.2)	-
	Day 7	6	982.5 (7.9)	1.5 [1.0, 3.0]	400.8 (26.9)	14,392 (16.7)	161
25	Day 1	6	2220 (35.6)	1.8 [1.0, 4.0]	686.5 (27.5)	27,775 (28.3)	-
	Day 7	6	3455 (24.1)	3.0 [1.5, 4.0]	1322 (27.8)	50,008 (26.6)	182
50	Day 1	6	4648 (18.7)	1.5 [1.0, 2.0]	1427 (26.3)	58,371 (18.9)	-
	Day 7	6	6538 (17.6)	1.8 [1.0, 3.0]	2242 (28.2)	89,710 (22.7)	154
100	Day 1	6	6248 (26.8)	2.5 [1.5, 6.0]	1813 (17.3)	79,774 (18.9)	-
	Day 7	6	9397 (20.8)	1.8 [1.0, 4.0]	3145 (26.1)	126,786 (23.7)	159
300	Day 1	6	13,717 (19.1)	2.5 [2.0, 6.0]	4431 (17.2)	180,714 (17.6)	-
	Day 7	6	19,900 (21.2)	4.0 [1.5, 4.0]	6758 (21.6)	277,200 (16.7)	158

Mean (CV%)
a) Median [range]

Treatments were given in a three-treatment, three-period, crossover design to investigate the PK of individual components. BIC (100 mg), FTC/TAF (200/25 mg), or BIC (100 mg) plus FTC/TAF (200/25 mg) was administered orally QD after a meal (moderate-fat meal; approximately 600 kcal with fat accounting for approximately 27% of total calorie) to healthy non-Japanese subjects (34 subjects for PK evaluation) for 7 days. Table 29 shows the effect of co-administered 3 components (BIC, FTC, and TAF) on the PK of the individual components.

Table 29. Effect of co-administered BIC and FTC/TAF on PK of individual components (least squares geometric mean ratio [90% CI])

Analyte	No. of subjects	C_{max}	AUC_{tau}[a)]	C_{tau}
BIC (100 mg) + FTC/TAF (200/25 mg) vs. BIC (100 mg)				
BIC	34	1.00 [0.96, 1.03]	1.01 [0.98, 1.04]	1.02 [0.98, 1.06]
BIC (100 mg) + FTC/TAF (200/25 mg) vs. FTC/TAF (200/25 mg)				
FTC	34[b)]	0.99 [0.94, 1.05]	1.02 [1.00, 1.04]	1.06 [1.01, 1.11]
TAF	34[b)]	1.37 [1.17, 1.60]	1.30 [1.24, 1.36]	-
TFV	34[b)]	1.10 [1.05, 1.16]	1.14 [1.10, 1.17]	1.15 [1.11, 1.19]

a) AUC_{last} for TAF, b) n = 33 in FTC/TAF group

6.2.1.3 Study in Japanese and non-Japanese subjects (CTD 5.3.3.3.8, Study GS-US-380-1991 [[redacted] to [redacted]])

A single dose of the BIC/FTC/TAF (50/200/25 mg) FDC tablet (Formulation 2) was administered orally under fasted conditions to healthy Japanese and non-Japanese (Caucasian) subjects (25 subjects each for PK evaluation) to investigate the PK of the individual components. Table 30 shows the results. No clear difference in the exposure to the individual components was observed between Japanese and non-Japanese subjects.

Table 30. PK parameters following single oral administration of the BIC/FTC/TAF FDC tablet to healthy Japanese or non-Japanese subjects

Analyte		Japanese (n = 25)	Non-Japanese (n = 25)	Least squares geometric mean ratio [90% CI] (Japanese/non-Japanese)
BIC	C_{max} (ng/mL)	6556 (17.9)	5224 (21.0)	1.26 [1.15, 1.39]
	AUC_{last} (ng·h/mL)	113,637 (20.9)	101,533 (30.7)[a)]	1.15 [1.01, 1.31]
FTC	C_{max} (ng/mL)	2680 (39.9)	2448 (21.7)	1.03 [0.88, 1.21]
	AUC_{last} (ng·h/mL)	10,965 (18.6)	10,359 (14.3)[a)]	1.05 [0.97, 1.14]
TAF	C_{max} (ng/mL)	300.6 (58.3)	262.4 (41.9)	1.06 [0.85, 1.31]
	AUC_{last} (ng·h/mL)	169.8 (53.1)	167.1 (41.2)[a)]	0.96 [0.77, 1.19]
TFV	C_{max} (ng/mL)	12.0 (30.3)	11.0 (24.4)	1.07 [0.93, 1.23]
	AUC_{last} (ng·h/mL)	267.1 (24.3)	267.1 (20.4)[a)]	0.99 [0.89, 1.11]

Mean (CV%)
a) n = 24

6.2.2 Studies in patients

6.2.2.1 Phase I study (Reference CTD 5.3.4.2.1, Study GS-US-141-1219 [October 2014 to February 2015])

BIC (5, 25, 50, or 100 mg) was administered orally QD for 10 days to non-Japanese patients with HIV-1 infection (16 subjects for PK evaluation), and PK of BIC was investigated. Table 31 shows the results.

The maximum change in HIV-1 RNA level from baseline to Day 11 in each dose group was −1.52, −2.18, −2.31, and −2.91 log_{10} copies/mL, respectively. The relationship between the BIC dose and the HIV-1 inhibitory index (C_{tau}/EC_{95} adjusted for protein [162 ng/mL, see Section 3.1.1.1]) was investigated using the above data. The prior assessment requestor explained that the results predicted the nearly maximum decrease in HIV-1 RNA level at the predicted exposure (C_{tau}) following administration of BIC 75 mg QD.

Table 31. PK parameters following multiple oral administration of BIC to patients with HIV-1 infection

Dose (mg)	Sampling time point	No. of patients	C_{max} (ng/mL)	t_{max}[a)] (h)	$t_{1/2}$[a)] (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
5	Day 1	4	493.3 (14.6)	1.0 [1.0, 1.5]	-	6262 (22.9)
	Day 10	4	741.5 (18.2)	1.5 [0.5, 4.0]	20.8 [13.6, 26.7]	9983 (26.7)
25	Day 1	4	2565 (12.9)	1.8 [1.0, 3.0]	-	31,292 (10.0)
	Day 10	4	3475 (20.5)	1.3 [1.0, 1.5]	15.9 [13.2, 21.9]	48,950 (40.0)
50	Day 1	4	4958 (13.5)	1.8 [1.5, 3.0]	-	68,477 (17.0)
	Day 10	4	6080 (21.8)	1.8 [1.0, 3.0]	17.8 [15.1, 21.3]	87,538 (32.7)
100	Day 1	4	7368 (31.1)	1.5 [1.0, 2.0]	-	94,589 (28.9)
	Day 10	4	12,235 (24.9)	2.7 [1.0, 4.0]	20.9 [16.1, 27.0]	178,902 (17.8)

Mean (CV%)
-, Not tested.
a) Median [range]

6.2.2.2 Phase II study (Reference CTD 5.3.5.1.1, Study GS-US-141-1475 [March 2015 to October 2016])

BIC (75 mg) and FTC/TAF (200/25 mg) were co-administered orally QD to treatment-naïve non-Japanese patients with HIV-1 infection (30 subjects for PK evaluation) to investigate PK at steady state (Week 4 or 8). Table 32 shows the results.

Table 32. PK parameters following multiple oral co-administration of BIC and FTC/TAF to patients with HIV-1 infection

Analyte	No. of patients	C_{max} (ng/mL)	t_{max}[a)] (h)	$t_{1/2}$[a)] (h)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
BIC	23	9344 (26.8)	2.0 [1.0, 24.0]	16.7 [9.0, 32.3][b)]	139,779 (27.0)[b)]	3509 (36.7)[c)]
FTC	23	1919 (24.5)	1.5 [0.6, 3.0]	5.5 [2.6, 7.1]	11,605 (27.9)	76.6 (34.4)[c)]
TAF	23	249.1 (55.2)	1.0 [0.0, 2.0]	0.4 [0.2, 0.7]	247.4 (56.8)	-
TFV	23	19.1 (23.6)	1.5 [0.5, 4.0]	37.7 [8.4, 132.3]	316.0 (23.4)	10.7 (24.7)[c)]

Mean (CV%)
-, Not tested
a) Median [range], b) n = 22, c) n = 21

6.2.2.3 Phase III studies (CTD 5.3.5.1.5, Study GS-US-380-1489 [ongoing since November 2015, data cut-off [redacted] 20[redacted]]; CTD 5.3.5.1.6, Study GS-US-380-1490 [ongoing since November 2015, data cut-off [redacted] 20[redacted]]; CTD 5.3.5.1.7, Study GS-US-380-1844 [ongoing since November 2015, data cut-off [redacted] 20[redacted]]; CTD 5.3.5.1.8, Study GS-US-380-1878 [ongoing since November 2015, data cut-off [redacted] 20[redacted]])

BIC/FTC/TAF (50/200/25 mg) FDC (Formulation 2 or 3)[21)] was administered orally QD to non-Japanese patients with HIV-1 infection to investigate PK at steady state (at Week 4 or 8). Table 33 shows the results.

Table 33. PK parameters following multiple oral administration of BIC/FTC/TAF FDC to patients with HIV-1 infection

Study	Analyte	No. of patients	C_{max} (ng/mL)	t_{max}[c)] (h)	$t_{1/2}$[c)] (h)	AUC_{tau} (ng·h/mL)	C_{tau} (ng/mL)
GS-US-380-1489[a)]	BIC	17	6705 (27.5)	1.5 [0.5, 6.0]	15.9 [7.9, 28.3]	96,182 (33.5)	2312 (40.7)
	FTC	17	1868 (34.5)	1.5 [0.5, 4.0]	6.7 [4.7, 8.2]	10,896 (29.8)	80.9 (37.1)
	TAF	17	225.5 (68.3)	0.5 [0.5, 2.0]	0.4 [0.3, 1.1]	206.0 (51.2)	-
GS-US-380-1490[a)]	BIC	17	7339 (37.3)	1.0 [0.5, 4.1]	18.6 [6.8, 26.5]	101,121 (43.8)	2576 (52.0)[d)]
	FTC	17	1920 (20.7)	1.0 [1.0, 3.1]	7.1 [2.3, 8.7]	11,238 (28.4)	97.7 (38.4)[d)]
	TAF	17	309.4 (59.9)	0.5 [0.5, 3.1]	0.4 [0.2, 1.1]	259.4 (59.9)	-
GS-US-380-1844[b)]	BIC	15	6625 (31.4)	1.0 [0.5, 4.0]	14.1 [8.8, 26.0]	93,582 (35.2)	2283 (61.7)
	FTC	15	2061 (35.5)	1.0 [0.5, 3.0]	6.6 [2.8, 9.4]	12,572 (27.2)	96.0 (33.6)[e)]
	TAF	15	182.2 (44.1)	0.5 [0.5, 1.5]	0.3 [0.2, 0.6]	149.8 (54.0)	-
GS-US-380-1878[b)]	BIC	28	6629 (25.5)	1.5 [0.5, 3.0]	16.2 [9.4, 25.4]	89,201 (27.5)	2038 (35.6)
	FTC	28	2445 (35.1)	1.0 [0.5, 2.1]	7.0 [5.9, 9.0]	13,634 (27.6)	104.4 (37.2)
	TAF	28	338.1 (55.2)	0.5 [0.5, 1.5]	0.4 [0.2, 0.8]	267.8 (63.1)	-

Mean (CV%)
-, Not tested
a) Subjects were treatment-naïve patients with HIV-1 infection, b) subjects were patients with HIV-1 infection with a history of previous anti-HIV treatment, c) median [range], d) n = 15, e) n = 14

6.2.3 Intrinsic factors

6.2.3.1 Foreign study in subjects with hepatic impairment (Reference CTD 5.3.3.3.1, Study GS-US-141-1478 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A single dose of BIC (75 mg) was administered orally after a meal to subjects with moderate hepatic impairment (Child-Pugh class B) or to subjects with normal hepatic function (n = 10 each). Table 34 shows PK parameters observed.

C_{max} and AUC_{inf} of BIC (bound + unbound) tended to be lower in subjects with moderate hepatic impairment than subjects with normal hepatic function. However, the prior assessment requestor explained that no clinically significant difference was observed in C_{max} and AUC_{inf} of unbound BIC between subjects with moderate hepatic impairment and subjects with normal hepatic function.

21) Formulation 2 was used during the early stage of the study, but switched to Formulation 3 in the mid-course of the study.

No clinical study was conducted in subjects with severe hepatic impairment.

Table 34. PK parameters following single oral administration of BIC to subjects with hepatic impairment and subjects with normal hepatic function

Severity of hepatic impairment	No. of subjects	Analyte	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	Least squares geometric mean ratio [90% CI] (subjects with hepatic impairment/subjects with normal hepatic function)	
					C_{max}	AUC_{inf}
Normal	10	Bound + unbound	7849 (27.8)	172,884 (23.4)		
		Unbound	48.1 (28.2)	1054 (22.7)		
Moderate	10	Bound + unbound	5013 (29.1)	113,086 (50.7)	0.64 [0.50, 0.81]	0.59 [0.41, 0.84]
		Unbound	39.6 (27.7)	880.9 (55.7)	0.83 [0.65, 1.05]	0.77 [0.56, 1.04]

Mean (CV%)

6.2.3.2 Foreign study in subjects with renal impairment (Reference CTD 5.3.3.3.2, Study GS-US-141-1479 [April 2015 to July 2015])

A single dose of BIC (75 mg) was administered orally after a meal to subjects with severe renal impairment (estimated glomerular filtration rate [eGFR], 15-29 mL/min) (n = 10) and to subjects with normal renal function (eGFR ≥90 mL/min) (n = 8). Table 35 shows PK parameters observed. The C_{max} and AUC of BIC (bound + unbound) tended to be lower in subjects with severe renal impairment than subjects with normal renal function. However, no clear difference was observed in the C_{max} or AUC of unbound BIC between the 2 groups.

Table 35. PK parameters following single oral administration of BIC to subjects with renal impairment and to subjects with normal renal function

Severity of renal impairment	No. of subjects	Analyte	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	Least squares geometric mean ratio [90% CI] (subjects with renal impairment/subjects with normal renal function)	
					C_{max}	AUC_{inf}
Normal	8	Bound + unbound	7228 (29.5)	170,106 (24.8)		
		Unbound	35.0 (28.4)	824.5 (24.7)		
Severe	10	Bound + unbound	5977 (34.8)	138,170 (44.4)	0.80 [0.60, 1.08]	0.73 [0.49, 1.08]
		Unbound	37.7 (21.6)	830.6 (32.1)	1.10 [0.87, 1.38]	0.99 [0.79, 1.24]

Mean (CV%)

6.2.4 Pharmacokinetic interactions (Reference CTD 5.3.3.4.1, Study GS-US-141-1485 [[redacted] 20[redacted] to [redacted] 20[redacted]]; Reference CTD 5.3.3.4.12, Study GS-US-380-1761 [[redacted] 20[redacted] to [redacted] 20[redacted]]; Reference CTD 5.3.3.4.13, Study GS-US-380-1999 [[redacted] 20[redacted] to [redacted] 20[redacted]]; Reference CTD 5.3.3.4.14, Study GS-US-380-3908 [[redacted] 20[redacted] to [redacted] 20[redacted]]; Reference CTD 5.3.3.4.15, Study GS-US-380-3909 [[redacted] 20[redacted] to [redacted] 20[redacted]]; Reference CTD 5.3.3.4.17, Study GS-US-380-4270 [[redacted] 20[redacted]])

Clinical studies were conducted in order to investigate the pharmacokinetic interactions between BIC or BIC/TAF/FTC FDC and concomitant drugs. Tables 36 shows the least squares geometric mean ratio [90% confidence interval (CI)] of PK parameters of BIC and/or other components administered with any concomitant drug to those of BIC and/or other components administered alone. Tables 37 shows the least squares geometric mean ratio [90% CI] of PK parameters of individual concomitant drugs administered with BIC/FTC/TAF FDC or BIC to those of individual concomitant drugs administered alone.

Table 36. Effect of concomitant drugs on PK parameters of individual components of BIC/FTC/TAF FDC

Concomitant drug	Dosage regimen				No. of subjects	Least squares geometric mean ratio [90% CI] (co-administration/alone)			
	Concomitant drug	BIC	FTC	TAF		Analyte	C_{max}	AUC[a)]	C_{tau}
ATV/ COBI	300/150 mg QD (under fed conditions)	75 mg Single dose	-	-	15	BIC	1.31 [1.23, 1.40]	4.06 [3.76, 4.37]	-
ATV	400 mg QD (under fed conditions)	75 mg Single dose	-	-	15	BIC	1.28 [1.23, 1.33]	4.15 [3.81, 4.51]	-
DRV/COBI	800/150 mg QD (under fed conditions)	75 mg QD	-	-	13	BIC	1.52 [1.40, 1.64]	1.74 [1.62, 1.87]	2.11 [1.95, 2.29]
Ledipasvir/ sofosbuvir	90/400 mg QD (under fed conditions)	75 mg QD	200 mg QD	25 mg QD	30	BIC	0.98 [0.94, 1.03]	1.00 [0.97, 1.03]	1.04 [0.99, 1.09]
						FTC	0.99 [0.94, 1.05]	0.99 [0.95, 1.02]	1.03 [0.99, 1.07]
						TAF	1.17 [1.00, 1.38]	1.27 [1.19, 1.34]	-
						TFV	1.43 [1.37, 1.50]	1.67 [1.60, 1.74]	1.81 [1.73, 1.90]
Rifabutin	300 mg QD (under fasted conditions)	75 mg QD	-	-	13	BIC	0.80 [0.67, 0.97]	0.62 [0.53, 0.72]	0.44 [0.37, 0.52]
Rifampicin	600 mg QD (under fed conditions)	75 mg Single dose	-	-	15	BIC	0.72 [0.67, 0.78]	0.25 [0.22, 0.27]	-
Sofosbuvir/ velpatasvir/ voxilaprevir	400/100/200 mg[b)] QD (under fed conditions)	50 mg QD	200 mg QD	25 mg QD	30	BIC	0.98 [0.94, 1.01]	1.07 [1.03, 1.10]	1.10 [1.05, 1.17]
						FTC	0.89 [0.83, 0.94]	0.95 [0.93, 0.97]	1.10 [1.05, 1.16]
						TAF	1.28 [1.09, 1.51]	1.58 [1.45, 1.73]	-
						TFV	1.51 [1.45, 1.58]	1.67 [1.62, 1.73]	1.74 [1.68, 1.80]
Voriconazole	300 mg twice daily (under fasted conditions)	75 mg Single dose	-	-	15	BIC	1.09 [0.96, 1.23]	1.61 [1.41, 1.84]	-
High-dose antacid[c)]	20 mL Single dose (simultaneously with BIC/FTC/TAF FDC, under fasted conditions)	50 mg Single dose	200 mg Single dose	25 mg Single dose	14	BIC	0.20 [0.16, 0.24]	0.21 [0.18, 0.26]	-
	20 mL Single dose (2 hours after dosing of BIC/FTC/TAF FDC, under fasted conditions)	50 mg Single dose	200 mg Single dose	25 mg Single dose	13	BIC	0.93 [0.88, 1.00]	0.87 [0.81, 0.93]	-
	20 mL Single dose (2 hours before dosing of BIC/FTC/TAF FDC, under fasted conditions)	50 mg Single dose	200 mg Single dose	25 mg Single dose	13	BIC	0.42 [0.33, 0.52]	0.48 [0.38, 0.59]	-
	20 mL Single dose (simultaneously with BIC/FTC/TAF FDC, under fed condition[d)])	50 mg Single dose	200 mg Single dose	25 mg Single dose	14	BIC	0.51 [0.43, 0.62]	0.53 [0.44, 0.64]	-
Calcium carbonate	1200 mg Single dose (simultaneously with BIC/FTC/TAF FDC, under fasted conditions)	50 mg Single dose	200 mg Single dose	25 mg Single dose	14	BIC	0.58 [0.51, 0.67]	0.67 [0.57, 0.78]	-
	1200 mg Single dose (simultaneously with BIC/FTC/TAF FDC, under fed conditions[d)])	50 mg Single dose	200 mg Single dose	25 mg Single dose	14	BIC	0.90 [0.78, 1.03]	1.03 [0.89, 1.20]	-
Ferrous fumarate	324 mg Single dose (simultaneously with BIC/FTC/TAF FDC, under fasted conditions)	50 mg Single dose	200 mg Single dose	25 mg Single dose	14	BIC	0.29 [0.26, 0.33]	0.37 [0.33, 0.42]	-
	324 mg Single dose (simultaneously with BIC/FTC/TAF FDC, under fed conditions)	50 mg Single dose	200 mg Single dose	25 mg Single dose	14	BIC	0.75 [0.65, 0.87]	0.84 [0.74, 0.95]	-

-, Not administered, not tested, or not applicable
a) Single-dose administration, AUC_{inf}; multiple-dose administration, AUC_{tau} (BIC, FTC, and TFV) or AUC_{last} (TAF)
b) Sofosbuvir/velpatasvir/voxilaprevir (400/100/100 mg) FDC + voxilaprevir 100-mg tablet were administered.
c) The drug 1 mL contains 80 mg of aluminum hydroxide, 80 mg of magnesium hydroxide, and 8 mg of simethicone.
d) BIC/FTC/TAF FDC alone was administered under fasted conditions.

Table 37. Effect of BIC/FTC/TAF or BIC on PK parameters of concomitant drugs

Concomitant drug	Dosage regimen				No. of subjects	Least squares geometric mean ratio [90% CI] (co-administration/alone)			
	Concomitant drug	BIC	FTC	TAF		Analyte	C_{max}	AUC[a)]	C_{tau}
Metformin	500 mg Twice daily	50 mg QD	200 mg QD	25 mg QD	30	Metformin	1.28 [1.21, 1.36]	1.39 [1.31, 1.48]	1.36 [1.21, 1.53]
Midazolam	2 mg Single dose	50 mg QD	200 mg QD	25 mg QD	14	Midazolam	1.03 [0.87, 1.23]	1.15 [1.00, 1.31]	-
Norgestimate/ ethinyl estradiol	0.180-0.250[c)]/ 0.025 mg QD	75 mg QD	-	-	15	Norelgestromin	1.23 [1.14, 1.32]	1.08 [1.05, 1.10]	1.10 [1.05, 1.15]
						Norgestrel	1.15 [1.10, 1.21]	1.13 [1.07, 1.19]	1.14 [1.06, 1.22]
						Ethinyl estradiol	1.15 [1.03, 1.27]	1.04 [0.99, 1.10]	1.05 [0.95, 1.14]
Ledipasvir/ sofosbuvir	90/400 mg QD	75 mg QD	200 mg QD	25 mg QD	30	Ledipasvir	0.85 [0.81, 0.90]	0.87 [0.83, 0.92]	0.90 [0.84, 0.96]
						Sofosbuvir	1.11 [1.00, 1.24]	1.07 [1.01, 1.13]	-
						GS-331007[b)]	1.10 [1.07, 1.13]	1.11 [1.08, 1.14]	1.02 [0.99, 1.06]
Sofosbuvir/ velpatasvir/ voxilaprevir	400/100/ 200 mg[d)] QD	50 mg QD	200 mg QD	25 mg QD	30	Sofosbuvir	1.14 [1.04, 1.25]	1.09 [1.02, 1.15]	-
						GS-331007[b)]	1.03 [0.99, 1.06]	1.03 [1.00, 1.06]	1.01 [0.98, 1.05]
						Velpatasvir	0.96 [0.91, 1.01]	0.96 [0.90, 1.02]	0.94 [0.88, 1.01]
						Voxilaprevir	0.90 [0.76, 1.06]	0.91 [0.80, 1.03]	0.97 [0.88, 1.06]

-, Not administered or not tested.
a) AUC_{inf} after single-dose administration, AUC_{tau} after multiple administration
b) Main nucleoside metabolite of sofosbuvir in the circulating blood
c) 0.180 mg on Day 1 to 7, 0.215 mg on Day 8 to 14, 0.250 mg on Day 15 to 21
d) Sofosbuvir/velpatasvir/voxilaprevir (400/100/100 mg) FDC + voxilaprevir 100-mg tablet were administered.

Taking account of the above results of the pharmacokinetic interaction studies, the prior assessment requestor explained that a precautionary statement will be provided regarding the use of BIC/FTC/TAF FDC in combination with atazanavir (ATV), rifabutin, rifampicin, magnesium/aluminum-containing drug (e.g., high-dose antacid), iron/calcium-containing drug (e.g., calcium carbonate, ferrous fumarate), metformin, etc.

6.2.5 Pharmacodynamics

6.2.5.1 QT/QTc study (CTD 5.3.4.1.1, Study GS-US-141-1480 [[redacted] to [redacted]])

A four-treatment, four-period, crossover study was conducted[22)] in healthy non-Japanese subjects (n = 48) to investigate the effect of BIC on QT/QTc interval. A single oral dose of placebo or BIC (75 or 300 mg) was administered under fed conditions, using moxifloxacin (400 mg) as the positive control. The least squares mean difference in the changes from baseline in Fridericia-corrected QT interval (QTcF) between the BIC 75 or 300 mg group and the placebo group (ΔΔQTcF) reached a maximum level after 48 hours for both the BIC 75 and 300 mg groups, with the maximum level [90% CI] being 0.2 [−1.9, 2.2] and 0.6 [−1.4, 2.7] ms, respectively. Since the upper limit of the two-sided 90% CI of ΔΔQTcF was <10 ms, the prior assessment requestor explained that BIC within the dose range up to 300 mg does not prolong QTc interval. Following the administration of BIC (300 mg), C_{max} was 24,681 ng/mL and AUC_{inf} was 581,283 ng·h/mL.

22) A washout period of ≥7 days was allowed between treatments.

6.2.5.2 Effect on renal function (Reference CTD 5.3.4.1.2, Study GS-US-141-1487 [[redacted] to [redacted]])

BIC (75 mg) or placebo was administered orally QD for 14 days to healthy non-Japanese subjects (20 per group) to investigate the effect of BIC on renal function. The mean change [95% CI] in the body surface area (BSA) adjusted actual glomerular filtration rate (aGFR) from baseline to Days 7, 14, and 21 was −0.1 [−5.3, 5.0], −0.7 [−5.1, 3.7], and −1.9 [−6.7, 2.9] mL/min/1.73 m^2, respectively, in the BIC group and 6.2 [2.6,9.9], 4.0 [0.7, 7.2], and 2.2 [−1.9, 6.2] mL/min/1.73 m^2 in the placebo group. Based on these results, the prior assessment requestor explained that BIC is unlikely to affect renal function.

6.2.6 PPK analysis and exposure-response analysis

6.2.6.1 PPK analysis of BIC (Reference CTD 5.3.3.5.1)

Using the PK data (8752 measuring points in 1318 subjects) collected from healthy subjects or patients with HIV-1 infection in 8 clinical studies,[23] PPK analysis (NONMEM version 7.3.0) was performed. The final model was described by the one-compartment model with the first-order absorption process with lag time. The parameters identified as covariates were concomitant proton pump inhibitor (PPI) for first order absorption rate constant (k_a), body weight for apparent total body clearance (CL/F), and body weight and HIV infection for Vc/F.[24] The final model was used to estimate PK parameters of BIC under steady state following multiple oral QD administration of BIC/FTC/TAF to patients with HIV-1 infection. The following results were obtained: C_{max}, 6146 ng/mL; AUC_{tau}, 102,001 ng·h/mL; and C_{tau}, 2610 ng/mL. In a dissolution test (paddle method, 75 rpm, pH 1.2, 4.5, and 6.8), the solubility of BIC decreased at pH 1.2. However, in the final model, PK parameters (C_{max}, C_{tau}, and AUC_{tau}) of BIC administered with PPI were estimated to decrease by 4.6%, increase by 2.1%, and show no change, respectively, compared to those of BIC administered without PPI, based on which the prior assessment requestor explained that concomitant PPI did not cause any clinically significant change in PK.

6.2.6.2 PPK analysis of TAF (Reference CTD 5.3.3.5.4)

PPK analysis (NONMEM version 7.3.0) was conducted using PK data of TAF (4201 measuring points in 1409 subjects) obtained from healthy subjects or patients with HIV-1 infection in 12 clinical studies.[25] The final model was described by the 2-compartment model with sequential zero- and first-order absorption processes. Sex and HIV infection were identified as the covariates for CL/F, and

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[23] Four phase I studies (Studies GS-US-141-1233, GS-US-380-1991, GS-US-380-3909, and GS-US-380-1999) and 4 phase III studies (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878)

[24] Possible covariates evaluated were baseline creatinine clearance, body weight, age, concomitant use with/without PPI, previous treatment (healthy subjects, treatment-naïve patients with HIV infection, or patients with HIV infection with a history of previous anti-HIV treatment), HIV infection (healthy subjects or patients with HIV infection), and sex for CL/F and Vc/F; concomitant use with/without PPI, dietary conditions (always after a meal, sometimes under fasted conditions, or always under fasted conditions) for k_a; and dietary conditions (always after a meal, sometimes under fasted conditions, or always under fasted conditions) for F1.

[25] Seven phase I studies (Studies GS-US-120-0104, GS-US-120-0107, GS-US-120-0108, GS-US-120-0117, GS-US-120-0118, GS-US-292-0101, and GS-US-320-1228) and 5 phase III studies (Studies GS-US-311-1089, GS-US-366-1160, GS-US-366-1216, GS-US-380-1489, and GS-US-380-1490)

HIV infection as the covariate for the time to distribution to depot compartment (D_1).[26] The final model was used to estimate PK parameters of TAF at steady state following multiple oral QD administration of BIC/FTC/TAF FDC to patients with HIV-1 infection. The following results were obtained: C_{max}, 119 ng/mL; and AUC_{tau}, 139 ng·h/mL.

6.2.6.3 Exposure-response analysis (Reference CTD 5.3.3.5.6)

The pooled data of the foreign phase III studies (Studies GS-US-380-1489 and GS-US-380-1490) in treatment-naïve patients with HIV-1 infection were analyzed to investigate the relationship between PK parameters[27] of plasma BIC and TAF, divided in quartiles, and the percentage of subjects with HIV-1 RNA <50 copies/mL at Week 48. None of the PK parameters showed correlation. Another analysis was made to investigate the relationship between the PK parameters of BIC and TAF in plasma (C_{max} and AUC_{tau}) and adverse events (diarrhoea, headache, nausea, nasopharyngitis, and fatigue) that were commonly observed in the foreign phase III studies. None of the PK parameters showed correlation with the occurrence of diarrhoea, headache, nausea, nasopharyngitis, or fatigue.

6.R Outline of the prior assessment conducted by PMDA

On the basis of the submitted data and on the results of the following reviews, PMDA has concluded that there is no particular problem currently from the point of view of biopharmaceutics and clinical pharmacology.

6.R.1 Comparison of the formulation for clinical development and the to-be-marketed formulation, and the effect of a meal

A formulation for clinical development (Formulation 2) was used during the early stage of the foreign phase III studies (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878), which was then switched to the to-be marketed formulation (BIC/FTC/TAF FDC) in the midcourse of these studies. The food effect on the to-be-marketed formulation was not investigated.

The explanation of the prior assessment requestor about the efficacy, safety, and the food effect in administration of the to-be-marketed formulation (BIC/FTC/TAF FDC):

- The food effect was investigated using Formulation 2. No food effect was observed [see Section 6.1.1].

- The only differences between Formulation 2 and the to-be-marketed formulation (BIC/FTC/TAF FDC) are the component ratios of magnesium stearate and microcrystalline cellulose in the FTC/TAF-containing layer. According to the guideline for bioequivalence issued by the US regulatory authority (Guidance for Industry: Immediate Release Solid Oral Dosage Forms,

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[26] Possible covariates evaluated were body weight, sex, HIV-infection (healthy subjects or patients with HIV infection), previou treatment (healthy subjects, treatment-naïve patients with HIV infection, or patients with HIV infection with a history of previous anti-HIV treatment), and formulation (TAF, RPV/FTC/TAF, BIC/FTC/TAF, FTC/TAF, BIC/FTC/TAF, etc.) for CL/F and Vc/F; HIV-infection (healthy subjects or patients with HIV infection), previous treatment (healthy subjects, treatment-naïve patients with HIV infection, or patients with HIV infection with a history of previous anti-HIV treatment), formulation (TAF, RPV/FTC/TAF, BIC/FTC/TAF, FTC/TAF, BIC/FTC/TAF, etc.), and dietary conditions (always after a meal, sometimes under fasted conditions, or always under fasted conditions) for D_1; and formulation (TAF, RPV/FTC/TAF, BIC/FTC/TAF, FTC/TAF, BIC/FTC/TAF, or other) and dietary conditions (always after a meal, sometimes under fasted conditions, or always under fasted conditions) for F_1.

[27] PK parameters investigated were C_{max}, AUC_{tau}, and C_{tau} for BIC, and C_{max} and AUC_{tau} for TAF.

Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, *In Vivo* Bioequivalence Documentation, 1995), evaluation based on the results of a bioequivalence study in humans and of a dissolution test is not mandatory. Both formulations were confirmed to have similar dissolution profile by a dissolution test (paddle method, 75 rpm, pH 1.2, 4.5, and 6.8).

- In the foreign phase III studies (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878) in which treatments were administered without regard to food, the formulation used was switched to the to-be-marketed formulation (BIC/FTC/TAF FDC) in the midcourse of these studies without any significant concerns about efficacy or safety [see Sections 7.R.1 and 7.R.2]. In the foreign phase III studies (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878), plasma C_{max}, AUC_{tau}, and C_{tau} of BIC in 5 subjects receiving only the to-be-marketed formulation (BIC/FTC/TAF FDC) and 18 subjects receiving only Formulation 2 were estimated using the final PPK model for BIC. Results showed that C_{max}, AUC_{tau}, and C_{tau} were 5660 ng/mL, 90,100 ng·h/mL, and 2130 ng/mL, respectively, in the population receiving the to-be-marketed formulation (BIC/FTC/TAF FDC), and 6150 ng/mL, 106,000 ng·h/mL, and 2820 ng/mL, respectively, in the population receiving Formulation 2, showing no significant differences in the exposure to BIC (C_{max}, AUC_{tau}, and C_{tau}) between two formulations. In all of the 5 subjects receiving only the to-be-marketed formulation (BIC/FTC/TAF FDC), reduction of HIV RNA <50 copies/mL was achieved at Week 48 without any serious or Grade ≥3 adverse events. Among serious adverse events that occurred after switching from Formulation 2 to the to-be-marketed formulation (BIC/FTC/TAF FDC), there were no events that were considered related to the study drug or resulted in treatment discontinuation.

- In all patients (1193 in total) in the foreign phase III studies (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878), the steady-state C_{tau} of BIC (2610 ng/mL, see Section 6.2.6.1) estimated from the final PPK model for BIC exceeded EC_{95} adjusted for protein content (162 ng/mL, see Section 3.1.1.1).

These results suggest that the food effect of the to-be-marketed formulation (BIC/FTC/TAF FDC) is similar to that of Formulation 2. It is possible to evaluate the efficacy and safety of the to-be-marketed formulation (BIC/FTC/TAF FDC) based on the results of the foreign phase III studies (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878).

PMDA's view:
The food effect in administration of the to-be-marketed formulation (BIC/FTC/TAF FDC) can be explained based on the results of the food effect study using Formulation 2, taking account of the explanation of the prior assessment requestor. Also, administration without regard to food is acceptable, taking account of the explanation of the prior assessment requestor from the aspect of the clinical pharmacology based on the results of the foreign phase III studies. In addition, the efficacy and safety of the to-be-marketed formulation (BIC/FTC/TAF FDC) may be evaluated based on the results of the foreign phase III studies, taking account of the explanation of the prior assessment requestor.

6.R.2 Justification for the dosage and administration

The explanation of the prior assessment requestor about the rationale for setting the dosage regimen of BIC/FTC/TAF FDC as "BIC/FTC/TAF 50/200/25 mg FDC QD," from a clinical pharmacological point of view:

- Exposure-response analysis for BIC was performed using the data of the phase I study (Study GS-US-141-1219) in non-Japanese patients with HIV-1 infection. Results predicted a nearly maximum reduction in HIV-1 RNA levels at the estimated exposure (C_{tau}) following administration of BIC 75 mg QD [see Section 6.2.2.1]. Therefore, the dosage regimen of BIC in the foreign phase II study (Study GS-US-141-1475) was 75 mg QD. The dosages of FTC and TAF were 200 mg and 25 mg, respectively, in line with the FTC/TAF (200/25 mg) FDC that had been developed in advance by Gilead Sciences, Inc. (US). Co-administration of BIC (75 mg) with FTC/TAF (200/25 mg) gave favorable results for the efficacy and safety in the foreign phase II study (Study GS-US-141-1475).

- The dose of BIC was investigated again for the development of BIC/FTC/TAF FDC. The geometrical mean ratios of C_{max} and AUC_{inf} of BIC in plasma following the administration of the BIC/FTC/TAF (50/200/25 mg) FDC (Formulation 2) to those following the administration of BIC 75 mg + FTC/TAF (200/25 mg) FDC were both 0.8 [see Section 6.1.1]. On the other hand, multiple administration of BIC/FTC/TAF (50/200/25 mg) FDC (Formulation 2) QD was also expected to achieve C_{tau} exceeding EC_{95} adjusted for protein (162 ng/mL, see Section 3.1.1.1). Therefore, BIC/FTC/TAF (50/200/25 mg) FDC QD was selected as the dosage regimen for the foreign phase III study, with consideration given to possible changes in the PK of BIC caused by intrinsic factors such as hepatic and renal impairment and extrinsic factors such as drug-drug interactions with CYP3A4 inhibitors or inducers.

- In all of the foreign phase III studies (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878), the steady-state C_{tau} of BIC in plasma following multiple administration of BIC/FTC/TAF (50/200/25 mg) FDC QD was >2000 ng/mL [see Section 6.2.2.3], exceeding EC_{95} adjusted for protein (162 ng/mL, see Section 3.1.1.1).

- Exposure to FTC following administration of BIC/FTC/TAF FDC to patients with HIV-1 infection in the phase III studies [see Section 6.2.2.3] was within the range of exposure[28)] observed in the phase III studies (Studies GS-US-236-0102 and GS-US-236-0103) on the FTC-containing product (EVG/COBI/FTC/tenofovir disoproxil fumarate [TDF] 150/150/200/300 mg) approved in and outside of Japan.

- Exposure to TAF following administration of BIC/FTC/TAF FDC to patients with HIV-1 infection in the phase III studies [see Section 6.2.2.3] was within the range of the exposure[29)] observed in the phase III studies (Studies GS-US-292-0104 and GS-US-292-0111) on TAF-containing product (EVG/COBI/FTC/TAF 150/150/200/10 mg) approved in and outside of Japan.

[28)] Review Report on Stribild Combination Tablets (dated February 19, 2013)
[29)] Review Report on Genvoya Combination Tablets (dated May 19, 2016)

The prior assessment requestor explained the rationale for the dosage regimen from a clinical pharmacological point of view. PMDA considers that the explanation is acceptable. The efficacy and safety of BIC/FTC/TAF 50/200/25 mg FDC QD are discussed in Sections 7.R.1 and 7.R.2.

7. Clinical Efficacy and Safety and Outline of the Prior Assessment Conducted by PMDA

The prior assessment requestor submitted, as the pivotal data on the efficacy and safety of BIC/FTC/TAF FDC, the results of 1 foreign phase II study (Study GS-US-141-1475) and 4 foreign phase III studies (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878) in patients with HIV-1 infection. Table 38 shows the outline of these studies. In this section, the results of the 4 foreign phase III studies are described.

Table 38. Outline of studies on efficacy and safety of BIC/FTC/TAF in patients with HIV-1 infection

Data category	Study (phase)	Subjects	Dosage regimen	No. of patients	Main endpoint
Evaluation	GS-US-380-1489 (III)	Patients with HIV-1 infection (treatment-naïve)	(a) BIC/FTC/TAF group: BIC/FTC/TAF 50/200/25 mg QD (b) DTG/ABC/3TC group: DTG/ABC/3TC 50/600/300 mg QD	(a) 314 (b) 315	Efficacy Safety PK
	GS-US-380-1490 (III)	Patients with HIV-1 infection (treatment-naïve)	(a) BIC/FTC/TAF group: BIC/FTC/TAF 50/200/25 mg QD (b) DTG + FTC/TAF group: DTG 50 mg QD + FTC/TAF 200/25 mg QD	(a) 320 (b) 325	Efficacy Safety PK
	GS-US-380-1844 (III)	Patients with HIV-1 infection (with a history of previous anti-HIV treatment[a)])	(a) BIC/FTC/TAF group: BIC/FTC/TAF 50/200/25 mg QD (b) DTG/ABC/3TC (stay on baseline regimen) group: DTG/ABC/3TC 50/600/300 mg QD	(a) 282 (b) 281	Efficacy Safety PK
	GS-US-380-1878 (III)	Patients with HIV-1 infection (with a history of previous anti-HIV treatment[b)])	(a) BIC/FTC/TAF group: BIC/FTC/TAF 50/200/25 mg QD (b) PI + NRTI (stay on baseline regimen) group: The dosage regimen used before the screening was continued.	(a) 290 (b) 287	Efficacy Safety PK
Reference	GS-US-141-1475 (II)	Patients with HIV-1 infection (treatment-naïve)	(a) BIC + FTC/TAF group: BIC 75 mg QD + FTC/TAF 200/25 mg QD (b) DTG + FTC/TAF group: DTG 50 mg QD + FTC/TAF 200/25 mg QD	(a) 65 (b) 33	Efficacy Safety PK

a) Patients who were virologically suppressed (HIV-1 RNA <50 copies/mL) on either single-agent DTG plus abacavir [ABC]/lmivudine [3TC] FDC or DTG/ABC/3TC FDC for ≥3 months before the screening.
b) Patients who were virologically suppressed (HIV-1 RNA <50 copies/mL) on combination regimen with ritonavir (RTV) or COBI, PI (ATV or DRV), and NRTI (FTC/TDF or ABC/3TC) for ≥6 months before the screening.

7.1 Phase II study

7.1.1 Foreign phase II study (Reference CTD 5.3.5.1.1, Study GS-US-141-1475 [March 2015 to October 2016])

A randomized, DTG + FTC/TAF-controlled, double-blind, parallel-group study was conducted in treatment-naïve adult patients with HIV-1 infection[30)] (target sample size, 75 subjects [50 in the BIC + FTC/TAF group, 25 in the DTG + FTC/TAF group]) in 22 sites in the US to investigate the efficacy and safety of BIC + FTC/TAF.

[30)] Patients aged 18 years who had not received anti-HIV drug for ≥11 days with plasma HIV-1 RNA ≥1000 copies/mL and eGFR of ≥70 mL/min at screening.

BIC (75 mg) plus FTC/TAF (200/25 mg) FDC or DTG (50 mg) plus FTC/TAF (200/25 mg) FDC were administered orally QD for 48 weeks.[31)]

A total of 98 randomized subjects who received at least 1 dose of the study drug (65 in the BIC + FTC/TAF group, 33 in the DTG + FTC/TAF group) were included in the safety analysis set and full analysis set (FAS), and the FAS was used for efficacy analysis.

The percentage of patients with HIV-1 RNA <50 copies/mL at Week 24,[32)] the primary efficacy endpoint, was 96.9% (63 of 65 patients) in the BIC + FTC/TAF group and 93.9% (31 of 33 patients) in the DTG + FTC/TAF group.

Adverse events were observed in 87.7% (57 of 65) of patients in the BIC + FTC/TAF group and in 72.7% (24 of 33) of patients in the DTG + FTC/TAF group. Adverse drug reactions[33)] were observed in 20.0% (13 of 65) of patients in the BIC + FTC/TAF group and in 21.2% (7 of 33) of patients in the DTG + FTC/TAF group. Table 39 shows adverse events and/or adverse drug reactions reported by ≥5% of patients in either group.

Table 39. Adverse events and/or adverse drug reactions reported by ≥5% of patients in either group

Event	Adverse events		Adverse drug reactions	
	BIC + FTC/TAF (N = 65)	DTG + FTC/TAF (N = 33)	BIC + FTC/TAF (N = 65)	DTG +F TC/TAF (N = 33)
Any event	57 (87.7)	24 (72.7)	13 (20.0)	7 (21.2)
Diarrhoea	9 (13.8)	4 (12.1)	3 (4.6)	3 (9.1)
Nausea	5 (7.7)	4 (12.1)	1 (1.5)	2 (6.1)
Upper respiratory tract infection	7 (10.8)	1 (3.0)	0	0
Headache	6 (9.2)	1 (3.0)	2 (3.1)	1 (3.0)
Arthralgia	4 (6.2)	2 (6.1)	0	0
Chlamydial infection	4 (6.2)	2 (6.1)	0	0
Fatigue	4 (6.2)	2 (6.1)	1 (1.5)	0
Furuncle	3 (4.6)	2 (6.1)	0	0
Urethritis	3 (4.6)	2 (6.1)	0	0
Back pain	4 (6.2)	0	0	0
Exposure to communicable disease	2 (3.1)	2 (6.1)	0	0
Vomiting	2 (3.1)	2 (6.1)	2 (3.1)	1 (3.0)
Anal fissure	1 (1.5)	2 (6.1)	0	0
Anxiety	1 (1.5)	2 (6.1)	0	0
Flatulence	1 (1.5)	2 (6.1)	0	1 (3.0)
Gastroenteritis	1 (1.5)	2 (6.1)	0	0
Rhinitis allergic	1 (1.5)	2 (6.1)	0	0
Chest pain	0	2 (6.1)	0	0
Costochondritis	0	2 (6.1)	0	0
Haemorrhoids	0	2 (6.1)	0	0
Pain	0	2 (6.1)	0	0
Pruritus	0	2 (6.1)	0	0
Viral infection	0	2 (6.1)	0	0

n (%)

No death occurred.

31) After completion of 48 weeks of treatment, the study treatment was continued under open-label conditions. Patients who entered the open-label extension phase were allowed to enter the extension phase with BIC/FTC/TAF FDC from Week 60. During the open-label extension phase, patients were to make a return visit every 12 weeks.
32) Missing data were treated and analyzed according to the FDA-defined snapshot algorithm.
33) Adverse events that were considered related to the study drug

Serious adverse events were observed in 3 patients in the BIC + FTC/TAF group (appendicitis, diabetic ketoacidosis, psychotic disorder, and suicidal ideation in 1 patient each [including duplicate counting]). For all of the serious adverse events, a causal relationship to the study drug was ruled out and the outcome was reported as resolved.

An adverse event leading to treatment discontinuation was observed in 1 patient in the BIC + FTC/TAF group (urticaria), and the event was assessed as related to the study drug.

No death or adverse events leading to treatment discontinuation were reported during the extended treatment period from Week 48 after the start of the study (data at Week 72). Serious adverse events were observed in 9 patients, but a causal relationship to the study drug was ruled for all events.

7.2 Phase III studies

7.2.1 Foreign phase III study (CTD 5.3.5.1.5, Study GS-US-380-1489 [ongoing since November 2015 (data cut-off [redacted] 20[redacted])])

A randomized, double-blind, parallel-group study was conducted in treatment-naïve[34)] adult patients with HIV-1 infection[35)] (target sample size, 600 subjects [300 per group]) in 122 sites in 9 counties including the US, Spain, the UK, and Canada in order to investigate the efficacy and safety of BIC/FTC/TAF FDC versus DTG/abacavir (ABC)/lmivudine (3TC) FDC.

BIC/FTC/TAF (50/200/25 mg) FDC or DTG/ABC/3TC (50/600/300 mg) FDC was administered orally QD for 144 weeks, without regard to food.

A total of 629 randomized patients who received at least 1 dose of the study drug (314 in the BIC/FTC/TAF group, 315 in the DTG/ABC/3TC group) were included in the safety analysis set and FAS, and the FAS was used for efficacy analysis.

The percentage of patients with HIV-1 RNA <50 copies/mL at Week 48,[32)] the primary efficacy endpoint, was 92.4% (290 of 314 patients) in the BIC/FTC/TAF group and 93.0% (293 of 315 patients) in the DTG/ABC/3TC group. The between-group difference[36)] [95.002% CI[37)]] was −0.6% [−4.8%, 3.6%], with the lower limit of the CI exceeding the non-inferiority margin (−12%) that had been established in advance, demonstrating the non-inferiority of BIC/FTC/TAF to DTG/ABC/3TC.

Up to Week 48, adverse events were observed in 84.4% (265 of 314) of patients in the BIC/FTC/TAF group and in 89.8% (283 of 315) of patients in the DTG/ABC/3TC group, and adverse drug reactions[38)] were observed in 26.1% (82/314) of patients in the BIC/FTC/TAF group and in 40.3%

34) Patients who have no history of previous anti-HIV treatment for ≥11 days.
35) Patients aged ≥18 years with plasma HIV-1 RNA ≥500 copies/mL and eGFR of ≥50 mL/min at screening.
36) Calculated by Mantel-Haenszel method using HIV-1 RNA level at screening (≤100,000 copies/mL or >100,000 copies /mL) and region (US or other regions) as the stratification factors.
37) Interim analyses were conducted at the time points when data at Week 12 were obtained from approximately half of the enrolled patients and when data at Week 24 or at discontinuation were obtained from all patients, in order to report the status of the study to the independent monitoring committee (early termination of the study for efficacy or futility had not been planned). It had been planned to consume the significance level α by 0.00001 in each interim analysis, resulting in a significance level of 0.04998 in the final analysis, with the confidence coefficient being 95.002%.
38) Adverse events that were considered related to the study drug

(127 of 315) of patients in the DTG/ABC/3TC group. Table 40 shows adverse events and/or adverse drug reactions reported by ≥5% of patients in either group.

Table 40. Adverse events and/or adverse drug reactions reported by ≥5% of patients in either group

Event	Adverse events		Adverse drug reactions	
	BIC/FTC/TAF (N =314)	DTG/ABC/3TC (N = 315)	BIC/FTC/TAF (N =314)	DTG/ABC/3TC (N = 315)
Any event	265 (84.4)	283 (89.8)	82 (26.1)	127 (40.3)
Nausea	32 (10.2)	72 (22.9)	17 (5.4)	55 (17.5)
Diarrhoea	40 (12.7)	41 (13.0)	19 (6.1)	13 (4.1)
Headache	36 (11.5)	43 (13.7)	16 (5.1)	15 (4.8)
Upper respiratory tract infection	20 (6.4)	34 (10.8)	0	0
Nasopharyngitis	23 (7.3)	29 (9.2)	0	0
Fatigue	19 (6.1)	27 (8.6)	9 (2.9)	10 (3.2)
Syphilis	12 (3.8)	25 (7.9)	0	0
Insomnia	14 (4.5)	20 (6.3)	5 (1.6)	9 (2.9)
Arthralgia	11 (3.5)	19 (6.0)	1 (0.3)	0
Vomiting	12 (3.8)	17 (5.4)	3 (1.0)	5 (1.6)
Cough	20 (6.4)	8 (2.5)	0	1 (0.3)
Bronchitis	10 (3.2)	16 (5.1)	0	0
Abdominal pain	9 (2.9)	16 (5.1)	3 (1.0)	6 (1.9)

n (%)

No death occurred.

Serious adverse events were observed in 19 patients in the BIC/FTC/TAF group (anaemia and overdose in 2 patients; suicidal ideation, gonorrhoea, neurosyphilis, pneumonia, abdominal hernia, abdominal wall abscess, anaemia of chronic disease, atrial fibrillation, deep vein thrombosis, delirium tremens, diabetic ketoacidosis, generalised tonic-clonic seizure, haematemesis, major depression, meningitis cryptococcal, mental disorder, mycobacterium avium complex infection, oesophageal food impaction, orchitis, pharyngeal abscess, psychotic disorder, pulmonary embolism, pyrexia, suicide attempt, testicular mass, and testicular pain in 1 patient each [some patients had more than one event]), and in 25 patients in the DTG/ABC/3TC group (suicidal ideation, depression, gastroenteritis, road traffic accident, and sepsis in 2 patients each; and gonorrhoea, neurosyphilis, pneumonia, abdominal pain, abscess limb, anal abscess, appendicitis, B-cell unclassifiable lymphoma high grade, bacteraemia, breast abscess, bronchitis, cardiac failure acute, chest discomfort, chest pain, renal failure chronic, dehydration, diabetes mellitus inadequate control, diarrhoea, respiratory failure, fungaemia, gastroenteritis viral, haemorrhoids thrombosed, hyperkalaemia, hypotension, international normalised ratio increased, keratitis, limb injury, lower limb fracture, myocardial infarction, nausea, neck pain, osteomyelitis, pancreatitis chronic, peripheral ischaemia, respiratory failure, spinal fracture, steatorrhoea, toxicity to various agents, vomiting, and white blood cell count increased in 1 patient each [some patients had more than one event]). A causal relationship to the study drug could not be ruled out for the adverse events in 1 patient in the BIC/FTC/TAF group (generalised tonic-clonic seizure) and in 1 patient in the DTG/ABC/3TC group (gastroenteritis/pancreatitis chronic/steatorrhoea), but the outcome was reported as resolved for all of them.

Adverse events leading to treatment discontinuation were observed in 4 patients in the DTG/ABC/3TC group (thrombocytopenia, nausea, pancreatitis chronic, steatorrhoea, depression, and rash generalized in 1 patient each [some patients had more than one event]). A causal relationship to the study drug

could not be ruled out for any of these adverse events, but the outcome was reported as resolved except in 2 patients (thrombocytopenia and depression).

Death occurred in 2 patients in the BIC/FTC/TAF group (overdose and sudden death) from Week 48 to 96 after the start of administration. A causal relationship to the study drug could not be ruled out for sudden death in 1 patient, which was caused by self-injury or suicide. Serious adverse events were observed in 17 patients in the BIC/FTC/TAF group and in 14 patients in the DTG/ABC/3TC group, and a causal relationship to the study drug could not be ruled out for events in 2 patients in the BIC/FTC/TAF group (sudden death and abortion spontaneous). An adverse event leading to treatment discontinuation was observed in 1 patient in the DTG/ABC/3TC group, but its causal relationship to the study drug was ruled out.

7.2.2 Foreign phase III study (CTD 5.3.5.1.6, Study GS-US-380-1490 [ongoing since November 2015 (data cut-off [redacted] 20[redacted])])

A randomized, double-blind, parallel-group study was conducted in treatment-naïve[34)] adult patients with HIV-1 infection [39)] (target sample size, 600 patients [300 per group]) in 126 sites in 10 countries including the US, UK, and Spain to investigate the efficacy and safety of BIC/FTC/TAF FDC versus the DTG tablet plus FTC/TAF FDC as the control regimen.

BIC/FTC/TAF (50/200/25 mg) FDC or DTG (50 mg) plus FTC/TAF (200/25 mg) FDC was administered orally QD for 144 weeks, without regard to food.

A total of 645 randomized patients receiving at least 1 dose of the study drug (320 in the BIC/FTC/TAF group, 325 in the DTG + FTC/TAF group) were included in the safety analysis set and FAS, and the FAS was used for efficacy analysis.

The percentage of patients[32)] with HIV-1 RNA <50 copies/mL at Week 48, the primary efficacy endpoint, was 89.4% (286 of 320 patients) in the BIC/FTC/TAF group and 92.9% (302 of 325 patients) in the DTG + FTC/TAF group. The between-group difference[36)] [95.002% CI[37)]] was −3.5% [−7.9%, 1.0%], with lower limit of the 95.002% CI exceeding the pre-specified non-inferiority margin (−12%), demonstrating the non-inferiority of BIC/FTC/TAF to DTG plus FTC/TAF.

Up to Week 48, adverse events were observed in 82.5% (264 of 320) of patients in the BIC/FTC/TAF group and in 83.7% (272 of 325) of patients in the DTG + FTC/TAF group, and adverse drug reactions[38)] were observed in 17.8% (57 of 320) of patients in the BIC/FTC/TAF group and in 25.5% (83 of 325) of patients in the DTG + FTC/TAF group. Table 41 shows adverse events and/or adverse drug reactions reported by ≥5% of patients in either group.

[39)] Patients aged 18 years with plasma HIV-1 RNA ≥500 copies/mL and eGFR of ≥30 mL/min in plasma at screening.

Table 41. Adverse events and adverse drug reactions reported by ≥5% of patients in either group

Event	Adverse events		Adverse drug reactions	
	BIC/FTC/TAF (N = 320)	DTG + FTC/TAF (N = 325)	BIC/FTC/TAF (N = 320)	DTG + FTC/TAF (N = 325)
Any event	264 (82.5)	272 (83.7)	57 (17.8)	83 (25.5)
Headache	40 (12.5)	40 (12.3)	13 (4.1)	10 (3.1)
Diarrhoea	37 (11.6)	39 (12.0)	10 (3.1)	11 (3.4)
Nausea	25 (7.8)	29 (8.9)	9 (2.8)	17 (5.2)
Nasopharyngitis	22 (6.9)	31 (9.5)	0	0
Fatigue	19 (5.9)	26 (8.0)	7 (2.2)	7 (2.2)
Upper respiratory tract infection	15 (4.7)	23 (7.1)	0	0
Lymphadenopathy	17 (5.3)	18 (5.5)	0	0
Pyrexia	14 (4.4)	21 (6.5)	0	0
Back pain	11 (3.4)	20 (6.2)	0	0
Insomnia	16 (5.0)	14 (4.3)	6 (1.9)	1 (0.3)
Influenza	17 (5.3)	10 (3.1)	0	0
Arthralgia	16 (5.0)	9 (2.8)	2 (0.6)	0

n (%)

Death occurred in 1 patient in the BIC/FTC/TAF group (cardiac arrest) and in 2 patients in the DTG + FTC/TAF group (death and pulmonary embolism), but their causal relationship to the study drug was ruled out.

Serious adverse events were observed in 39 patients in the BIC/FTC/TAF group (appendicitis and cellulitis in 3 patients each, suicide attempt, anal abscess, and rhabdomyolysis in 2 patients each, acute kidney injury, subcutaneous abscess, abdominal pain, abortion incomplete, abscess neck, acute respiratory failure, adenocarcinoma gastric, anaemia, anal fistula, anal infection, back pain, cardiac arrest, cardiac failure congestive, central nervous system lymphoma, chest pain, chronic kidney disease, colitis, depression, depression suicidal, diabetes mellitus inadequate control, diarrhoea, drug abuse, Escherichia bacteraemia, gastroenteritis, gunshot wound, headache, hepatitis A, hyperglycaemia, hyperkalaemia, hypoglycaemia, hypokalaemia, influenza, major depression, myocardial infarction, oedema peripheral, peripheral ischaemia, pneumothorax, pyelonephritis, pyrexia, septic shock, Staphylococcal infection, and systemic inflammatory response syndrome in 1 patient each [some patients had more than one event]) and in 23 patients in the DTG + FTC/TAF group (appendicitis and road traffic accident in 2 patients each, cellulitis, suicide attempt, acute kidney injury, subcutaneous abscess, alcohol poisoning, bacterial infection, bipolar disorder, chronic obstructive pulmonary disease, concussion, constipation, death, deep vein embolism, dyspnoea, eye infection syphilitic, haemorrhoids, head injury, hypertensive crisis, interstitial lung disease, iridocyclitis, ischaemic stroke, local swelling, muscle haemorrhage, orchitis, ovarian cyst, pneumonia, pneumonia parainfluenzae virus, pulmonary embolism, rectal haemorrhage, seasonal affective disorder, sepsis, tendon injury, toxicity to various agents, and wound infection in 1 patient each [some patients had more than one event]). A causal relationship to the study drug could not be ruled out in 2 patients in the BIC/FTC/TAF group (chest pain and suicide attempt in 1 patient each), but the outcome was reported as resolved except for suicide attempt.

Adverse events leading to treatment discontinuation were observed in 5 patients in the BIC/FTC/TAF group (cardiac arrest, abdominal distension, dyspepsia, chest pain, tension headache, depressed mood, insomnia, paranoia, and sleep disorder in 1 patient each [some patients had more than one event]) and in 1 patient in the DTG + FTC/TAF group (erythema and pruritus in 1 patient each). A causal

relationship of adverse events to the study drug could not be ruled out in 3 patients in the BIC/FTC/TAF group (chest pain, abdominal distension, sleep disorder, dyspepsia, tension headache, depressed mood, and insomnia in 1 patient each [some patients had more than one event]), but the outcome was reported as resolved except in 2 patients (abdominal distension and sleep disorder in 1 patient each).

From Week 48 to Week 96, death occurred in 2 patients in the BIC/FTC/TAF group (adenocarcinoma gastric, hypertensive heart disease, and cardiac failure congestive in 1 patient each [some patients had more than one event]) and in 1 patient in the DTG + FTC/TAF group (lymphoma), but a causal relationship of death to the study drug was ruled out in all of them. Serious adverse events were observed in 16 patients in the BIC/FTC/TAF group and in 10 patients in the DTG + FTC/TAF group, and a causal relationship to the study drug could not be ruled out in 1 patient in the BIC/FTC/TAF group (atrial flutter, dizziness, and pancreatitis acute) and in 2 patients in the DTG + FTC/TAF group (depression and deep vein thrombosis in 1 patient each). Adverse events leading to treatment discontinuation were observed in 1 patient in the BIC/FTC/TAF group and in 4 patients in the DTG + FTC/TAF group, and their causal relationship to the study drug could not be ruled out in 1 patient in the BIC/FTC/TAF group (depression) and in 3 patients in the DTG + FTC/TAF group (depression in 2 patients, lipoatrophy in 1 patient).

7.2.3 Foreign phase III study (CTD 5.3.5.1.7, Study GS-US-380-1844 [ongoing since November 2015 (data cut-off [redacted] 20[redacted])])

A randomized, double-blind, parallel-group study was conducted in adult patients with HIV-1 infection,[40] who remained virologically suppressed (HIV-1 RNA <50 copies/mL) for ≥3 months on the DTG/ABC/3TC regimen (target sample size, 520 subjects [260 per group]), in order to investigate the efficacy and safety of BIC/FTC/TAF FDC versus DTG/ABC/3TC as the control regimen. The study took place in 96 sites in 9 countries including the US, Germany, and Spain.

BIC/FTC/TAF (50/200/25 mg) FDC or DTG/ABC/3TC (50/600/300 mg) FDC was administered orally QD for 48 weeks.[41]

A total of 563 randomized patients (282 in the BIC/FTC/TAF group, 281 in the DTG/ABC/3TC [stay on baseline regimen (SBR)] group) receiving at least 1 dose of the study drug were included in the safety analysis set and FAS, and the FAS was used for efficacy analysis.

The percentage[32] of patients with virologic failure[42] at Week 48, the primary efficacy endpoint, was 1.1% (3 of 282 patients) in the BIC/FTC/TAF group and 0.4% (1 of 281 patients) in the DTG/ABC/3TC (SBR) group. The between-group difference[43] [95.002% CI[37]] was 0.7% [−1.0%,

[40] Patients aged ≥18 years with HIV-1 RNA <50 copies/mL without resistance mutation (including suspected resistance) to FTC, TFV, DTG, ABC, or 3TC and with eGFR of ≥50 mL/min at the screening.
[41] Subjects were allowed to receive BIC/FTC/TAF FDC under open-label conditions until the following time point, whichever came first, after completing 48 weeks of treatment: (a) up to Week 96, (b) until BIC/FTC/TAF became commercially available, or (c) until discontinuation of the study in the pertinent country. During the extension phase, patients were required to receive tests every 12 weeks.
[42] Patients who met any of the following 3 criteria: (a) HIV-1 RNA ≥50 copies/mL at Week 48, (b) treatment discontinuation due to a lack of efficacy, or (c) among patients who discontinued the treatment for reasons other than a lack of efficacy, patients who had HIV-1 RNA ≥50 copies/mL at the final test.
[43] Calculated based on the unconditional exact method.

2.8%], with the upper limit of 95.002% CI falling below the pre-specified non-inferiority margin (4%), demonstrating the non-inferiority of BIC/FTC/TAF to DTG/ABC/3TC.

Within 48 weeks after the start of administration, adverse events were observed in 79.8% (225 of 282) of patients in the BIC/FTC/TAF group and in 80.1% (225 of 281) of patients in the DTG/ABC/3TC (SBR) group. Adverse drug reactions[38)] were observed in 8.2% (23 of 282) of patients in the BIC/FTC/TAF group and in 15.7% (44 of 281) of patients in the DTG/ABC/3TC (SBR) group. Table 42 shows adverse events and/or adverse drug reactions reported by≥5% of patients in either group.

Table 42. Adverse events and/or adverse drug reactions reported by ≥5% of patients in either group

Event	Adverse events		Adverse drug reaction	
	BIC/FTC/TAF (N = 282)	DTG/ABC/3TC (SBR) (N = 281)	BIC/FTC/TAF (N = 282)	DTG/ABC/3TC (SBR) (N = 281)
Any event	225 (79.8)	225 (80.1)	23 (8.2)	44 (15.7)
Upper respiratory tract infection	29 (10.3)	27 (9.6)	0	0
Nasopharyngitis	20 (7.1)	22 (7.8)	0	0
Headache	19 (6.7)	21 (7.5)	7 (2.5)	8 (2.8)
Diarrhoea	24 (8.5)	14 (5.0)	2 (0.7)	4 (1.4)
Arthralgia	19 (6.7)	10 (3.6)	0	0
Insomnia	8 (2.8)	14 (5.0)	0	3 (1.1)

n (%)

Death occurred in 2 patients in the BIC/FTC/TAF group (sudden cardiac death and death), but their causal relationship to the study drug was ruled out.

Serious adverse events were observed in 15 patients in the BIC/FTC/TAF group (suicidal ideation in 2 patients, acute coronary syndrome, acute myocardial infarction, alcohol abuse, cerebrovascular accident, death, depression suicidal, endocarditis, eye infection syphilitic, hyponatraemia, hypovolaemia, infectious colitis, intentional overdose, lymphadenitis bacterial, myalgia, overdose, spinal column stenosis, sudden cardiac death, suicide attempt, vertebrobasilar insufficiency, and wrist fracture in 1 patient each [some patients had more than one event]) and in 22 patients in the DTG/ABC/3TC (SBR) group (atrial fibrillation in 2 patients, suicidal ideation, abnormal behaviour, abscess limb, anal abscess, ankle fracture, appendicitis, bile duct stone, bipolar disorder, cellulitis, cellulitis of male external genital organ, drug withdrawal syndrome, haematuria, hiatus hernia, influenza, intestinal obstruction, macular detachment, nephrolithiasis, post procedural sepsis, respiratory syncytial virus infection, retinal detachment, schizophrenia, subcutaneous abscess, tooth abscess, umbilical hernia, and vitreous haemorrhage in 1 patient each [some patients had more than one event]). A causal relationship of an adverse event to the study drug could not be ruled out in 1 patient in the BIC/FTC/TAF group (cerebrovascular accident), but the outcome was reported as resolved.

Adverse events leading to treatment discontinuation were observed in 6 patients in the BIC/FTC/TAF group (headache in 2 patients, vomiting, cerebrovascular accident, abnormal dreams, and suicidal ideation in 1 patient each), and in 2 patients in the DTG/ABC/3TC (SBR) group (headache and pruritus in 1 patient each). A causal relationship of the adverse events to the study drug could not be

ruled out except in 1 patient in the BIC/FTC/TAF group (suicidal ideation), but the outcome was reported as resolved except in 1 patient in the BIC/FTC/TAF group (abnormal dreams).

During the extended administration period from 48 weeks after the start of the study, death occurred in 2 patients (unknown cause and cardiogenic shock), and serious adverse events were observed in 48 patients, but their causal relationship to the study drug was ruled out. Adverse events leading to treatment discontinuation were observed in 2 patients (headache and irritability in 1 patient each), and their causal relationship to the study drug could not be ruled out, but the outcome was reported as resolved for both of them.

7.2.4 Foreign phase III study (CTD 5.3.5.1.8, Study GS-US-380-1878 [ongoing since November 2015 (data cut-off [redacted] 20[redacted])])

A randomized, open-label, parallel-group study was conducted in 121 sites in 10 countries including the US UK, and Germany to investigate the efficacy and safety of BIC/FTC/TAF FDC. The study was conducted in adult patients[44] with HIV-1 infection (target sample size, 520 subjects [260 per group]) who remained virologically suppressed (HIV-1 RNA <50 copies/mL) for ≥6 months on a stable combination regimen with ritonavir (RTV) or COBI, PI (ATV or DRV), and NRTI (FTC/TDF or ABC/3TC). The stay on baseline regimen (SBR) was used as the control in the study.

BIC/FTC/TAF FDC (50/200/25 mg QD) or the regimen used at the screening was administered orally for 48 weeks.[41]

A total of 577 randomized patients (290 in the BIC/FTC/TAF group, 287 in the PI + NRTI [SBR] group) receiving at least 1 dose of the study drug was included in the safety analysis set and FAS, and the FAS was used for efficacy analysis.

The percentage[32] of patients with virologic failure[42] at Week 48, the primary efficacy endpoint, was 1.7% (5 of 290 patients) in the BIC/FTC/TAF group and 1.7% (5 of 287 patients) in the PI + NRTI (SBR) group. The between-group difference[43] [95.002% CI] was 0.0% [−2.5%, 2.5%], with the upper limit of 95.002% CI falling below the pre-specified non-inferiority margin (4%), demonstrating the non-inferiority of BIC/FTC/TAF FDC to the baseline regimen.

Up to Week 48, adverse events were observed in 80.3% (233 of 290) of patients in the BIC/FTC/TAF group and in 78.7% (226 of 287) of patients in the PI + NRTI (SBR) group, and adverse drug reactions[38] were observed in 18.6% (54 of 290) of patients in the BIC/FTC/TAF group and in 2.1% (6 of 287) of patients in the PI + NRTI (SBR) group. Table 43 shows adverse events and/or adverse drug reaction reported by ≥5% of patients in either group.

[44] Patients aged ≥18 years with HIV-1 RNA <50 copies/mL at screening, without previous treatment with INSTI, without resistance mutations (including suspected resistance) to FTC, TFV, ABC, or 3TC, and with eGFR of ≥50 mL/min.

Table 43. Adverse events and/or adverse drug reactions reported by ≥5% of patients in either group

Event	Adverse events		Adverse drug reactions	
	BIC/FTC/TAF (N = 290)	PI + NRTI (SBR) (N = 287)	BIC/FTC/TAF (N = 290)	PI + NRTI (SBR) (N = 287)
Any event	233 (80.3)	226 (78.7)	54 (18.6)	6 (2.1)
Nasopharyngitis	21 (7.2)	34 (11.8)	0	0
Headache	35 (12.1)	12 (4.2)	14 (4.8)	0
Upper respiratory tract infection	21 (7.2)	22 (7.7)	0	0
Diarrhoea	24 (8.3)	18 (6.3)	6 (2.1)	0
Back pain	13 (4.5)	17 (5.9)	0	0
Arthralgia	12 (4.1)	15 (5.2)	2 (0.7)	0

n (%)

Death occurred in 1 patient in the BIC/FTC/TAF group (lung neoplasm malignant) and in 1 patient in the PI + NRTI (SBR) group (head injury), but a causal relation of the death to the study drug was ruled out in both of them.

Serious adverse events were observed in 17 patients in the BIC/FTC/TAF group (hepatitis A in 2 patients, acute myocardial infarction, chest pain, coronary artery stenosis, schizophrenia, acute hepatitis C, asthma, brain cancer metastatic, cellulitis, cervical radiculopathy, joint dislocation, malignant lung tumor, metabolic encephalopathy, optic disc disorder, deforming arthritis, pneumonia, pyelonephritis, schizoaffective disorder, sinus node dysfunction, upper respiratory tract infection, and ureterolithiasis in 1 patient each [some patients had more than one event], and in 20 patients in the PI + NRTI (SBR) group (acute myocardial infarction, chest pain, coronary artery stenosis, schizophrenia, abdominal pain, acetabulum fracture, acute kidney injury, anal abscess, anal fistula, anogenital warts, anxiety, appendicitis, atrial fibrillation, gallbladder neoplasm, diarrhoea, diverticular perforation, diverticulitis, enterocutaneous fistula, foetal death, head trauma, hepatitis C, hepatitis acute, hypovolaemic shock, localised infection, lower gastrointestinal haemorrhage, myocardial infarction, stoma site abscess, suicide attempt, thrombotic stroke, and ureteric obstruction in 1 patient each [some patients had more than one event]). A causal relationship to the study drug could not be ruled out for an adverse event in 1 patient in the BIC/FTC/TAF group (schizophrenia), but the outcome was reported as resolved.

Adverse events leading to treatment discontinuation were observed in 2 patients in the BIC/FTC/TAF group (schizophrenia and rash) and in 1 patient in the PI + NRTI (SBR) group (acetabulum fracture and acute kidney injury). A causal relationship to the study drug could not be ruled out for an adverse event in 1 patient in the BIC/FTC/TAF group (schizophrenia), but the outcome was reported as resolved.

During the extended administration period from 48 weeks after the start of the study, death (of unknown reason) occurred in 1 patient, but its causal relationship to the study drug was ruled out. Serious adverse events were observed in 47 patients, and their causal relationship to the study drug could not be ruled out in 2 patients (suicidal ideation and deep vein thrombosis in 1 patient each), but the outcome was reported as resolved. Adverse events leading to treatment discontinuation were observed in 2 patients (rash, pruritus, dizziness, insomnia, headache, and irritability in 1 patient each [a patient experienced one or more events]). A causal relationship to the study drug could not be ruled

out for any of them, but the outcome was reported as resolved, except for rash and pruritus which persisted.

7.R Outline of the prior assessment conducted by PMDA

7.R.1 Efficacy

Based on the following reviews, PMDA concluded that the efficacy of BIC/FTC/TAF FDC is promising in adult patients with HIV-1 infection who are treatment-naïve or those who are virologically suppressed on anti-HIV therapy. However, since no information on the use of the BIC/FTC/TAF FDC in Japanese patients is currently available, post-marketing information on the efficacy of the BIC/FTC/TAF FDC and on resistance mutations should be collected and any new findings should be communicated appropriately to healthcare professionals.

The above conclusions of PMDA will be discussed at the Prior Assessment Meeting.

7.R.1.1 Efficacy in treatment-naïve adult patients with HIV-1 infection

The explanation of the prior assessment requestor about the efficacy of BIC/FTC/TAF in treatment-naïve adult patients with HIV-1 infection:

Table 44 shows the efficacy data from the foreign phase III studies (Studies GS-US-380-1489 and GS-US-380-1490 [see Sections 7.2.1 and 7.2.2]) in treatment-naïve adult patients with HIV-1 infection. The primary endpoint of both studies was the percentage of subjects with HIV-1 RNA <50 copies/mL at Week 48. The lower limit of the 95.002% CI of the difference in the percentage of such subjects between the BIC/FTC/TAF group and the control group exceeded the pre-specified non-inferiority margin (−12%), demonstrating the non-inferiority of BIC/FTC/TAF to DTG/ABC/3TC and to DTG + FTC/TAF. The percentage of subjects with HIV-1 RNA <50 copies/mL at Week 96 was 87.9% (276 of 314 patients) in the BIC/FTC/TAF group and 89.8% (283 of 315 patients) in the DTG/ABC/3TC group in Study GS-US-380-1489, and 84.1% (269 of 320 patients) in the BIC/FTC/TAF group and 86.5% (281 of 325 patients) in the DTG + FTC/TAF group. Emergence of new resistance mutation to the study drug was not observed in either study up to Week 96.

Table 44. Efficacy in treatment-naïve patients
(Week 48, FAS)

	GS-US-380-1489		GS-US-380-1490	
	BIC/FTC/TAF	DTG/ABC/3TC	BIC/FTC/TAF	DTG + FTC/TAF
Percentage of patients with HIV-1 RNA <50 copies/mL (n/N)[a)]	92.4% (290/314)	93.0% (293/315)	89.4% (286/320)	92.9% (302/325)
Between-group difference [95.002% CI][a),b)]	−0.6% [−4.8, 3.6]%		−3.5% [−7.9, 1.0]%	
Percentage of patients with virologic failure (n/N)[a),c)]	1.0% (3/314)	2.5% (8/315)	4.4% (14/320)	1.2% (4/325)

a) Missing data were treated according to the FDA-defined snapshot algorithm.
b) Calculated by Mantel-Haenszel method with HIV-1 RNA levels (≤100,000 copies/mL or >100,000 copies/mL) at screening and region (US or other) as the stratification factors. It had been planned to consume the significance level α by 0.00001 in each interim analysis at Week 12 and 24, resulting in a significance level of 0.04998 in the final analysis, with the resultant CI being 95.002%.
c) Patients who met any of the following 3 criteria: (a) HIV-1 RNA ≥50 copies/mL at Week 48, (b) treatment discontinuation due to a lack of efficacy, or (c) patients who discontinued the treatment for reasons other than a lack of efficacy and had HIV-1 RNA ≥50 copies/mL at the final test.

Table 45 shows efficacy in subgroup analysis according to patient characteristics. In the BIC/FTC/TAF group, the percentage of patients with HIV-1 RNA <50 copies/mL at Week 48 was lower in the

subgroup with baseline HIV-1 RNA >100,000 copies/mL than in the subgroup with baseline HIV-1 RNA ≤100,000 copies/mL. This difference was considered to be due to a small number of subjects with baseline HIV-1 RNA >100,000 copies/mL, along with missing data for efficacy analyses or several cases of lost to follow-up, suggesting that the baseline HIV-1 RNA level does not affect the efficacy. No particular tendency was observed in the analysis of other subgroups.

Table 45. Percentage of patients with HIV-1 RNA <50 copies/mL, based on subgroup analysis according to patient characteristics (Week 48, FAS)

	GS-US-380-1489		GS-US-380-1490	
	BIC/FTC/TAF	DTG/ABC/3TC	BIC/FTC/TAF	DTG + FTC/TAF
Baseline HIV-1 RNA				
≤100,000 copies/mL	93.5% (244/261)	93.6% (248/265)	90.2% (229/254)	92.6% (251/271)
>100,000 copies/mL	86.8% (46/53)	90.0% (45/50)	86.4% (57/66)	94.4% (51/54)
Baseline CD4+ cell count				
<200/μL	83.3% (30/36)	81.3% (26/32)	95.5% (42/44)	100% (34/34)
≥200/μL	93.5% (260/278)	94.3% (267/283)	88.4% (244/276)	92.1% (268/291)
Age				
<50	91.2% (250/274)	93.4% (256/274)	89.8% (237/264)	92.5% (246/266)
≥50	100% (40/40)	90.2% (37/41)	87.5% (49/56)	94.9% (56/59)
Sex				
Male	92.3% (263/285)	93.3% (263/282)	90.0% (252/280)	93.8% (270/288)
Female	93.1% (27/29)	90.9% (30/33)	85.0% (34/40)	86.5% (32/37)
Race				
Black	91.2% (104/114)	93.8% (105/112)	85.6% (83/97)	92.0% (92/100)
Non-black	92.9% (184/198)	92.6% (188/203)	91.0% (203/223)	93.3% (210/225)
Country/Region				
US	93.0% (212/228)	92.7% (216/233)	87.0% (168/193)	92.2% (178/193)
Other regions	90.7% (78/86)	93.9% (77/82)	92.9% (118/127)	93.9% (124/132)

PMDA's view:

The foreign phase III studies (Studies GS-US-380-1489 and GS-US-380-1490) in treatment-naïve adult patients with HIV-1 infection were conducted using the regimens for treatment-naïve patients recommended by the US clinical practice guideline (Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV [United States Department of Health and Human Services (US DHHS)])[45] and by the Japanese clinical practice guideline (Guideline for anti-HIV therapy). Both studies demonstrated the non-inferiority of BIC/FTC/TAF to the control regimen in terms of the primary endpoint. The efficacy of BIC/FTC/TAF is therefore promising in treatment naïve adult patients with HIV-1 infection. In the subgroup with baseline HIV-1 RNA >100,000 copies/mL, the percentage of patients with HIV RNA <50 copies/mL at Week 48 tended to be lower in the BIC/FTC/TAF group than in the control group. However, PMDA accepts the explanation of the prior assessment requestor that the difference was partly due to the limited number of patients with baseline HIV-1 RNA >100,000 copies/mL. The efficacy of BIC/FTC/TAF is therefore promising in patients with HIV-1 RNA >100,000 copies/mL as well.

7.R.1.2 Efficacy in adult patients with HIV-1 infection who were virologically suppressed on anti-HIV therapy

The explanation of the prior assessment requestor about the efficacy of BIC/FTC/TAF in adult patients with HIV-1 infection who were virologically suppressed on a stable anti-HIV therapy for more than 3 or 6 months:

[45] https://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf (last accessed on November 1, 2018)

Table 46 shows the efficacy data from the foreign phase III studies (Studies GS-US-380-1844 and GS-US-380-1878 [see Sections 7.2.3 and 7.2.4]) in adult patients with HIV-1 infection who were virologically suppressed on anti-HIV therapy.[46)] The primary endpoint of this the studies was the percentage of patients with virologic failure at Week 48. The upper limit of the 95.002% CI of the difference in the percentage of such patients between the BIC/FTC/TAF group and the control group fell below the pre-specified non-inferiority margin (4%) in both studies, demonstrating the non-inferiority of BIC/FTC/TAF to the baseline regimen.

Table 46. Efficacy in patients[a)] who were virologically suppressed on anti-HIV therapy (Week 48, FAS)

	GS-US-380-1844		GS-US-380-1878	
	BIC/FTC/TAF	DTG/ABC/3TC (SBR)	BIC/FTC/TAF	PI + NRTI (SBR)[e)]
Percentage of patients with virologic failure (n/N)[b),c)]	1.1% (3/282)	0.4% (1/281)	1.7% (5/290)	1.7% (5/287)
Between-group difference [95.002% CI][b),d)]	0.7% [−1.0%, 2.8%]		−0.0% [−2.5%, 2.5%]	
Percentage of patients with HIV-1 RNA <50 copies/mL (n/N)[b)]	93.6% (264/282)	95.0% (267/281)	92.1% (267/290)	88.9% (255/287)

a) In Study GS-US-380-1844, patients who remained virologically suppressed for ≥3 months on the DTG/ABC/3TC regimen.
In Study GS-US-380-1878, patients who remained virologically suppressed for ≥6 months on RTV or COBI, PI (ATV or DRV) and NRTI (FTC/TDF or ABC/3TC) combination regimen.
b) Missing data were treated according to the FDA-defined snapshot algorithm.
c) Patients who met any of the following 3 criteria: (a) HIV-1 RNA ≥50 copies/mL at Week 48, (b) treatment discontinuation due to a lack of efficacy, or (c) patients who discontinued the treatment for reasons other than a lack of efficacy and had HIV-1 RNA ≥50 copies/mL at the final test.
d) Calculated by unconditional exact method. It had been planned to consume the significance level α by 0.00001 in each interim analysis at Week 12 and 24, resulting in a significance level of 0.04998 in the final analysis, with the resultant CI being 95.002%.
e) RTV or COBI + PI (ATV or DRV) + NRTI (FTC/TDF or ABC/3TC) combination regimen

Table 47 shows the efficacy classified by patient characteristics. No particular tendency was observed in the efficacy.

Table 47. Percentage of patients with HIV-1 RNA <50 copies/mL, based on subgroup analysis according to patient characteristics (Week 48, FAS)

	GS-US-380-1844		GS-US-380-1878	
	BIC/FTC/TAF	DTG/ABC/3TC (SBR)	BIC/FTC/TAF	PI + NRTI (SBR)
Age				
<50	94.9% (150/158)	94.4% (167/177)	91.5% (150/164)	88.0% (154/175)
≥50	91.9% (114/124)	96.2% (100/104)	92.9% (117/126)	90.2% (101/112)
Sex				
Male	93.1% (230/247)	96.0% (242/252)	93.0% (226/243)	88.9% (208/234)
Female	97.1% (34/35)	86.2% (25/29)	87.2% (41/47)	88.7% (47/53)
Race				
Black	94.9% (56/59)	93.5% (58/62)	89.9% (71/79)	84.7% (61/72)
Non-black	93.3% (208/223)	95.4% (206/216)	92.9% (196/211)	90.2% (194/215)
Country/Region				
US	95.1% (193/203)	95.5% (189/198)	92.2% (153/166)	88.4% (145/164)
Other regions	89.9% (71/79)	94.0% (78/83)	91.9% (114/124)	89.4% (110/123)

PMDA asked the prior assessment requestor to explain whether the previous anti-HIV therapy may affect the efficacy of BIC/FTC/TAF.

The explanation of the prior assessment requestor:

[46)] Study GS-US-380-1844, Anti-HIV therapy with the DTG/ABC/3TC regimen
Study GS-US-380-1878, Anti-HIV therapy with combination regimen of RTV or COBI + PI (ATV or DRV) + NRTI (FTC/TDF or ABC/3TC)

Regimens pre-specified as anti-HIV therapy used before switching to BIC/FTC/TAF FDC were DTG/ABC/3TC regimen in Study GS-US-380-1844 and RTV or COBI + PI (ATV or DRV) + NRTI (FTC/TDF or ABC/3TC) combination regimen[47] in Study GS-US-380-1878. Efficacy after switching to BIC/FTC/TAF FDC was observed in both studies, as shown in Table 46. In the ongoing clinical studies, efficacy data were similar between the BIC/FTC/TAF group and the SBR group (patients[48] with HIV-1 infection who had remained virologically suppressed on one of the EVG/COBI/FTC/TAF, EVG/COBI/FTC/TDF, and ATV + RTV + FTC/TDF regimens for ≥3 months). Specifically, the percentage of patients who were virologically suppressed at Week 48 after switching to the BIC/FTC/TAF FDC was 95.7% (224 of 234 subjects), and the percentage of patients with virological success in the SBR group was 95.3% (225 of 236 subjects). Thus, the above clinical studies demonstrated favorable efficacy of BIC/FTC/TAF in patients who switched to the BIC/FTC/TAF FDC from other anti-HIV therapies, including multiple regimens recommended by the Japanese guideline for anti-HIV treatment.

Study GS-US-380-1844 enrolled patients who were virologically suppressed on a stable anti-HIV therapy for ≥3 months before switching to the BIC/FTC/TAF FDC, whereas in Study GS-US-380-1878, patients required virological suppression of ≥6 months. PMDA therefore asked the prior assessment requestor to explain whether this difference may affect the efficacy of BIC/FTC/TAF.

The explanation of the prior assessment requestor:
No detailed information was available on how long individual subjects remained virologically suppressed before participation in the clinical studies of BIC/FTC/TAF FDC. Therefore, it was impossible to conduct a subgroup analysis classified by the duration of virological suppression. However, there was no difference in the percentage of patients with virologic failure at Week 48 between the BIC/FTC/TAF group and the control group of Studies GS-US-380-1844 and GS-US-380-1878 (see Table 46). Also, no new resistance mutations to the study drug were detected in either study. The ongoing clinical studies also includes patients with HIV-1 infection who were virologically suppressed on a stable therapy with EVG/COBI/FTC/TAF, EVG/COBI/FTC/TDF, or ATV + RTV + FTC/TDF regimen for ≥3 months, and efficacy has been demonstrated. No data after Week 48 were available from any of the clinical studies so far conduced.

Based on the design and efficacy results of the clinical studies as shown above, the efficacy of the BIC/FTC/TAF FDC should be promising in patients who were virologically suppressed on a stable anti-HIV therapy for ≥3 months before switching to BIC/FTC/TAF FDC.

PMDA's view:
The primary efficacy endpoint results were evaluated for the foreign phase III studies (Studies GS-US-380-1844 and GS-US-380-1878) conducted in adult patients with HIV-1 infection who were virologically suppressed on anti-HIV therapy, and the non-inferiority of BIC/FTC/TAF to the baseline

47) The breakdown of baseline anti-HIV therapy was as follows: ATV + FTC/TDF regimen (105 patients in the BIC/FTC/TAF group, 110 patients in the PI + NRTI [SBR] group), ATV + ABC/3TC regimen (21 patients in the BIC/FTC/TAF group, 23 patients in the PI + NRTI [SBR] group), DRV + FTC/TDF regimen (140 patients in the BIC/FTC/TAF group, 133 patients in the PI + NRTI [SBR] group), and DRV + ABC/3TC regimen (24 patients in the BIC/FTC/TAF group, 21 patients in the PI + NRTI [SBR] group).
48) Baseline anti-HIV therapy regimens before randomization: EVG/COBI/FTC/TAF regimen (249 patients), EVG/COBI/FTC/TDF regimen (197 patients), and ATV + RTV + FTC/TDF regimen (24 patients)

regimen as the control regimen was demonstrated by the study data. Therefore, the efficacy of BIC/FTC/TAF is promising in adult patients with HIV-1 infection who are virologically suppressed on a stable anti-HIV therapy.

PMDA also confirmed that the efficacy of BIC/FTC/TAF was demonstrated in the clinical studies which investigated switching from different regimens to BIC/FTC/TAF FDC.

Although no detailed information is available on the efficacy in subgroup analysis according to the duration of sustained virological suppression, the efficacy of BIC/FTC/TAF did not differ between Study GS-US-380-1844 enrolling patients who had remained virologically suppressed for ≥3 months and Study GS-US-380-1878 in patients with ≥6-month sustained virological suppression. In addition, given that the indication of BIC/FTC/TAF FDC approved in the US allows the administration of therapy in patients who are virologically suppressed for "at least 3 months" on a stable anti-HIV therapy, BIC/FTC/TAF FDC is indicated for the treatment of patients who are virologically suppressed for ≥3 months. The explanation of prior assessment requestor is acceptable.

Because of the limited information available from the clinical studies, post-marketing information should be collected from adult patients with HIV-1 infection who were virologically suppressed on a stable anti-HIV therapy before switching to BIC/FTC/TAF FDC. The information to be collected should include information on previous treatment (including the duration of treatment) and the long-term efficacy of BIC/FTC/TAF FDC. Any new findings should be communicated appropriately to healthcare professional, as necessary.

7.R.1.3 Emergence of resistance mutations and effect on efficacy

The explanation of the prior assessment requestor about the emergence of resistance mutations in the foreign phase III studies (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878):

In the foreign phase III studies, BIC/FTC/TAF FDC was administered to a total of 1206 patients, of whom 13 patients were subjected to resistance analysis.[49)] No new resistance mutations to INSTI, PI, NNRTI, or NRTI were detected in any of these patients after treatment with BIC/FTC/TAF FDC. Table 48 shows the efficacy of BIC/FTC/TAF FDC in subgroups classified by the presence/absence of main resistance mutations to INSTI, PI, NNRTI, or NRTI (*Top Antivir Med.* 2017;24:132-41) at baseline in foreign phase III studies. Presence or absence of resistance mutations at baseline did not have any clear effect on the efficacy of BIC/FTC/TAF FDC.

[49)] Patients who met any of the following criteria were subjected to resistance analysis: (1) Patients who experienced virologic rebound (a rebound in HIV-1 RNA to ≥50 copies/mL after having achieved HIV-1 RNA <50 copies/mL, or an increase of ≥1 $1og_{10}$), (2) patients with HIV-1 RNA ≥50 copies/mL at study drug discontinuation or at Week 48, and (3) patients with HIV-1 RNA ≥200 copies/mL. Of the 13 patients subjected to resistance analysis, 2 patients were ineligible for resistance analysis because HIV-1 RNA level was too low, and another 2 patients did not provide results because of the failure in the test for resistance mutation.

Table 48. Percentage of patients with HIV-1 RNA <50 copies/mL in subgroups classified by presence or absence of resistance mutations at baseline (Week 48, FAS)

	GS-US-380-1489		GS-US-380-1490		GS-US-380-1844		GS-US-380-1878	
	BIC/FTC/TAF	DTG/ABC/3TC	BIC/FTC/TAF	DTG + FTC/TAF	BIC/FTC/TAF	DTG/ABC/3TC (SBR)	BIC/FTC/TAF	PI + NRTI (SBR)
Overall	92.4 (290/314)	93.0 (293/315)	89.4 (286/320)	92.9 (302/325)	90.7 (127/140)	97.1 (134/137)	99.3 (133/141)	86.4 (108/125)
Primary INSTI resistance mutation[a)]								
Yes	100 (3/3)	75.0 (3/4)	100 (3/3)	100 (6/6)	0	1/2	1/1	0
No	92.3 (287/311)	93.2 (289/310)	89.8 (282/314)	93.0 (294/316)	80.0 (16/20)	100 (11/11)	66.7 (4/6)	64.3 (9/14)
Secondary INSTI resistance mutation[b)]								
Yes	92.6 (138/149)	92.1 (140/152)	90.9 (160/176)	94.3 (149/158)	69.2 (9/13)	100 (5/5)	100 (3/3)	66.7 (4/6)
No	92.1 (152/165)	93.8 (152/162)	88.7 (125/141)	92.1 (151/164)	100 (7/7)	87.5 (7/8)	50.0 (2/4)	62.5 (5/8)
Primary NRTI resistance mutation[c)]								
Yes	100 (6/6)	100 (5/5)	80.0 (8/10)	80.0 (4/5)	2/2	100 (4/4)	87.5 (7/8)	80.0 (8/10)
No	92.2 (284/308)	92.9 (288/310)	89.7 (278/310)	93.1 (298/320)	90.6 (125/138)	97.0 (130/134)	94.7 (126/133)	87.0 (100/115)
Primary NNRTI resistance mutation[d)]								
Yes	94.4 (34/36)	94.1 (48/51)	85.0 (34/40)	92.7 (38/41)	92.3 (12/13)	100 (13/13)	100 (29/29)	76.9 (20/26)
No	92.1 (256/278)	92.8 (245/264)	90.0 (252/280)	93.0 (264/284)	90.6 (115/127)	96.8 (121/125)	92.9 (104/112)	88.9 (88/99)
Primary PI resistance mutation[e)]								
Yes	91.7 (11/12)	90.9 (10/11)	100 (4/4)	100 (10/10)	100 (6/6)	100 (5/5)	100 (6/6)	100 (5/5)
No	92.4 (279/302)	93.1 (283/304)	89.2 (282/316)	92.7 (292/315)	90.3 (121/134)	97.0 (129/133)	94.1 (127/135)	85.8 (103/120)

% (n/N) [the denominator is the number of patients who provided the results of the test for resistance mutation at the pertinent site at baseline]
a) T66I/A/K, E92Q/G, T97A, F121Y, Y143R/H/C, S147G, Q148H/K/R, N155H/S, R263K; b) 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; c) M41L, K65R/E/N, D67N, T69 insertion, K70E/R, L74V/I, Y115F, Q151M, M184V/I, L210W, T215Y/F, K219E/Q/N/R; d) 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; e) D30N, V32I, M46I/L, I47V/A, G48V, I50V/L, I54M/L, Q58E, T74P, L76V, V82A/F/L/S/T, N83D, I84V, N88S, L90M

PMDA confirmed that, in the clinical studies of BIC/FTC/TAF FDC, no new resistance mutations were detected in adult patients with HIV-1 infection who were treatment-naïve, or those who were virologically suppressed on anti-HIV therapy. PMDA also confirmed that there were no particular concerns about the efficacy in the subgroups classified by the presence or absence of resistance mutation at baseline.

However, given that multiple mutations associated with reduced susceptibility to BIC were noted in some *in vitro* studies [see Section 3.R.1] and that only limited information is available on the resistance mutation in patients treated with BIC/FTC/TAF FDC, post-marketing information on resistance mutation should be collected continuously and any new findings should be communicated to healthcare professionals, as appropriate.

7.R.2 Safety

Based on the reviews presented in the subsections below, PMDA concluded that the safety of BIC/FTC/TAF FDC in adult patients with HIV-1 infection who are treatment-naive, or those who are virologically suppressed on anti-HIV therapy is acceptable. However, since no information is currently available on the use of BIC/FTC/TAF FDC in Japanese patients, post-marketing information on the

safety of BIC/FTC/TAF FDC should be collected continuously and any new findings should be communicated appropriately to healthcare professionals.

The above conclusions of PMDA will be discussed at the Prior Assessment Meeting.

7.R.2.1 Outline of safety

The explanation of the prior assessment requestor about the outline of the safety of BIC/FTC/TAF FDC in adult patients with HIV-1 infection:

Table 49 shows the outline of safety in the foreign phase III studies (pooled data of Studies GS-US-380-1489 and GS-US-380-1490, Studies GS-US-380-1844 and GS-US-380-1878). The incidences of adverse events, Grade ≥3 adverse events, serious adverse events, adverse events leading to treatment discontinuation, and death were similar between the BIC/FTC/TAF group and the control group in each study. There were no noteworthy findings among major adverse events observed in the BIC/FTC/TAF group [see Section 7.2]. There were no noteworthy events in the foreign phase II study either (Study GS-US-141-1475; see Section 7.1.1).

The 4 foreign phase III studies included 28 patients co-infected with HIV and HBV at baseline (16 in the BIC/FTC/TAF group) and 25 patients co-infected with HIV and HCV (10 in the BIC/FTC/TAF group). Adverse events specific to these patient populations were increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST), and Grade ≥3 changes in these parameters were observed in 2 patients co-infected with HIV and HBV and 2 patients co-infected with HIV and HCV. These events were considered to be due to co-infection with HBV or HCV. Other safety profiles were generally similar between the patient population with co-infection and the patient population without co-infection. The caution will be advised on the discontinuation of BIC/FTC/TAF FDC in patients complicated with chronic hepatitis B virus infection and monitoring for adverse drug reactions in patients co-infected with HBV, as are the cases with other products containing FTC/TAF.

Thus, the safety and tolerability of BIC/FTC/TAF FDC in adult patients with HIV-1 infection are considered to be generally favorable.

Table 49. Outline of safety in foreign phase III studies
(Week 48, safety analysis set)

	Treatment naïve patients			Patients who were virologically suppressed on anti-HIV therapy			
	GS-US-380-1489 + GS-US-380-1490	GS-US-380-1489	GS-US-380-1490	GS-US-380-1844		GS-US-380-1878	
	BIC/FTC/TAF (N = 634)	DTG/ABC/3TC (N = 315)	DTG + FTC/TAF (N = 325)	BIC/FTC/TAF (N = 282)	DTG/ABC/3TC (SBR) (N = 281)	BIC/FTC/TAF (N = 290)	PI + NRTI (SBR) (N = 287)
Adverse events	529 (83.4)	283 (89.8)	272 (83.7)	225 (79.8)	225 (80.1)	233 (80.3)	226 (78.7)
Grade ≥3 adverse events[a)]	56 (8.8)	24 (7.6)	25 (7.7)	16 (5.7)	10 (3.6)	13 (4.5)	18 (6.3)
Adverse drug reactions	139 (21.9)	127 (40.3)	83 (25.5)	23 (8.2)	44 (15.7)	54 (18.6)	6 (2.1)
Serious adverse events	58 (9.1)	25 (7.9)	23 (7.1)	15 (5.3)	22 (7.8)	17 (5.9)	20 (7.0)
Adverse events leading to treatment 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)

n (%)
a) Grades were classified according to GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities

PMDA's view:
In the foreign clinical studies in adult patients with HIV-1 infection, the safety profile of BIC/FTC/TAF was not significantly different from that of the control regimen in each study, and thus the safety of BIC/FTC/TAF is acceptable. Since there is no information on the use of BIC/FTC/TAF FDC in Japanese patients, post-marketing information on the safety of BIC/FTC/TAF FDC should be collected continuously and any new findings should be communicated appropriately to healthcare professionals.

The caution should be advised on the effect of BIC/FTC/TAF on renal function and bone mineral density, as are the cases with approved TAF-containing products.

Effects of BIC/FTC/TAF on the neuropsychiatric system, safety profile in patients co-infected with HBV or HCV, and on congenital anomaly (neural tube defect) in newborns are discussed in the following sections.

7.R.2.2 Effect on neuropsychiatric system

The explanation of the prior assessment requestor about the effect of BIC/FTC/TAF on the neuropsychiatric system, taking account of adverse events related to the neuropsychiatric system reported in patients treated with DTG (*BMC Infect Dis*. 2017;17:622):
Table 50 shows the incidences of adverse events[50)] coded to nervous system disorders or psychiatric disorders and adverse events[51)] coded to suicide/self-injury in the foreign phase III studies (Studies GS-US-380-1489, GS-US-380-1490, GS-US-380-1844, and GS-US-380-1878). The incidence of adverse events coded to nervous system disorders or psychiatric disorders was similar between the BIC/FTC/TAF group and the DTG-based regimen group as the control group in Studies GS-US-380-1489, GS-US-380-1490, and GS-US-380-1844. In Study GS-US-380-1878, the adverse events tended to occur more frequently in the BIC/FTC/TAF group than in the control group, but the incidence was comparable to that in the BIC/FTC/TAF group of other studies.

[50)] Events coded to the SOC "nervous system disorders" or "psychiatric disorders" of MedDRA ver. 19.1.
[51)] Events coded to the SMQ "suicide/self-injury" of MedDRA ver. 19.1.

Table 50. Adverse events (those reported by ≥1% of patients in the BIC/FTC/TAF group) coded to nervous system disorders or psychiatric disorders and adverse events coded to suicide/self-injury

	Treatment naïve patients		Patients who were virologically suppressed on anti-HIV therapy			
	GS-US-380-1489 and GS-US-380-1490		GS-US-380-1844		GS-US-380-1878	
	BIC/FTC/TAF (N = 634)	DTG-based regimen (N = 640)	BIC/FTC/TAF (N = 282)	DTG/ABC/3TC (SBR) (N = 281)	BIC/FTC/TAF (N = 290)	PI + NRTI (SBR) (N = 287)
All nervous system disorders and psychiatric disorders	195 (30.8)	219 (34.2)	62 (22.0)	87 (31.0)	108 (37.2)	49 (17.1)
Headache	76 (12.0)	83 (13.0)	19 (6.7)	21 (7.5)	35 (12.1)	12 (4.2)
Insomnia	30 (4.7)	34 (5.3)	8 (2.8)	14 (5.0)	10 (3.4)	6 (2.1)
Anxiety	16 (2.5)	26 (4.1)	2 (0.7)	4 (1.4)	10 (3.4)	5 (1.7)
Dizziness	19 (3.0)	26 (4.1)	6 (2.1)	6 (2.1)	9 (3.1)	2 (0.7)
Depression	23 (3.6)	21 (3.3)	3 (1.1)	10 (3.6)	4 (1.4)	4 (1.4)
Abnormal dreams	11 (1.7)	13 (2.0)	2 (0.7)	7 (2.5)	3 (1.0)	0
Sleep disorder	8 (1.3)	10 (1.6)	2 (0.7)	0	0	2 (0.7)
Paraesthesia	8 (1.3)	7 (1.1)	2 (0.7)	4 (1.4)	9 (3.1)	2 (0.7)
Depressed mood	11 (1.7)	3 (0.5)	0	1 (0.4)	2 (0.7)	0
Libido decreased	6 (0.9)	6 (0.9)	3 (1.1)	2 (0.7)	1 (0.3)	1 (0.3)
Syncope	3 (0.5)	4 (0.6)	3 (1.1)	1 (0.4)	1 (0.3)	0
Somnolence	5 (0.8)	9 (1.4)	0	2 (0.7)	3 (1.0)	0
Neuropathy peripheral	2 (0.3)	4 (0.6)	0	3 (1.1)	3 (1.0)	2 (0.7)
Dysgeusia	1 (0.2)	1 (0.2)	0	1 (0.4)	3 (1.0)	0
Suicide/self-injury (SMQ)	7 (1.1)	5 (0.8)	3 (1.1)	1 (0.4)	0	1 (0.3)

n (%)

Most of nervous system disorders and psychiatric disorders reported in the BIC/FTC/TAF group were Grade 1 or 2 and non-serious. Serious adverse events for which a causal relationship to BIC/FTC/TAF could not be ruled out were observed in 5 patients (generalised tonic-clonic seizure, chest pain, suicide attempt, cerebrovascular accident, and schizophrenia in 1 patient each), but their outcome was reported as resolved, except for suicidal attempt which persisted.

Data from the foreign phase III studies (Studies GS-US-380-1489 and GS-US-380-1490) were analyzed to compare exposure to BIC (AUC_{tau} and C_{max}) between patients who had any of headache, insomnia, anxiety, dizziness, and depression and those who did not. No clear relationship was observed between the BIC exposure and the onset of each event. Most of the patients in the BIC/FTC/TAF group who showed adverse events coded to suicide/self-injury had had a history of depression or other mental disorders before the start of treatment with BIC/FTC/TAF FDC, suggesting that there is no evidence of a relationship between BIC/FTC/TAF FDC and the risk of suicide.

PMDA's view:

The results of the foreign phase III studies showed that the risk of adverse events coded to nervous system disorders or psychiatric disorders, associated with the use of BIC/FTC/TAF FDC, was not greater than the risk of adverse events associated with DTG-based regimens. There is currently no evidence of a relationship between BIC/FTC/TAF FDC and the risk of suicide. On the other hand, there is literature reporting that study data suggested a relationship between blood DTG concentrations and the onset of neuropsychiatric disorder-related events (*BMC Infect Dis.* 2017;17:622) and that discontinuation of DTG due to neuropsychiatric disorder-related events occurred more frequently in women and elderly patients (*HIV Med.* 2017;18:56-63). Because of the limited data available from the

clinical studies, post-marketing information on the effect of BIC/FTC/TAF on the neuropsychiatric system should be collected continuously, and any new findings should be communicated appropriately to healthcare professionals.

7.R.2.3 Effect on congenital anomaly (neural tube defect) in the offspring

Signals suggesting neural tube defect were reported among newborns to mothers receiving DTG-based products. The overseas guidelines[52)] recommend, as a tentative measure, not to initiate the use of DTG in patients who are planning to become pregnant or patients who are within 8 weeks from the last menstruation. Taking account of the above issue, PMDA asked the prior assessment requestor to explain the potential risk of congenital anomaly (neural tube defect) in newborns exposed to BIC/FTC/TAF.

The explanation of the prior assessment requestor:
The outcome of pregnancy has so far been reported in 17 patients receiving BIC/FTC/TAF FDC (cumulative data as of May 31, 2018). Spontaneous abortion was reported in 7 of them, and the 7 patients were found to have been exposed to BIC/FTC/TAF before pregnancy. Since all of these patients were enrolled in clinical studies, the early detection of pregnancy was allowed, possibly causing a bias to the number of patients with spontaneous abortion. Of the remaining 10 patients, 4 underwent induced abortion and 6 patients gave live birth. Of the 6 newborns, 1 had patent urachus, whereas in other 5 newborns, no congenital anomalies including neural tube defect and other congenital cerebral/central nervous anomalies were reported. Foetal death was reported in 1 patient with twin pregnancy receiving BIC/FTC/TAF FDC (survival of 1 fetus and death of the other were confirmed by ultrasonography), and the pregnancy was ongoing at the time point of data cut-off. No pregnancy was reported in patients receiving BIC monotherapy.

The results of the non-clinical studies were examined. There was no evidence of central nervous toxicity or neural tube defect in animals treated with BIC in the safety pharmacology studies [see Section 3.3] or in the studies of embryo-fetal development in rats and rabbits [see Section 5.5].

Thus, despite the limited information available currently, the data so far obtained show no evidence of increased risk of adverse outcome of pregnancy, congenital anomalies such as neural tube defect, spontaneous abortion, or still birth that is related to the use of BIC-based therapy during pregnancy.

PMDA's view:
Because of the limited available information on congenital anomalies (e.g., neural tube defect) in newborns to mothers receiving BIC/FTC/TAF FDC, relevant information, including the information on drugs in the same class, should be collected continuously and, if any new information becomes available, appropriate measures should be taken.

[52)] Recommendations Regarding the Use of Dolutegravir in Adults and Adolescents with HIV who are Pregnant or of Child-Bearing Potential. US Department of Health and Human Services: 2018 (dated May 30, 2018)

7.R.3 Clinical positioning and significance of fixed dose combination

The explanation of the prior assessment requestor about the clinical positioning of BIC/FTC/TAF FDC and the significance of the fixed-dose combination:

The Japanese clinical practice guideline (Guidelines for anti-HIV therapy) recommends, as the first-line therapy for HIV infection, combination regimen with 2 backbone NRTIs and 1 key drug (INSTI, PI, or NNRTI).

The US clinical practice guideline (Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV [US DHHS])[45)] recommends the BIC/FTC/TAF FDC as one of the first-line therapies for HIV infection. The guideline allows switching from a current treatment regimen to another regimen, recommended by the guideline, in patients with no history of resistance to anti-HIV drugs who are virologically suppressed on the current regimen.

Because treatment for HIV infection takes a long time, a suitable drug should be chosen with consideration to improved compliance, safety, and long-term outcome. The Guidelines for anti-HIV therapy state that "once-daily administration regimen is advantageous for the maintenance of compliance, and should be selected in preference in patients who newly start anti-HIV therapy." BIC/FTC/TAF FDC is a fixed-dose combination drug containing INSTI (BIC) and NRTIs (FTC and TAF), and its dosage is one tablet taken QD. The BIC/FTC/TAF FDC is thus expected to provide benefits such as improved compliance, decreased risk of emergence of resistance-associated viruses, and increased convenience for patients.

Based on the above, the prior assessment requestor considers that as is the case in foreign countries, BIC/FTC/TAF FDC can serve as one of the treatment options for patients with HIV-1 infection who have no history of anti-HIV therapy or those who are virologically suppressed on anti-HIV therapy and have no mutation associated with resistance to any component of BIC/FTC/TAF FDC.

PMDA's view:

On the basis of the reviews presented in Sections 7.R.1 and 7.R.2 and given the recommendations in the guidelines available in and outside of Japan, BIC/FTC/TAF FDC is expected to serve as one of the treatment options for patients with HIV-1 infection who have no history of anti-HIV therapy or those who are virologically suppressed on anti-HIV therapy and have no mutations associated with resistance to BIC/FTC/TAF, as are the cases with anti-HIV drugs recommended by the Guidelines for anti-HIV therapy.

7.R.4 Indication

As a result of the reviews presented in Sections 7.R.1 and 7.R.2, PMDA considers that the efficacy of BIC/FTC/TAF FDC is promising in patients with HIV-1 infection with acceptable safety profile, and has therefore concluded that the proposed indication of BIC/FTC/TAF FDC ("HIV-1 infection") is acceptable. PMDA also considers, based on the reviews presented in Sections 7.R.1.1 and 7.R.1.2, that Physicians should be advised that the following patients be eligible for the treatment with BIC/FTC/TAF FDC:

- Patients with no history of anti-HIV treatment

- Patients who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a current anti-HIV regimen for ≥3 months (before switching) with no history of virologic failure and no known mutations associated with resistance to BIC, FTC, or TFV.

The above conclusions of PMDA will be discussed at the Prior Assessment Meeting.

7.R.5 Dosage and administration

Based on the reviews of the efficacy, safety, rationale for the dosage regimen, and the effect of food [see Sections 7.R.1, 7.R.2, 6.R.1, and 6.R.2], PMDA has concluded that the intended dosage and administration ("one Biktarvy tablet taken orally once daily") is acceptable.

The above conclusions of PMDA will be discussed at the Prior Assessment Meeting.

7.R.6 Post-marketing investigations

The prior assessment requestor plans to participate in the joint HIV-related drugs (HRD) surveillance[53] and to conduct a use-results survey as an all-case surveillance, as follows:

- Objective: To collect information on the safety and efficacy of BIC/FTC/TAF FDC in clinical use
- Planned sample size: All patients available for collection of information in each surveillance facility

The prior assessment requestor also plans to conduct a specified use-results survey to confirm the safety of BIC/FTC/TAF FDC in pregnant women and their newborns.

PMDA considers that information on the development of mutations associated with resistance to BIC/FTC/TAF should also be collected in the post-marketing setting.

The above conclusions of PMDA will be discussed at the Prior Assessment Meeting.

8. Overall Evaluation during Preparation of the Prior Assessment Report (1)

On the basis of the data submitted for prior assessment, PMDA has concluded that BIC/FTC/TAF FDC is expected to have efficacy in the treatment of patients with HIV-1 infection who have no history of anti-HIV treatment or those who are virologically suppressed on anti-HIV therapy, and BIC/FTC/TAF FDC has acceptable safety in view of its benefits. BIC/FTC/TAF FDC (Biktarvy) is a novel fixed-dose combination drug containing the new active ingredient BIC and approved active ingredients FTC and TAF. Biktarvy can serve as a treatment option for patients with HIV-1 infection, and is thus of clinical significance.

PMDA has concluded that Biktarvy may be approved if Biktarvy is not considered to have particular problems based on comments from the Prior Assessment Meeting.

[53] A surveillance conducted jointly by marketing authorization holders of anti-HIV drugs to investigate the safety and efficacy of anti-HIV drugs in the post-marketing setting.

Review Report (1)

February 5, 2019

Product Submitted for Approval

Brand Name	Biktarvy Combination Tablets
Non-proprietary Name	Bictegravir Sodium/Emtricitabine/Tenofovir Alafenamide Fumarate
Applicant	Gilead Sciences K.K.
Date of Application	December 14, 2018

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Prior Assessment Meeting and the Expert Discussion, and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Prior Assessment Meeting and the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Prior Assessment Meeting and the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Prior Assessment Report (1) (Sections "7.R.1 Efficacy," "7.R.3 Clinical positioning and significance of fixed-dose combination," "7.R.4 Indication," "7.R.5 Dosage and administration," and "7.R.6 Post-marketing investigations").

PMDA conducted additional reviews on the following matters and took appropriate measures.

1.1 Effect on congenital anomaly (neural tube defect) in newborns

The expert advisors raised the following comments on Section "7.R.2.3 Effect on congenital anomaly (neural tube defect) in newborns" in "7.R.2 Safety" of the Prior Assessment Report (1):

- In the foreign phase III study (Study GS-US-380-1489), spontaneous abortion was reported only in the BIC/FTC/TAF group (1 patient) as a serious adverse event for which a causal relationship to the study drug could not be ruled out. This should be a matter of concern.

- A signal of neural tube defect was reported in newborns to mothers receiving a product containing DTG, a drug in the same class of BIC. The foreign guideline[54)] tentatively recommends not to administer DTG to patients who are planning to become pregnant and patients in the first trimester (within 14 weeks from the last menstruation). In view of the seriousness of the event, this information should be provided in the package insert.

Based on the comments raised in the Prior Assessment Meeting and the Expert Discussion and on the explanation of the applicant, PMDA instructed the applicant to provide the information reported for DTG-based therapy in the package insert in order to inform physicians that BIC/FTC/TAF FDC potentially causes the congenital anomaly (neural tube defect), and to provide any new findings immediately to healthcare professionals. The applicant agreed to the instruction.

1.2 Risk management plan (draft)

In view of the reviews presented in Sections "7.R.1 Efficacy" and "7.R.6 Post-marketing investigations" in the Prior Assessment Report (1) and comments raised in the Prior Assessment Meeting and the Expert Discussion, PMDA considers that post-marketing surveillance should also cover the following issues and, when new findings become available, the applicant should take appropriate measures, including provision of the information to healthcare professionals:

- Efficacy of BIC/FTC/TAF FDC in treatment naïve patients with baseline HIV-1 RNA >100,000 copies/mL
- The following information on patients with a history of anti-HIV treatment:
  - Efficacy of BIC/FTC/TAF FDC, classified by previous treatment regimen (and daily dose for DTG)
  - Effect of the duration of the previous treatment regimen on the efficacy of BIC/FTC/TAF FDC (including long-term efficacy)
  - Effect of mutations associated with resistance to any INSTI on the efficacy of BIC/FTC/TAF FDC
- Development of mutations associated with resistance to BIC/FTC/TAF

PMDA instructed the applicant to address the above, to which the applicant agreed.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for BIC/FTC/TAF FDC should include the safety and efficacy specifications presented in Table 51, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 52 and 53.

54) Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. Developed by the HHS Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission – A Working Group of the Office of AIDS Research Advisory Council (OARAC) (Last updated December 7, 2018)

Table 51. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Immune reconstitution inflammatory syndrome • Nephrotoxicity • Bone-related events/decreased bone density • Hepatitis flare after discontinuation of BIC/FTC/TAF FDC in patients co-infected with HIV-1/HBV • Lactic acidosis and severe hepatomegaly	• Pancreatitis • Redistribution/accumulation of body fat • Interactions mediated by OCT2 and MATE1 transporters that are involved in renal excretion	• Long-term use • Safety in pregnant women • Safety in Japanese patients with HIV-1 infection
Efficacy specification		
• Efficacy in Japanese patients with HIV-1 infection • Long-term efficacy (including the emergence of drug resistance and cross resistance)		

Table 52. Summary of additional pharmacovigilance activities, efficacy surveillance and studies, and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Survey and study on efficacy	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey (all-case surveillance) • Specified use-results survey (pregnant women)	• General use-results survey (all-case surveillance)	• Early post-marketing phase vigilance

Table 53. Outline of post-marketing surveillance plan (draft)

General use-results survey (all-case surveillance)	
Objective	To confirm the safety and efficacy of Biktarvy in clinical practice
Survey method	All-case surveillance by participation in joint HRD surveillance[a)]
Population	Japanese patients with HIV-1 infection
Observation period	The surveillance will be started on the day of marketing of Biktarvy and will be continued for 9 years from the date of marketing authorization
Planned sample size	All patients available for data collection
Main survey items	Patient characteristics, use of Biktarvy, past history of treatment with anti-HIV drugs, use of concomitant drugs, adverse events, and efficacy
Specified use-results survey (pregnant women)	
Objective	To confirm the safety of Biktarvy in pregnant women and newborns in clinical practice
Survey method	To be conducted as joint HRD survey[a)]
Population	Japanese patients with HIV-1 infection in whom the outcome of pregnancy is confirmed.
Observation period	From the day of marketing of Biktarvy until the end of the re-examination period (newborns will be followed up for 1 year)
Planned sample size	All patients receiving Biktarvy and available for confirmation of the outcome of pregnancy
Main survey items	Pregnant women: Patient characteristics, anti-HIV drugs prescribed, concomitant drugs prescribed, concomitant therapies, delivery conditions, patient outcome (if the survey is discontinued), abnormal changes in laboratory values, adverse events, efficacy Newborns: Characteristics of newborns, drugs prescribed, anti-HIV antibody, HIV-RNA level, CD4 count, CDC classification, time-course changes in height and weight, abnormal changes in laboratory test values, adverse events

a) A surveillance jointly conducted by marketing authorization holders of anti-HIV drugs to investigate the safety and efficacy of anti-HIV drugs in the post-marketing setting.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following conditions. Because (i) the product was designated as an orphan drug with the indication proposed in the present application and (ii) it is a drug with a new active ingredient and a new prescription fixed-dose combination drug, the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. The drug substance bictegravir sodium is not classified as a poisonous drug or a powerful drug, but the drug product is classified as a powerful drug.

Indication

Human immunodeficiency virus type 1 (HIV-1) infection

Dosage and Administration

The usual adult dosage is 1 tablet (containing 50 mg of bictegravir, 200 mg of emtricitabine, and 25 mg of tenofovir alafenamide) taken orally once daily.

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.

2. The applicant is required to request the physician to provide the patient with sufficient information and obtain the patient's informed consent prior to the use of the product. In the informed consent process, the physician should explain that collection of further data on the efficacy and safety of the product is ongoing.

3. The applicant is required to submit the data from relevant clinical studies currently ongoing or being planned overseas and the results of analyses thereof as soon as the studies are completed.

4. The applicant is required to conduct a post-marketing surveillance covering all patients treated with the product in Japan, as a general rule, until the end of the re-examination period, thereby collecting information on the use status (e.g., patient characteristics, efficacy and safety [including the efficacy and safety of the product in combination with other drugs], and drug-drug interaction data), reporting the results periodically, and submitting the results of the surveillance at the time of submission of the application for re-examination.

List of Abbreviations

3TC	Lamivudine
ABC	Abacavir
aGFR	Actual glomerular filtration rate
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATV	Atazanavir
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration versus time curve during 24 hours
AUC_{inf}	Area under plasma concentration-time curve up to infinity
AUC_{last}	Area under plasma concentration-time curve up to last quantifiable concentration
AUC_{tau}	Area under plasma concentration-time curve over the dosing interval
BA	Bioavailability
BCRP	Breast cancer resistance protein
BIC	Bictegravir
BIC/FTC/TAF FDC	Biktarvy combination tablets
BSA	Body surface area
BSEP	Bile salt export pump
CC_{50}	Concentration that resulted in 50% cytotoxicity
CL/F	Apparent total body clearance
C_{max}	Maximum plasma concentration
COBI	Cobicistat
C_{tau}	Plasma concentration at the end of the dosing interval
CYP	Cytochrome P450
DMSO	Dimethylsulfoxide
DRV	Darunavir
DTG	Dolutegravir
EC_{50}	50% effective concentration
EC_{95}	95% effective concentration
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
EVG	Elvitegravir
FAS	Full analysis set
FTC	Emtricitabine
Guidelines for Treatment of HIV-infected patients	Practice Guidelines for Treatment HIV-infected Patients (Research Group for Study on How to Conquer HIV Infection and Complications, the HIV/AIDS Control Research Project funded by the FY 2017 Health, Labour and Welfare Policy Research Grants, March 2018 edition)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IC_{50}	50% inhibitory concentration
INSTI	Integrase strand-transfer inhibitor
k_a	First order absorption rate constant
K_I	Inhibitor concentration at 50% of maximum inhibition rate
LC-UV	Liquid chromatography-ultraviolet
MATE	Multidrug and toxin extrusion protein
mRNA	Messenger RNA
NNRTI	Nonnucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
OAT	Organic anion transporter

OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
PBMC	Peripheral blood mononuclear cell
P-gp	P-glycoprotein
PI	Protease inhibitor
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPI	Proton pump inhibitor
PPK	Population pharmacokinetics
QD	quaque die
QTc	Corrected QT interval
QTcF	Fridericia-corrected QT interval
RTV	Ritonavir
$t_{1/2}$	Estimate of the terminal elimination half-life
TAF	Tenofovir alafenamide
TFV	Tenofovir
t_{max}	Time to maximum concentration
UGT	UDP glucuronosyltransferase
V/F	Apparent volume of distribution