Report on the Deliberation Results

June 1, 2016

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

Brand Name	Genvoya Combination Tablets
Non-proprietary Name	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate (JAN*)
Applicant	Japan Tobacco Inc.
Date of Application	March 4, 2016

Results of Deliberation

In the meeting held on May 30, 2016, 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 re-examination period is 10 years, the drug substance (tenofovir alafenamide fumarate) and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

Conditions for Approval

The applicant is required to:

1. Develop and appropriately implement a risk management plan;

2. Request physicians to obtain patients' informed consent to the use of the product after having thoroughly informed them that additional data on the efficacy and safety of the product are still being collected;

3. Submit the results and analyses of ongoing or planned clinical studies promptly after the study completion; and

4. Conduct a post-marketing surveillance which must, as a general rule, cover all patients treated with the product in Japan, until the expiration of the re-examination period; collect information on the use status of the product (patient characteristics, efficacy and safety [including the efficacy and safety of the product in combination with other drugs], data on drug-drug interactions); then submit periodical reports thereof; and finally submit all the surveillance results when applying re-examination.

* *Japanese Accepted Name (modified INN)*

Review Report

May 19, 2016

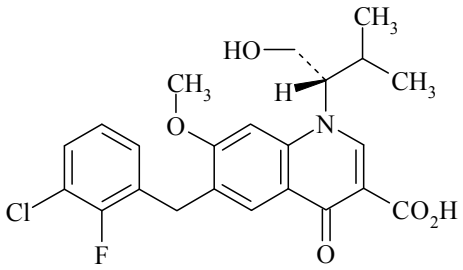
Pharmaceuticals and Medical Devices Agency

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.

Brand Name	Genvoya Combination Tablets
Non-proprietary Name	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate
Applicant	Japan Tobacco Inc.
Date of Application	March 4, 2016
Dosage form/Strength	Tablets: Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 11.2 mg of tenofovir alafenamide fumarate (10 mg as tenofovir alafenamide).
Application Classification	Prescription drug, (1) Drug with new active ingredients and (2) new combination drug

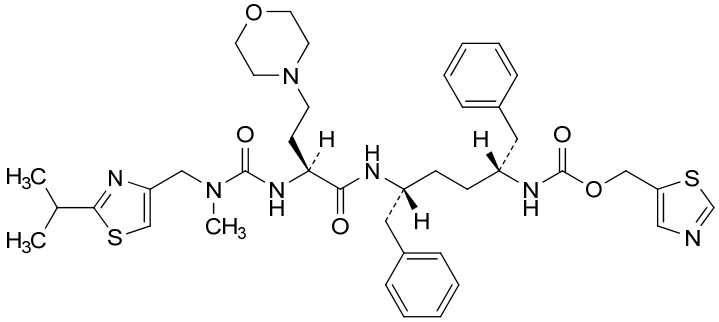
Chemical Structure

Elvitegravir



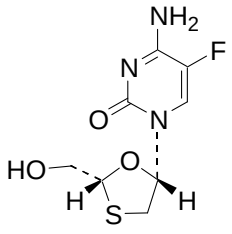
Molecular formula: $C_{23}H_{23}ClFNO_5$
Molecular weight: 447.88
Chemical name:
6-[(3-Chloro-2-fluorophenyl)methyl]-1-[(2*S*)-1-hydroxy-3-methylbutan-2-yl]-7-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

Cobicistat



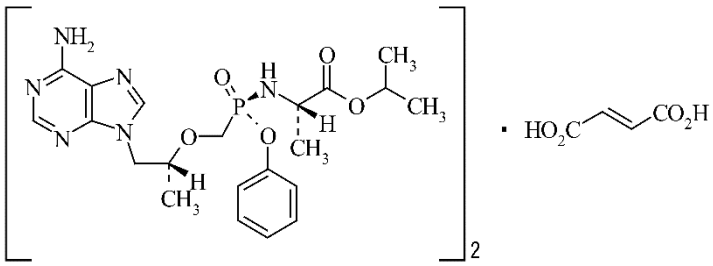
Molecular formula: $C_{40}H_{53}N_7O_5S_2$
Molecular weight: 776.02
Chemical name:
1,3-Thiazol-5-ylmethyl{(2*R*,5*R*)-5-[(2*S*)-2-(3-methyl-3-{[2-(1-methylethyl)-1,3-thiazol-4-yl]methyl}ureido)-4-(morpholin-4-yl)butanamido]-1,6-diphenylhexan-2-yl}carbamate

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 (Designation No. 290 of 2012 [24 *yaku*], Notification No. 1114-1 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 14, 2012 [elvitegravir]; Designation No. 291 of 2012, Notification No. 1114-1 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated November 14, 2012 [cobicistat]; Designation No. 172 of 2004 [16 *yaku*], Notification No. 1013001 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated October 13, 2004 [emtricitabine]; Designation No. 368 of 2015 [27 *yaku*], Notification No. 1119-1 from the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated November 19, 2015 [tenofovir alafenamide fumarate])

The product is eligible for prior assessment based on the Notification No. 1015 of 1998 from the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHW, dated November 12, 1998 (date of approval in the U.S., November 5, 2015). The current prior assessment is based on the application dossier submitted in the U.S.

Reviewing Office Office of New Drug IV

Results of Review
As shown in the Attachment, on the basis of the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with human immunodeficiency virus type 1 (HIV-1) infection has been demonstrated and its safety is acceptable in view of its observed benefits.

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.

Indication
HIV-1 infection

Dosage and Administration
The usual dosage for adults and adolescents (≥12 years of age) with body weight ≥35 kg is one tablet (containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide) administered orally once daily after a meal.

Conditions for Approval
The applicant is required to:

1. Develop and appropriately implement a risk management plan;

2. Request physicians to obtain patients' informed consent to the use of the product after having thoroughly informed them that additional data on the efficacy and safety of the product are still being collected;

3. Submit the results and analyses of ongoing or planned clinical studies promptly after the study completion; and

4. Conduct a post-marketing surveillance which must, as a general rule, cover all patients treated with the product in Japan, until the expiration of the re-examination period; collect information on the use status of the product (patient characteristics, efficacy and safety [including the efficacy and safety of the product in combination with other drugs], data on drug-drug interactions); then submit periodical reports thereof; and finally submit all the surveillance results when applying re-examination.

Attachment

Prior Assessment Report (1)

March 3, 2016

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

Product Submitted for Prior Assessment

Intended Brand Name	Genvoya Combination Tablets
Non-proprietary Name	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate
Prior Assessment Requestor	Japan Tobacco Inc.
Dosage Form/Strength	Tablets: Each tablet contains 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 11.2 mg of tenofovir alafenamide fumarate (10 mg as tenofovir alafenamide).
Intended Indication	HIV-1 infection
Intended Dosage and Administration	The usual adult dosage is one tablet (containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide) administered orally once daily after a meal. To adolescents (≥12 years of age) with body weight ≥35 kg, one tablet may be administered orally once daily after a meal.
Date of Preparatory Meeting for Prior Assessment	November 20, 2015
Items Warranting Special Mention	The product is eligible for prior assessment based on the Notification No. 1015 of 1998 from the Evaluation and Licensing Division, Pharmaceutical and Medical Safety Bureau, MHW, dated November 12, 1998 (date of approval in the U.S., November 5, 2015). The current prior assessment is based on the application dossier submitted in the U.S.

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List of Abbreviations

AhR	Aryl hydrocarbon receptor
AST	Aspartate aminotransferase
ATV	Atazanavir
AUC	Area under the plasma/PBMC concentration versus time curve
AUC_{inf}	Area under the plasma/PBMC concentration versus time curve extrapolated to infinite time
AUC_{last}	Area under the plasma concentration versus time curve from 0 to the last quantifiable concentration
AUC_{tau}	Area under the plasma concentration versus time curve over the dosing interval
$AUC_{0\text{-}t}$	Area under the plasma concentration versus time curve from 0 to the time t
$AUC_{0\text{-}24}$	Area under the plasma concentration versus time curve during the first 24 hours
AZT	Azidothymidine
BA	Bioavailability
BCRP	Breast cancer resistance protein
BMD	Bone mineral density
BNPP	Bis-p-nitrophenyl phosphate
C_{max}	Maximum observed plasma/PBMC concentration of drug
CL_{cr}	Creatinine clearance
CL_r	Renal clearance
COBI	Cobicistat
CYP	Cytochrome P450
DRV	Darunavir
EC_{50}	50% effective concentration
EFV	Efavirenz
EVG	Elvitegravir
FAS	Full analysis set
FTC	Emtricitabine
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV-1	Human immunodeficiency virus type 1
HIV-2	Human immunodeficiency virus type 2
IC_{50}	50% inhibitory concentration
LC	Liquid chromatography
NRTI	Nucleoside or nucleotide reverse transcriptase inhibitor

OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P_{app}	Apparent permeability coefficient
PBMC	Peripheral blood mononuclear cell
P-gp	P-glycoprotein
PK	Pharmacokinetics
PPK	Population pharmacokinetics
PXR	Pregnane X receptor
QD	Quaque die (once daily)
RTV	Ritonavir
STB	Stribild Combination Tab.
$t_{1/2}$	Estimate of the terminal elimination half-life of the drug in plasma/PBMC
t_{max}	Time (observed time point) of C_{max}
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
TFV-DP	Tenofovir diphosphate
TFV	Tenofovir
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1
PMDA	Pharmaceuticals and Medical Devices Agency
E/C/F/TAF FDC	Genvoya Combination Tablets

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

The initial antiretroviral treatment recommended by Research Group for Conquering HIV Infection and Complications. *Guideline for anti-HIV treatment* [in Japanese]. the Research Project on HIV/AIDS funded by the FY 2014 Health and Labour Sciences Research Grants; March, 2015. includes combination regimen of 2 nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) and 1 non-NRTI; combination regimen of 2 NRTIs, a protease inhibitor, and low-dose ritonavir (RTV); and combination regimen of 2 NRTIs and 1 integrase strand transfer inhibitor.

Genvoya Combination Tablets, the intended brand name, (hereinafter referred to as E/C/F/TAF FDC), was developed by Gilead Sciences, Inc. (U.S.) as a combination drug containing the following active ingredients: tenofovir alafenamide fumarate (TAF), a newly discovered prodrug of tenofovir (TFV; an NRTI); emtricitabine (FTC), an approved NRTI; elvitegravir (EVG), an approved integrase strand transfer inhibitor; and cobicistat (COBI), an approved drug that increases exposure to anti-HIV drugs by inhibiting cytochrome P450 (CYP) 3A.

The possible metabolic pathway from TAF to tenofovir diphosphate (TFV-DP [active form]) in peripheral blood mononuclear cells (PBMCs) is as shown in Figure 1 (*Antivir Ther.* 2014;19:1-18). Because TAF is metabolized to TFV by cathepsin A in PBMCs, plasma TFV levels can be reduced compared with those after administration of tenofovir disoproxil fumarate (TDF), an approved prodrug of TFV,[1)] thus the incidence of kidney-related adverse events, known to be characteristic of TDF products, is expected to be reduced. In Japan, "Stribild Combination Tab." containing TDF (a prodrug of TFV), FTC, EVG, and COBI as active ingredients was approved as an anti-HIV-1 drug in March 2013.

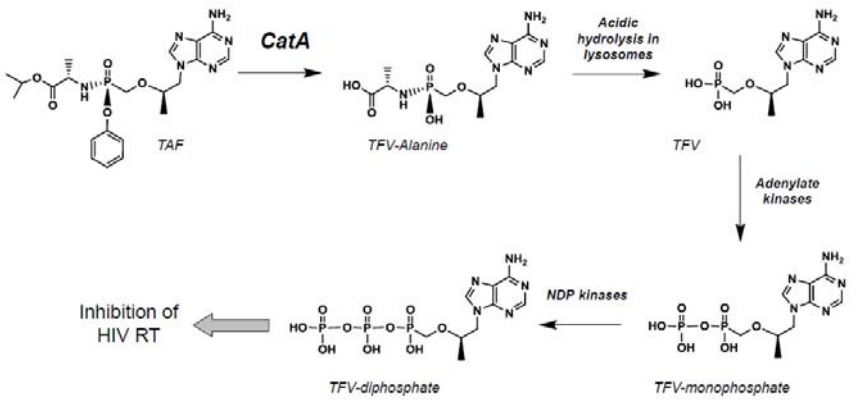

Figure 1. Possible metabolic pathway from TAF to TFV-DP (active form) in PBMCs (CatA = cathepsin A)

E/C/F/TAF FDC was approved in the U.S. and Europe in November 2015 on the basis of the clinical data from (a) phase III studies in HIV-1 patients who had not been treated previously with anti-HIV drugs (Studies GS-US-292-0104 and GS-US-292-0111) and (b) a phase III study in HIV-1 patients on anti-HIV therapy containing TDF (Study GS-US-292-0109).

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

The drug substance is comprised of EVG, a mixture of COBI and silicon dioxide, FTC, and TAF fumarate. No new data on the drug substances other than TAF fumarate have been submitted because these drug substances are identical to those used in "Stribild Combination Tab.," for which marketing approval was granted to the prior assessment requestor.

2.1 Drug substance (TAF fumarate)

Gilead Alberta ULC submitted the drug master file for TAF fumarate (Master File registration number 227MF10232).

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1) Oral administration of E/C/F/TAF FDC (containing 10 mg of TAF) gave a >4-fold concentration of TFV-DP in PBMCs and >90% lower plasma TFV concentration as compared with those oral administration of Stribild Combination Tab. (containing 300 mg of TDF) [see "6.2.2.2.1 Phase III study"] gave.

2.1.1 Characterization

The drug substance TAF fumarate is a white to grayish white powder or a white to dusky yellow-red powder and its solubility, melting point, distribution coefficient, pKa, chirality, hygroscopicity, and crystalline polymorphism have been determined. TAF fumarate consists of TAF and hemifumarate (2:1 molar ratio of free base to fumarate). [redacted] ([redacted]) and [redacted] ([redacted]) were found in the drug substance during its development, but only [redacted], which is thermodynamically more stable, is confirmed to be produced during commercial-scale production.

The chemical structure of the drug substance has been elucidated by elemental analysis, mass spectrometry, nuclear magnetic resonance spectrometry (^{1}H-NMR, ^{13}C-NMR, and ^{31}P-NMR), infrared spectrophotometry, ultraviolet spectrophotometry, and single-crystal X-ray crystallography. TAF fumarate has 3 chiral centers.

2.1.2 Manufacturing process

The manufacturing process is as shown in Attachment.

2.1.3 Control of drug substance

The proposed specifications for drug substance TAF fumarate include content, description, identification (infrared spectrophotometry), melting point (differential scanning calorimetry), purity (appearance of solution, heavy metals, related substances [liquid chromatography (LC)], [redacted] [LC], residual solvents [gas chromatography], volatile impurities [[redacted], gas chromatography]), water content, fumarate content, particle size, and assay (LC).

2.1.4 Stability of drug substance

As shown in the Attachment, a retest period of 24 months has been proposed for the drug substance when stored at 2°C to 8°C.

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is a film-coated tablet containing the following drug substances: 150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 11.2 mg of TAF fumarate (10 mg as TAF). It also contains, as excipients, hydroxypropylcellulose, sodium lauryl sulfate, lactose hydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and [redacted].

2.2.2 Manufacturing process

The drug product is manufactured by a process comprising granulation/drying, sizing, compression/sizing, blending, tableting, coating, packaging, labeling, testing, and storage. [redacted], [redacted], and [redacted] were defined as critical steps, and process control items and control values are specified in these processes.

The Quality by Design (QbD) approach was used in the development stage primarily to conduct the following:

- To identify [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] as critical quality attributes (CQAs)

- To identify critical process parameters (CPPs) and establish control strategy on the basis of quality risk assessments and design of experiments

2.2.3 Control of drug product

The proposed specifications for the drug product include content, description, identification (LC and ultraviolet spectrophotometry), purity (degradation products [LC]), water content, microbial limits, uniformity of dosage units (content uniformity test), dissolution, and assay (LC).

2.2.4 Stability of drug product

Stability studies were conducted in the drug product as shown in Table 1. Photostability studies demonstrated that the drug product is photostable.

Table 1. Stability studies for the drug product

Study	Primary batches	Temperature	Humidity	Storage container	Storage period
Long-term	3 batches	25°C	60%RH	High-density polyethylene bottle, silica gel (desiccant)	30 months
Intermediate	3 batches	30°C	75%RH		24 months
Accelerated	6 batches	40°C	75%RH		6 months

On the basis of the above, a shelf life of 30 months has been proposed for the drug product when stored at room temperature in a high-density polyethylene bottle (with silica gel desiccant). The long-term testing will be continued for [redacted] months.

2.R Outline of the prior assessment conducted by PMDA

On the basis of the submitted data, PMDA has concluded that the quality of the drug substances including TAF fumarate and the drug product is controlled appropriately. The master file registrant submitted the data regarding master file separately and the results of review by PMDA are shown in the Attachment.

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

The pharmacological activity of TAF was evaluated in primary pharmacodynamics, secondary pharmacodynamics, and safety pharmacology studies.

3.1 Primary pharmacodynamics

3.1.1 Cathepsin A activity in cells (CTD 4.2.1.1-13)

TAF, the free base form of TAF fumarate, is metabolized by cathepsin A to TFV (*Mol Pharmacol.* 2008;74:92-100) and phosphorylated to TFV-DP, the putative inhibitor of HIV-1 reverse transcriptase. Intracellular cathepsin A activity was evaluated *in vitro* as measured by the rate of TAF metabolism in human CD4-positive T cells and monocyte-derived macrophages. The mean rate of TAF metabolism was 2.7 and 3.0 pmol/min·μg protein in resting and mitotic CD4-positive T cells, respectively, and 7.1 pmol/min·μg protein in monocyte-derived macrophages.

3.1.2 *In vitro* antiviral activity

3.1.2.1 Antiviral activity against laboratory strains (CTD 4.2.1.1-13)

Antiviral activity of each test substance was evaluated in human CD4-positive T cells infected with HIV-1 pseudotyped with envelope protein of vesicular stomatitis virus (VSV-g) and in monocyte-derived macrophages infected with HIV-1 BaL. The mean 50% effective concentration (EC_{50}) of TAF, TFV, azidothymidine (AZT) (a NRTI), and efavirenz (EFV) (a non-NRTI) were 11.0, 6721, 18.2, and 0.4 nmol/L for pseudotyped HIV-1, respectively, and 9.7, 799, 15.3, and 0.9 nmol/L for HIV-1 BaL, respectively.

3.1.2.2 Antiviral activity against clinical isolates (CTD 4.2.1.1-4)

Antiviral activity of TAF was evaluated in human PBMCs infected with clinically isolated HIV-1 (26 strains) or human immunodeficiency virus type 2 (HIV-2) (3 strains). The 50% inhibitory concentration (IC_{50}) of TAF for HIV-1 and HIV-2 in the infected cells ranged from 0.1 to 12.0 nmol/L and from 0.9 to 2.6 nmol/L, respectively.

3.1.2.3 Effects of different drugs on antiviral activity of TAF (CTD 4.2.1.1-1)

Inhibitory effects of telaprevir and boceprevir (not approved in Japan) on cathepsin A were evaluated. The mean IC_{50} values were 0.3 and 0.2 μmol/L, respectively. The effect of each test substance on the antiviral activities of TAF and TDF was also evaluated in primary human CD4-positive T cells infected with pseudotyped HIV-1, yielding the results shown in Table 2.

Table 2. Effects of different drugs on antiviral activities of TAF and TDF

Test substance	Concentration (μmol/L)	Fold change[a)]	
		TAF	TDF
Telaprevir	5.2	23.93	1.64
Boceprevir	3.3	2.91	1.32
DRV	8.9	0.88	1.39
ATV	6.3	1.08	1.47
COBI	2.2	0.94	1.80

a) (EC_{50} of TAF or TDF used concomitantly with a test substance)/(EC_{50} of TAF or TDF used alone).

3.1.2.4 Effect of concomitant use of TAF and other anti-HIV drugs (CTD 4.2.1.1-2)

The effect of concomitant use of TAF and other anti-HIV drugs was evaluated in MT-2 cells infected with HIV-1 (IIIB), yielding the results shown in Table 3.

Table 3. Effect of concomitant use of TAF and other anti-HIV drugs

Test substance	Volume [(μmol/L)^2%][a)]	Effect of concomitant use[b)]
TAF/TFV	24	Additive effect
TAF/FTC	131	Strong synergistic effect
TAF/EFV	100	Strong synergistic effect
TAF/NVP	41	Weak synergistic effect
TAF/EVG	271	Strong synergistic effect
TAF/RAL	205	Strong synergistic effect
TAF/DTG	179	Strong synergistic effect
TAF/ATV	96	Moderate synergistic effect
TAF/DRV	56	Moderate synergistic effect
TAF/COBI	17	Additive effect

NVP, Nevirapine (a non-NRTI); RAL, Raltegravir (an integrase strand transfer inhibitor); DTG, Dolutegravir (an integrase strand transfer inhibitor)

a) Mean value calculated by MacSynergy II™ software based on the reports by Prichard MN et al. (*Antiviral Res.* 1990;14:181-205, *Antimicrob Agents Chemother.* 1993;37:540-545).

b) The effect was classified as follows: antagonistic (<-25), additive (-25 to <25), weakly synergistic (25 to <50), moderately synergistic (50 to <100), and strongly synergistic (≥100) for the calculated volume [(μmol/L)^2%].

3.1.2.5 Antiviral activities against viruses other than HIV (CTD 4.2.1.1-3)

Antiviral activities of TAF against viruses other than HIV (adenovirus, dengue virus type 2, influenza A virus, parainfluenza virus, respiratory syncytial virus, Coxsackie B virus, rhinovirus, herpes simplex virus type 1, herpes simplex virus type 2, human cytomegalovirus, varicella zoster virus, vaccinia virus, hepatitis C virus (HCV), and simian immunodeficiency virus) were evaluated. IC_{50} for parainfluenza virus and simian immunodeficiency virus was approximately 843 and 1.21 nmol/L, respectively, and those for other viruses were >1000 nmol/L.

3.1.3 *In vitro* cytotoxic activity (CTD 4.2.1.1-5, 4.2.1.1-6, 4.2.1.1-7)

Cytotoxic activities of TAF, TDF, and TFV were evaluated as measured by luminescence signal from viable cells, yielding the results shown in Table 4.

Table 4. Cytotoxic activities of TAF, TDF, and TFV

Cell	50% cytotoxic concentration (CC_{50}) (μmol/L)		
	TAF	TDF	TFV
HepG2 cell	>44.4[a)]	>44.4[a)]	>44.4[a)]
MT-2 cell	>53.0[a)]	37.1[a)]	7605[a)]
MT-4 cell	>23.2[a)]	22.9[a)]	6264[a)]
Human osteoblast	>1000	>1000	-
Mitotic PBMC	6.8	19.6	2150
Resting PBMC	25.1	69.7	>2652

Mean; -, Not evaluated

a) Geometric mean

3.1.4 Resistance profile

3.1.4.1 Resistance selection experiments (CTD 4.2.1.1-8, 4.2.1.1-9, 4.2.1.1-10)

HIV-1 (IIIB) infected MT-2 cells were incubated in the presence of TAF or TFV and emergence of resistance mutations was evaluated. Amino acid mutations detected after resistance induction and the fold resistance of each mutant strain against each test substance are shown in Table 5.

Table 5. Amino acid mutations detected in HIV-1 (IIIB) and fold resistance of each mutant strain

Test substance	Incubation time (days)	Amino acid mutation	Fold resistance				
			TAF	TFV	FTC	EFV	EVG
TAF	148	K65R	6.5	5.5	8.5	1.4	1.7
TFV	154	K65R, K65R + S68/N/R/K	6.5	5.1	6.7	1.5	1.4

Fold resistance is defined as (EC_{50} for mutant strain)/(EC_{50} for wild-type strain).

MT-2 cells infected with HIV-1 (LAI) with or without strains with TDF-resistant mutations (K65R, Q151M, or TAMs[2)] [M41L, L210W, and T215Y]) introduced were incubated in the presence of TAF, and emergence of TAF-resistant mutations was evaluated. Before incubation with TAF, EC_{50} of TAF and TFV for HIV-1 (LAI) was approximately 15 nmol/L and 3.5 μmol/L, respectively, and the fold resistance values of HIV-1 (LAI-K65R), HIV-1 (LAI-Q151M), and HIV-1 (LAI-3TAMs[3)]) against TAF and TFV were both 3, 3, and 13, respectively. Amino acid mutations detected after resistance induction and the fold resistance of each mutant strain against each test substance are shown in Table 6.

Table 6. Amino acid mutations detected in HIV-1 (LAI) with or without TDF-resistant mutation strains and fold resistance of each mutant strain

Virus strain	Test substance	Amino acid mutation	Fold resistance				
			TAF	TFV	RAL	AZT	EFV
HIV-1 (LAI)	TAF	K65R	3.5	3.7	1.0	0.7	0.6
	TFV	K65R + S68N	5.2	5.4	1.6	1.2	0.6
HIV-1 (LAI-K65R)	TAF	K65R + S68N	6.8	6.3	1.5	2.3	1.0
	TFV	K65R + S68N	6.1	5.9	1.2	2.2	1.4
HIV-1 (LAI-Q151M)	TAF	Q151M + T69I	26.1	22.1	1.5	>90	3.4
	TFV	Q151M + T69I	32.5	34.5	2.2	>90	2.7
HIV-1 (LAI-3TAMs[a)])	TAF	3TAMs[a)] + L429I	8.6	6.1	1.9	>90	>54
	TFV	3TAMs[a)] + L429I	9	6.1	1.7	>90	>54

Fold resistance is defined as (EC_{50} for mutant strain)/(EC_{50} for wild-type strain).
a) M41L + L210W + T215Y

In addition, MT-2 cells infected with HIV-1 (LAI) with or without strains with TDF-resistant mutations (K65R, T69ins,[4)] Q151M, or TAMs[2)] [M41L, D67N, K70R, L210W, T215Y/F, and K219E/N/Q/R]) introduced were incubated in the presence of TAF or TFV, and the time to breakthrough infection was determined by examining syncytium formation after HIV-1 infection, yielding the results shown in Table 7.

Table 7. Time (days) to syncytium formation after infection with HIV-1 (LAI) with or without TDF-resistant mutant strains

Amino acid mutation	Time (days) to breakthrough infection	
	TAF	TFV
Wild type	>28	>28
3TAMs[a)]	>28	>28
3TAMs[b)]	>28	13
K65R	>28	18
K65R + Q151M	>28	8
4TAMs[c)]	>28	8
T69ins	>28	4
5TAMs[d)]	8	4
5TAMs[e)]	8	4

a) D67N + K70R + K219Q, b) M41L + L210W + T215Y, c) D67N + K70R + T215F + K219Q, d) M41L + D67N + L210W + T215Y + K219R, e) M41L + D67N + L210W + T215Y + K219R

3.1.4.2 Antiviral activity against HIV-1 strain with NRTI-resistant mutation (CTD 4.2.1.1-12)

The fold resistance values against each test substance were determined in MT-2 cells infected with HIV-1 (xxLAI) with or without strains with NRTI-resistant mutations introduced. The results are shown in Table 8.

2) Thymidine-analog associated mutations
3) M41L + L210W + T215Y
4) A mutant strain with an amino acid insertion at position 69

Table 8. Antiviral activity against HIV-1 xxLAI with or without NRTI-resistant mutant strains

Amino acid mutation	Fold resistance					
	TAF	TFV	AZT	FTC	DRV	EVG
K65R	3.3	3.3	0.6	6.5	0.9	0.8
K70E	2.2	2.1	0.3	2.5	1.0	1.0
M184V	1.1	0.9	0.5	>>	0.9	1.0
D67E + T69SSG	10.1	10.1	>>	9.0	1.2	1.6
A62V + K65R	2.2	2.3	0.4	6.0	-	0.7
K65R + Q151M	13.2	13.9	>>	>>	1.0	1.1
K65R + M184V	3.3	3.1	1.8	>>	0.8	0.7
M41L + L210W + T215Y[a)]	3.0	3.8	>>	2.0	0.7	0.6
K65R + K70T + M184V	8.9	6.2	4.6	>>	1.2	1.8
K65R + Y115F + M184V	5.0	3.9	1.1	>>	1.1	1.1
M41M/L + D67N + L210L/W + T215F[b)]	3.4	3.8	>>	2.8	1.2	1.3
M41L + D67D/N + L210W + T215Y[b)]	10.3	7.2	>>	5.0	1.0	1.0
D67N + K70R + M184V + K219Q[a)]	4.3	3.7	25.5	>>	1.2	1.9
M41L + D67N + L210W + T215Y + K219K/R[c)]	6.4	5.2	>>	15.2	0.7	0.7
D67N + T69T/A + K70R + T215F + K219Q[b)]	6.1	5.1	>>	3.9	1.1	1.2
M41L + D67N + T69D + L210W + T215Y + K219R[c)]	25.5	21.9	>>	28.4	1.0	0.9
M41L + D67N + K70R + M184V + T215F + K219Q[c)]	4.5	4.1	>>	>>	1	0.6
M41L + T69D + M184V + L210W + T215Y + K219R[b)]	6.3	4.7	>>	>>	1.5	2.0
D67N + T69N + K70R + M184V + T215T/A/I/V + K219Q[a)]	3.6	3.3	>>	>>	0.8	0.9
M41L + T69SSS + V75I/L/M + M184M/I/V + L210W + T215Y	14.3	10.9	>>	>>	0.5	0.9
D67N + K70R + V75M + M184V + T215F + K219Q[b)]	2.3	2.6	>>	>>	0.7	0.9
M41L + D67N + T69N + K70R + M184V + T215F + K219E[c)]	6.9	6.5	>>	>>	1.1	1.1
M41L + D67N + T69D + L74I + L210W + T215Y + K219R[c)]	22.9	19.6	>>	5.4	1.7	1.3
M41L + A62V + K65R + T69I + K70T + L74V + V75I + Y115F + F116Y + Q151M + M184V	5.9	4.1	>>	>>	1.1	0.9

Mean: -, Not evaluated; >>, 1 or more values were >55 or the mean value was >48 among triplicate measurements.
Fold resistance is defined as (EC_{50} for mutant strain)/(EC_{50} for wild-type strain).
TAM: M41L, D67N, K70R, L210W, T215F/Y, and K219Q/E/N/R
a) Three TAMs are included; b) 4 TAMs are included; c) 5 TAMs are included.

3.2 Secondary pharmacodynamics

3.2.1 Effect on mitochondria (CTD 4.2.1.2-1)

The effect of TAF on mitochondria was evaluated in HepG2 cells. The mean amount of mitochondrial DNA after 10-day incubation with 1 μmol/L of TAF was 94.6% that in the negative control group while that after incubation with 2 μmol/L of zalcitabine (dideoxycytidine) in the positive control group was 11.5% that in the negative control group.

3.2.2 Effects on erythroid and myeloid progenitor cells (CTD 4.2.1.2-2)

The effects of TAF on human bone marrow erythroid and myeloid progenitor cells were evaluated. IC_{50} values (ranges)[5)] of TAF for erythroid and myeloid progenitor cells after 14-day incubation[6)] with TAF were both >3 μmol/L, while those after incubation with 5-fluorouracil (positive control) were from 3.2 to 4.1 μmol/L and from 1.1 to 4.0 μmol/L, respectively.

3.2.3 Effect on kidney epithelial cells (CTD 4.2.1.2-3)

Cytotoxic activities of TAF and TFV were evaluated in kidney epithelial cells expressing organic anion transporter (OAT)1 and OAT3,[7)] yielding the results shown in Table 9.

5) The results obtained from 3 different cell lines.
6) TAF was added to give final concentrations of 0.0013, 0.004, 0.012, 0.037, 0.11, 0.33, 1, and 3 μmol/L, and 5-fluorouracil was added to give final concentrations of 0.05, 0.14, 0.4, 1.2, 3.7, 11, 33, and 100 μmol/L.
7) Accumulation of non-cyclic nucleotides such as TFV mediated by OATs in proximal tubular cells has been reported to be involved in the pathogenesis of TDF-induced renal disorders (*Expert Opin Drug Saf.* 2010;9:545-559).

Table 9. Cytotoxic activities of TAF and TFV against OAT-expressing kidney epithelial cells

Test substance	50% cytotoxic concentration (CC_{50}) (μmol/L) (Fold change[a)])			EC_{50}[b)] (μmol/L)	Selectivity Index[c)] (OAT1)	Selectivity Index[c)] (OAT3)
	Wild-type cells	OAT1-expressing cells	OAT3-expressing cells			
TAF	163 (1.0)	319 (0.5)	47 (3.5)	0.011	29,000	4270
TFV	>2000 (1.0)	94 (>21.3)	553 (>3.6)	6.7	14	82

Mean
a) (CC_{50} for wild-type cells)/(CC_{50} for OAT-expressing cells); b) EC_{50} in human CD4-positive T cells infected with pseudotyped HIV-1;
c) (CC_{50} for OAT-expressing cells)/(EC_{50} for pseudotyped HIV-1)

3.3 Safety pharmacology (CTD 4.2.1.3-1, 4.2.1.3-2, 4.2.1.3-3, 4.2.1.3-4)

The effects of TAF on central nervous, cardiovascular, and gastrointestinal systems were evaluated (Table 10).

Table 10. Summary of safety pharmacology studies

Organ tested	Test system	Endpoint, method, etc.	Dose level or concentration	Route of administration	Notable findings
Central nervous system	Male SD rats (n = 10/group)	FOB testing	0, 80, 800 mg/kg	Oral	None
Cardiovascular system	HEK-293 cells (n = 3/concentration)	hERG current	0, 1, 10 μmol/L[a)]	*in vitro*	0 μmol/L: 0.8% inhibition 1 μmol/L: 0.9% inhibition 10 μmol/L: 0.3% inhibition
	Male Beagle dogs (n = 3/group)	Telemetry	24, 80 mg/kg	Oral	None
Gastrointestinal system	Male SD rats (n = 9/group)	Gastrointestinal transit	0, 80, 800 mg/kg	Oral	0 and 80 mg/kg: None 800 mg/kg: Decreased gastric emptying rate

a) Concentration is expressed as TAF hemifumarate equivalent.

The prior assessment requestor's explanation on the effect of TAF on the respiratory system:
Since safety pharmacology studies of TAF had been completed by [redacted], which is before the issue date of "Safety Pharmacology Studies for Human Pharmaceuticals" (PMSB/ELD Notification No. 902, dated June 21, 2001), no quantitative evaluation of respiratory parameters other than the respiration rate was performed. In functional observational battery (FOB) test in rats, respiratory pattern was qualitatively examined in addition to respiration rate determination, and the results showed no apparent differences between before and after the start of treatment. Because TAF is rapidly absorbed and converted to TFV in rats, the data from FOB test in rats possibly explain that a limited exposure to TAF has no clear impact on the respiration rate or respiratory pattern.

On the other hand, the incidence of adverse drug reactions classified as "Respiratory, thoracic and mediastinal disorders"[8)] in phase III studies in treatment-naïve HIV-1 patients (Studies GS-US-292-0104 and GS-US-292-0111) was 0.5% (4 of 866) of patients in the E/C/F/TAF FDC group and 0.8% (7 of 867) of patients in the Stribild Combination Tab. (STB) group; therefore, TAF is unlikely to affect the respiratory system.

3.R Outline of the prior assessment conducted by PMDA

Antiviral activity of and resistance to TAF

PMDA's view:
On the basis of the submitted data, antiviral activity of TAF against HIV-1 can be expected. In addition, the *in vitro* resistance selection experiments demonstrated no apparent difference in the resistance profile between TAF and TDF. However, since treatment experience with E/C/F/TAF FDC is limited, information on TAF-resistant mutations should be collected after the market launch, and provided appropriately to healthcare professionals in clinical settings when new findings become available. Efficacy of E/C/F/TAF FDC in HIV-1 patients is described in "7.R.1 Efficacy."

8) A System Organ Class (SOC) of MedDRA ver. 17.0

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

TAF (^{14}C-labeled and unlabeled TAF) was administered to mice, rats, monkeys, and dogs to evaluate its pharmacokinetics (PK). Because TAF is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporting polypeptide (OATP)1B1, and OATP1B3, concomitant use of TAF and COBI, which inhibits P-gp and BCRP, may result in increased absorption of TAF, and concomitant use of TAF and COBI or EVG, both of which inhibit OATP1B1 and OATP1B3, may result in increased exposure to TAF. However, the PK of each active ingredient of E/C/F/TAF FDC was not evaluated in non-clinical studies because (i) the PK of E/C/F/TAF FDC was evaluated in clinical studies [see "6.1.1.1 Phase I study," "6.1.1.2 Phase I study," and "6.2.4.2 Study on interaction of FTC/TAF in combination with EFV or with DRV and COBI"]; and (ii) pharmacokinetic drug interaction is unlikely to occur due to the following reasons:

- The plasma protein unbound fractions of TAF in dogs and humans were 48.0% and 46.8%, respectively, and protein binding displacement is unlikely to occur.
- Although TAF is a weak substrate of CYP3A, contribution of CYP3A in metabolism of TAF is considered to be small because TFV-DP (a TAF metabolite) levels were not affected by concomitant use of COBI, a CYP3A inhibitor.
- Although TAF is a weak inhibitor of CYP3A, strong inhibition by COBI minimizes the inhibitory effect of TAF.
- TAF does not inhibit or induce any metabolic enzymes other than CYP3A, and does not inhibit any transporters.

Concentrations of TAF and TFV in plasma, PBMCs, and biological samples were measured by LC/tandem mass spectrometry.[9)] In some studies, high performance liquid chromatography (HPLC) (lower limit of quantification [LLOQ], 31 ng/mL for TFV in rat plasma and 25 ng/mL for TAF and TFV in dog plasma; detection limit, 1 μg/mL for TFV in dog PBMCs[10)]) was used. Tissue distribution in rats and mice was evaluated by whole body autoradiography (LLOQ, 311 ng eq./g in mice and 45.6 ng eq./g in rats); tissue distribution in dogs, by liquid scintillation counting technique (LLOQ, 60.6 ng eq./g); and metabolites were analyzed by radio-HPLC or LC/tandem mass spectrometry.

In this section, the test substances used (TAF free base, TAF hemifumarate, and TAF monofumarate) are all expressed as TAF.

4.1 Absorption

4.1.1 *In vitro* (CTD 4.2.2.2-7)

Apparent permeability coefficient (P_{app}) of TAF at 10 μmol/L was determined in monolayers of Caco-2 cells. The results showed that the efflux ratio was 20.2. After monolayers of Caco-2 cells were treated with 10 μmol/L of TAF and 10 μmol/L of cyclosporin A, an efflux transport inhibitor, the efflux ratio was 1.00.

4.1.2 Single-dose studies (CTD 4.2.2.2-1, 4.2.2.2-3, 4.2.2.2-4, 4.2.2.2-6, 4.2.2.2-9)

The PK parameters of TAF and TFV after a single oral dose of TAF was administered to mice, rats, dogs, and monkeys were as shown in Table 11.[11)] C_{max} and AUC of TAF were not consistently dose-proportional in mice, while they increased more than dose-proportionally in dogs and monkeys. C_{max} and AUC of TFV showed a more than dose-proportional increase in mice, rats, and monkeys. In dogs, AUC was dose proportional while the increase in C_{max} was less than dose-proportional. In mice, a maximum of approximately 2-fold gender differences were observed in C_{max} and AUC of TFV.

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9) The LLOQ is 10 ng/mL for TAF and TFV in rat and mouse plasma; 1 ng/mL for TAF and TFV in monkey plasma; 1.99 and 0.99 ng/mL for TFV in monkey PBMCs (4.2.2.2-9 and 4.2.2.2-10, respectively); 1 and 10 ng/mL for TAF and TFV in rabbit plasma, respectively; 3 ng/mL for TFV in rat plasma (4.2.3.2-5); 1 ng/mL for TAF and TFV in dog plasma; 3 ng/mL for TFV in dog PBMCs (4.2.3.2-6); and 0.99 ng/mL for TFV in monkey plasma and PBMCs (4.2.3.2-2).

10) TFV concentration in rat plasma (4.2.2.2-11), and TAF and TFV concentrations in dog plasma and PBMCs (4.2.2.2-1)

11) For mice and rats, data obtained with TAF hemifumarate are presented because the PK did not differ between TAF monofumarate and TAF hemifumarate. For dogs, data obtained with TAF monofumarate are presented because the PK did not differ between TAF free base and TAF monofumarate.

Table 11. PK parameters of TAF and TFV following a single oral dose of TAF

Test system	Dose level (mg/kg)	n	TAF				TFV			
			C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (ng·h/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (ng·h/mL)
Mouse	10	4 males/ time point	-	-	-	-	175	0.3	9.8	735
		4 females/ time point	-	-	-	-	100	0.5	8.2	354
	30	4 males/ time point	8.8	0.08	-	-	615	0.3	9.5	2639
		4 females/ time point	117	0.50	-	-	421	0.3	10.9	2053
	100	4 males/ time point	648	0.25	-	194	1988	0.5	8.0	10,026
		4 females/ time point	280	0.50	-	104	1733	0.5	11.0	7131
Rat[a)]	5	3 males	-	-	-	-	39.3	0.6	-	88.5
	25	3 males	-	-	-	-	364	0.8	7.9	1810
	100	3 males	-	-	-	-	1670	0.7	7.9	9759
Dog	5	5 males	1011	0.3	0.2	481	319	1.7	11.7	1431
	10	2 males/ time point	3490	0.1	0.2	1380	640	1.0	> 24	2720
	20	5 males	5822	0.2	0.3	3250	967	0.6	22.0	5192
Monkey	0.5	3/sex	2.8	0.4	0.6	1.2	7.7	1.0	4.6	39.9
	5	3/sex	125	0.8	0.2	95.1	161	1.3	9.9	1037
	50	3/sex	4143	0.5	0.4	3811	1326	1.0	17.3	9934

Mean; -, Not evaluated

a) TAF values were below the LLOQ at all time points.

After male dogs (n = 5) received an oral dose of TAF 20 mg/kg, C_{max} and AUC_{0-t} of TFV in their PBMCs were 59.7 µg/mL and 805 µg·h/mL, respectively. After male dogs (n = 2) received an oral dose of TAF 10 mg/kg, C_{max} and AUC_{0-t} of TFV-DP in their livers were 56.4 µg/mL and 1017 µg·h/mL, respectively.

Male dogs (n = 5) received an intravenous dose of TAF 6.2 mg/kg or an oral dose of TAF 4.8 to 20 mg/kg, and the calculated absolute bioavailability (BA) of TAF ranged from 41.2% to 76.3%.

At 96 hours after monkeys (n = 3/sex) received an oral dose of TAF 50 mg/kg, TFV concentration in PBMCs was 3.03 ng/10^6 cells, which was increased to 8.68 ng/10^6 cells when phosphatase was added to PBMCs.

4.1.3 Repeat-dose studies (CTD 4.2.2.2-10; toxicokinetics, CTD 4.2.3.2-5, 4.2.3.2-6, 4.2.3.2-9, 4.2.3.5.2-2, 4.2.3.5.2-4)

The PK parameters of TAF and TFV in animals receiving repeated oral doses of TAF are as shown in Table 12. In mice receiving oral doses of TAF 10 to 100 mg/kg/day for 13 weeks, less than 2-fold gender differences were observed in C_{max} and AUC of TFV. After repeated doses of TAF, no apparent accumulation of TFV was observed in mice, rats, or monkeys, while approximately a 3- to 5-fold increase in AUC of TFV was observed in dogs.

Table 12. PK parameters of TAF and TFV following repeated oral doses of TAF

Test system	Dose (mg/kg)	n	Sampling time point	TAF		TFV	
				C_{max}[a] (ng/mL)	AUC[b] (ng·h/mL)	C_{max}[a] (ng/mL)	AUC[b] (ng·h/mL)
Mouse	10	3/sex/time point	Day 1	-	-	59.5	171
			After 13 weeks	-	-	69.2	213
	30	3/sex/time point	Day 1	-	-	292	1282
			After 13 weeks	-	-	330	1507
	100	3/sex/time point	Day 1	-	-	1011	6534
			After 13 weeks	-	-	863	7397
Rat	5	8/sex	Day 1	-	-	309	604
			After 26 weeks	-	-	267	670
	25	8/sex	Day 1	-	-	1284	3364
			After 26 weeks	-	-	1523	3758
	100	8/sex	Day 1	-	-	4944	12,415
			After 26 weeks	-	-	4911	15,534
Dog	2	6/sex	Day 1	40 (81)	17 (34)	39 (78)	201 (402)
		4/sex	After 39 or 40 weeks	69 (137)	39 (78)	91 (181)	590 (1181)
	6	6/sex	Day 1	120 (721)	62 (369)	42 (254)	218 (1306)
		4/sex	After 39 or 40 weeks	237 (1420)	172 (1033)	90 (541)	742 (4451)
	18/12[c]	8/sex	Day 1	200 (3595)	115 (2070)	44 (799)	211 (3801)
		6/sex	After 39 or 40 weeks	218 (2619)	163 (1954)	110 (1319)	1144 (13,732)
Monkey	3	3/sex	Day 1	-	-	90.3	472
		3/sex	Day 28	18.8	-	50.4	352
	30	3/sex	Day 1	-	-	904	6670
		2 males and 3 females	Day 28	1370	1030	963	5870
Pregnant Rat	25	3/time point	Day 17	-	-	870	2803
	100	3/time point	Day 17	149	242	4130	17,392
	250	3/time point	Day 17	597	1382	7350	55,728
Pregnant rabbit	10	3	Day 20	155	-	260	2018
	30	3	Day 20	937	1135	676	5005
	100	3	Day 20	9190	11,043	2970	27,251

Mean; -, Not evaluated

a) For dogs, dose-normalized values (unnormalized values) are presented in ng/mL/mg/kg and in ng/mL, respectively.

b) AUC values are shown as $AUC_{0\text{-}inf}$ on Day 1 and AUC_{tau} after repeated doses for rats and monkeys, and as $AUC_{0\text{-}t}$ for mice, dogs, pregnant rats and rabbits.

c) Following repeated oral doses of TAF 18 mg/kg/day to dogs, poor general condition and decreases in body weight and food consumption were observed and the dose of TAF was changed to 12 mg/kg/day at Week 7 and Week 8 in males and females, respectively.

After 39 or 40 weeks of oral administration of TAF 2, 6, and 12 mg/kg/day to dogs, $AUC_{0\text{-}24}$ values of TFV in PBMCs were 0.26, 1.26, and 3.26 μg·h/10^6 cells, respectively.

TFV concentration in PBMCs[12] in monkeys receiving oral doses of TAF 30 mg/kg/day for 28 days was 27.2 μg/mL.

4.2 Distribution

4.2.1 Plasma protein binding and distribution in red blood cells (CTD 4.2.2.3-1, 4.2.2.3-2, 4.2.2.3-3, 4.2.2.3-4, 4.2.2.5-1)

Protein binding of TAF was evaluated in dog and human plasma to which TAF 2 μmol/L was added, yielding a plasma protein unbound fraction of 48.0% and 46.8%, respectively.[13]

After ^{14}C-TAF was administered to mice, rats, and dogs, the blood/plasma radioactivity concentration ratio ranged from 0.73 to 27.7, from 0.54 to 0.94, and from 0.61 to 1.24 respectively.

4.2.2 Tissue distribution (CTD 4.2.2.3-1, 4.2.2.3-2, 4.2.2.3-3)

In albino and pigmented male mice (n = 1 each/time point), tissue radioactivity concentrations were determined after a single oral dose of ^{14}C-TAF 100 mg/kg. In albino mice, radioactivity peaked within

12) TFV concentrations were determined in PBMCs collected before treatment on Day 28.

13) Evaluation was not performed in rodents because TAF is very unstable in plasma of some rodent species due to the high expression levels of esterases in plasma.

1 hour post-dose in most tissues, and radioactivity was detected at 168 hours post-dose in multiple tissues. Tissues with high radioactivity (excluding gastrointestinal tract) included the liver, gallbladder, bladder, diaphragm, renal cortex, kidneys, and renal medulla (the peak level was 447,000, 335,000, 174,000, 167,000, 92,300, 86,100, and 70,000 ng eq./g, respectively). In pigmented mice, the radioactivity levels in the lens and uvea were higher than those in albino mice, but distribution in skin was similar between pigmented and albino mice. Thus, the prior assessment requestor explained that the higher radioactivity levels seen in ocular tissues do not suggest binding to melanin-containing tissues.

In albino and pigmented male rats (n = 1/time point each), tissue radioactivity concentrations were determined after a single oral dose of ^{14}C-TAF 5 mg/kg. In both albino and pigmented rats, radioactivity peaked within 0.25 hours post-dose in most tissues, and radioactivity was below the LLOQ at 168 hours post-dose in all tissues excluding the liver. Tissues with high radioactivity (excluding gastrointestinal tract) included the renal cortex, kidneys, renal medulla, and liver (the peak level was 12,400, 9520, 8240, and 6730 ng eq./g, respectively, in albino rats and 8890, 7750, 6900, 10,300 ng eq./g, respectively, in pigmented rats). In ocular tissues, low levels of radioactivity were detected, but fell below the LLOQ within 8 hours post-dose in all ocular tissue sites. No difference was found in distribution to tissues including skin and eyes between albino and pigmented rats.

In male dogs that had previously received repeated oral doses of unlabeled TAF 15 mg/kg for 4 days and those that had not (n = 2 each/time point), tissue radioactivity concentrations were determined after a single oral dose of ^{14}C-TAF 15 mg/kg. Tissues with high radioactivity included the kidneys and liver (the peak level was 162,000 and 109,000 ng eq./g, respectively, following repeated administration and 99,700 and 97,600 ng eq./g, respectively, following a single administration). The radioactivity was detected at 24 hours post-dose in multiple tissues.

4.2.3 Placental transfer

The prior assessment requestor explained that since TFV (a TAF metabolite) has been shown to cross the placenta, cautionary statements regarding administration to pregnant, possibly pregnant, or lactating women will be included in the package insert etc., although placental transfer of TAF was not evaluated.

4.3 Metabolism

4.3.1 Possible metabolic pathways

Metabolic pathways of TAF deduced from the evaluation data shown in “4.3.2 *In vitro* metabolism” and “4.3.3 *In vivo* metabolism” are shown in Figure 2.

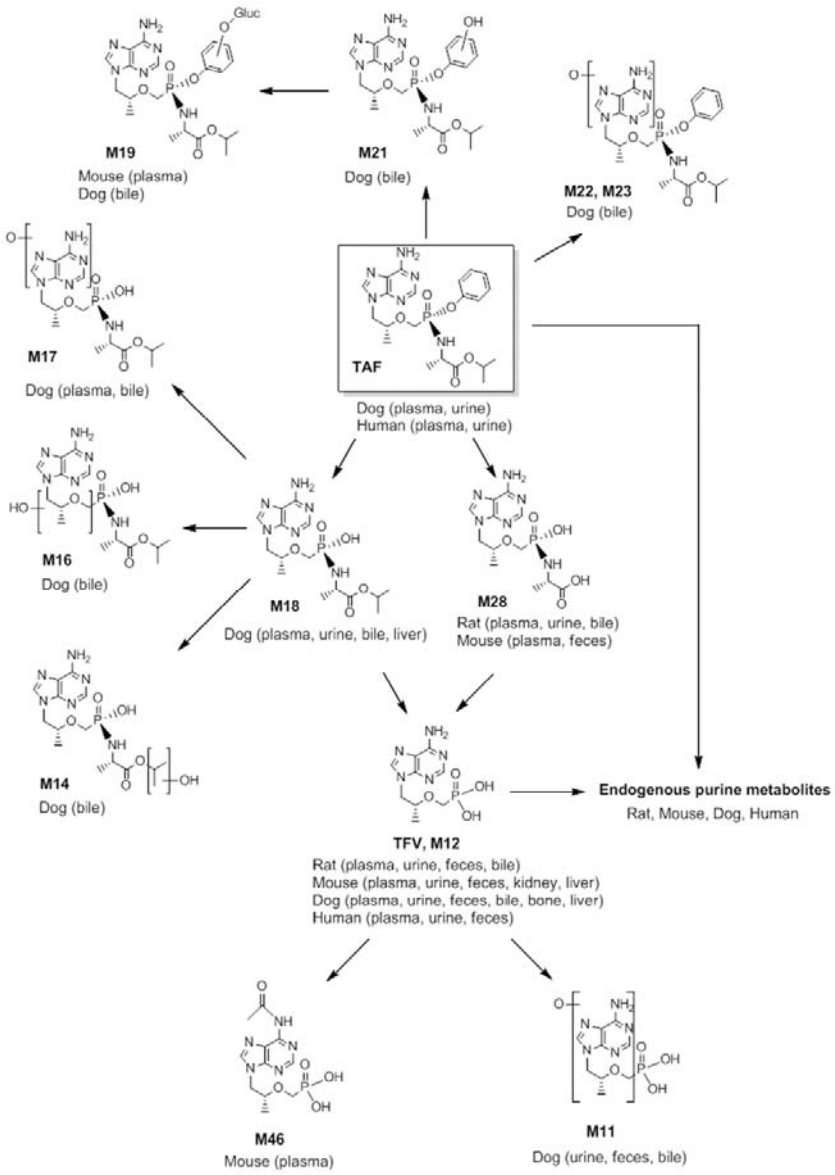

Figure 2. Possible metabolic pathways of TAF

4.3.2 *In vitro* metabolism (CTD 4.2.2.4-3, 4.2.2.4-5, 4.2.2.4-6, 4.2.2.4-7, 4.2.2.6-2)

The half-lives of TAF in plasma, intestinal S9 fraction, and liver S9 fraction were 74.7, 58.3, and 20.6 minutes, respectively, in humans and 69.5, 47.1, and 31.1 minutes, respectively, in dogs.

TAF metabolism was evaluated in a system expressing human CYP[14] and reduced nicotinamide adenine dinucleotide phosphate (NADPH)-CYP reductase, which showed TAF metabolism by CYP3A4, but the rate of TAF metabolism was 1.9/min, equivalent to 26.6% of that by testosterone (positive control). Metabolism by other CYP enzymes was not detected.

TAF is metabolized by cathepsin A and is converted to TFV in PBMCs and cells in lymphoid tissues (*Antimicrob Agents Chemother.* 2007;51:543-550, *Mol Pharmacol.* 2008;74:92-100). In primary hepatocytes, TAF is mainly metabolized by carboxyesterase 1 and converted to TFV-DP [see "4.5.1 Enzyme inhibition and induction"].

The intracellular TFV-DP concentrations after 24-hour incubation of primary human hepatocytes with 5 μmol/L of TAF, TDF, or TFV were 1470, 302, and 12.1 pmol/10^6 cells, respectively.

[14] CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4

4.3.3 *In vivo* metabolism (CTD 4.2.2.4-1, 4.2.2.4-2, 4.2.2.4-4, 5.3.3.1-1)

In male mice (n = 30) to which ^{14}C-TAF 100 mg/kg was administered orally, 54.8% of total radioactivity in plasma was present as TFV, and other metabolites detected included M5, M19, M27A (allantoin), M27B (uric acid), M28, M45, and M46. In urine, 18.1% of total radioactivity was present as TFV, and other metabolites detected included M5, M27A, M32, and M35; in feces, 30.7% of total radioactivity was present as TFV, and other metabolites detected included M27A and M28. TFV was mainly detected in the kidneys and liver and M7 (xanthine) was mainly detected in the turbinate.

In male rats (n = 15) to which ^{14}C-TAF 5 mg/kg was administered orally, 66.7% of total radioactivity in plasma was present as TFV, and other metabolites detected included M27A and M28. In urine, 17.1% of total radioactivity was present as TFV, and other metabolites detected included M27A, M32, and M44; in feces, 63.3% of total radioactivity was present as TFV. In bile-duct-cannulated male rats (n = 3) to which ^{14}C-TAF 5 mg/kg was administered orally, 17.1% of total radioactivity in urine was present as TFV, and other metabolites detected included M27A, M28, M32, and M44. In feces, 61.7% of total radioactivity was present as TFV, and biliary metabolites included TFV, M27B, and M28.

In male dogs (n = 3) to which ^{14}C-TAF 15 mg/kg was administered orally, 68.3% of total radioactivity in plasma was present as TFV, and other plasma metabolites detected included unchanged TAF, M2, M3, M5, M9, M10, M17, M18, and M20. In urine, 24.2% of total radioactivity was present as TFV, and other metabolites detected included unchanged TAF, M2, M4, M5, M11, M15, and M18; in feces, 20.8% of total radioactivity was present as TFV, and other metabolites detected included M2 and M11. TFV was mainly detected in the bone and liver. Following oral administration of ^{14}C-TAF 15 mg/kg in bile-duct-cannulated male dogs (n = 3), 16.8% of total radioactivity in urine was present as TFV, and other metabolites detected included unchanged TAF, M1, M2, M4, M5, M11, and M23; in feces, 26.4% of total radioactivity was present as TFV, and other metabolites detected included M11. Biliary metabolites detected included TFV, unchanged TAF, M2, M4, M5, M6, M11, M14, M16, M17, M18, M19, M21, M22, and M23.

In human plasma, 73.9% of total radioactivity was present as M27B, and other metabolites detected included unchanged TAF, TFV, and M33. In human urine, 22.2% of total radioactivity was present as TFV, and other metabolites detected included unchanged TAF, M7, M8, and M27B; in human feces, 31.4% of total radioactivity was present as TFV [see "6.2.1.1 TAF"].

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion (CTD 4.2.2.3-2, 4.2.2.3-3, 4.2.2.5-1)

In male mice (n = 4) to which ^{14}C-TAF 100 mg/kg was administered orally, approximately 61% of the administered radioactivity was excreted within the first 48 hours post-dose, resulting in urinary and fecal excretion rates of 27.7% and 41.3%, respectively, by 168 hours post-dose.

In bile-duct cannulated (n = 5) and uncannulated (n = 3) male rats to which ^{14}C-TAF 5 mg/kg was administered orally, most of the administered radioactivity was excreted within the first 24 hours post-dose, resulting in urinary, fecal, and biliary excretion rates of 23.2%, 72.6%, and 2.11%, respectively, in bile-duct-cannulated rats; and urinary and fecal excretion rates of 22.2% and 71.9%, respectively, in uncannulated rats by 168 hours post-dose.

In bile-duct-cannulated and uncannulated male dogs (n = 3 each) to which ^{14}C-TAF 15 mg/kg was administered orally, most of the administered radioactivity was excreted within the first 48 hours post-dose, resulting in urinary, fecal, and biliary excretion rates of 26.5%, 42.7%, and 14.0%, respectively, by 168 hours post-dose in bile-duct-cannulated dogs, and urinary and fecal excretion rates of 35.9% and 37.4%, respectively, in uncannulated dogs by 168 hours post-dose.

4.4.2 Excretion in milk

The prior assessment requestor explained that since TFV (a TAF metabolite) has been shown to be excreted in milk, cautionary statements regarding administration to pregnant, possibly pregnant, or lactating women will be included in the package insert etc., although excretion of TAF in milk was not evaluated.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition and induction (CTD 4.2.2.6-1, 4.2.2.6-3, 4.2.2.6-4, 4.2.2.6-9, 4.2.2.6-10, 4.2.2.6-11, 4.2.2.6-14)

Inhibition of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) by TAF was evaluated in human liver microsomes. TAF inhibited CYP3A-mediated metabolism of midazolam and testosterone with IC_{50} values of 7.6 and 7.4 μmol/L, respectively. TAF inhibited CYP isoforms other than CYP3A with IC_{50} values of >25 μmol/L.

Time- and cofactor-dependent inhibitions of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) by TAF were evaluated in human liver microsomes. The maximum change in activity observed was a 17.4% inhibition of CYP2C8. Thus, TAF was not considered to inhibit CYP isoforms in a time- or cofactor-dependent manner.

UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) inhibition by TAF was evaluated in microsomes of insect cells expressing human UGT1A1, yielding an IC_{50} value of >50 μmol/L.

Metabolic stability of TAF was evaluated in human intestinal S9 fraction in the presence of atazanavir (ATV), darunavir (DRV), RTV, or COBI, yielding the results that none of these drugs, at up to 100 μmol/L, had an effect on the metabolic stability of TAF.

Enzymes involved in the metabolism of TAF to TFV-DP were explored by treating primary human hepatocytes with TAF and a metabolic inhibitor(s) (cathepsin A inhibitor [telaprevir or boceprevir], carboxylesterase-1 inhibitor [bis-p-nitrophenyl phosphate (BNPP)], CYP3A4 and P-gp inhibitor [COBI], or telaprevir and BNPP). The intracellular TFV-DP concentration after treatment with 50 μmol/L of BNPP was equivalent to 33.6% of that in the control cells, indicating an inhibition of TAF metabolism. Telaprevir, boceprevir, or COBI had little inhibitory effect on the metabolism of TAF. Combination treatment with telaprevir and BNPP showed a stronger inhibition than single agent treatment with BNPP.

Induction of CYP isoforms (CYP1A2, CYP2B6, and CYP3A), P-gp, and UGT1A1 was evaluated in cryopreserved human hepatocytes treated with 1 or 10 μmol/L of TAF once daily for 3 days. No induction by TAF was observed even at 1 μmol/L, which exceeds plasma exposure[15)] in humans at the clinical dose (10 mg/day as TAF).

Metabolic enzyme induction by activation of aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR) by TAF was evaluated in human AhR- or PXR-expressing cells. TAF, at up to 50 μmol/L, did not activate AhR, and, at 15 and 50 μmol/L, it activated PXR by ≤5% and approximately 23%, respectively, as rifampicin (positive control) did. The prior assessment requestor explained that the above results demonstrate that TAF does not activate AhR or PXR at a concentration comparable to the maximum plasma concentration (0.34 μmol/L)[15)] in humans receiving TAF at the clinical dose.

4.5.2 Potential as a substrate or inhibitor of drug transporters (CTD 4.2.1.2-3, 4.2.2.6-5, 4.2.2.6-7, 4.2.2.6-8, 4.2.2.6-12, 4.2.2.6-13)

Inhibitory effects of TAF were evaluated on OATP1B1, OATP1B3, P-gp, BCRP, OAT1, OAT3, organic cation transporter (OCT)1, OCT2, H^+/organic cation antiporter 1 (MATE1), and bile acid transporter. The results showed no inhibitory effects on any of these transporters (IC_{50} >100 μmol/L). No uptake of TAF by OCT1 was observed in Chinese hamster ovary cells expressing OCT1, and TAF was found not to be a substrate of OCT1.

The P_{app} values of TAF were determined in monolayers of Caco-2 cells treated with TAF 10 μmol/L alone or in combination with 90 μmol/L of COBI, which inhibits P-gp, yielding the efflux ratios of approximately 20 or 1.6, respectively.

The P_{app} value of TAF was determined in MDCKII cells expressing P-gp (MDR1) or BCRP. The results showed that the efflux ratios in MDCKII cells expressing P-gp (MDR1) and in MDCKII cells expressing BCRP were 13.8-fold and approximately 2-fold, respectively, that in wild-type cells and were decreased

15) Estimated by population pharmacokinetic (PPK) analysis performed in phase III studies (Studies GS-US-292-0104 and GS-US-292-0111).

to a level comparable to that in wild-type cells in the presence of cyclosporin A or Ko134. The absolute BA of orally administered TAF (2 mg/kg) was evaluated in male dogs (n = 3/group) that had or had not previously received cyclosporin A 75 mg, a P-gp inhibitor. C_{max}, AUC_{0-t}, and the absolute BA of TAF in the cyclosporin A group were approximately 10-fold those in the control group. Pretreatment with cyclosporin A had no notable effect on the plasma levels of TFV, and C_{max} and AUC_{0-t} of TFV-DP in PBMCs from dogs in the cyclosporin A group were approximately 2-fold those in PBMCs from dogs in the control group. The above data from the study in Caco-2 cell monolayers and from the study in dogs receiving cyclosporin A suggested that TAF is a substrate of P-gp and BCRP, and that inhibition of these transporters may increase the absorption of TAF.

Intracellular uptakes of TAF by OATP1B1 and OATP1B3 were evaluated in Chinese hamster ovary cells expressing these transporters. The uptake rates into OATP1B1- and OATP1B3-expressing cells were approximately 30% and 168% higher, respectively, than that into wild-type cells, while in the presence of rifampicin, an inhibitor of OATP1B1 and OATP1B3, they were approximately 48% and 76% lower, respectively, than that into wild-type cells. These results suggest that TAF is a substrate of OATP1B1 and OATP1B3.

Intracellular uptakes of TAF and TFV by OAT1 and OAT3 were evaluated in HEK293T cells expressing these transporters. The uptake amounts of TAF into OAT1- or OAT3-expressing HEK293T cells were similar to that into wild-type cells, and were not affected by the presence of probenecid, an OAT inhibitor. However, the uptake amounts of TFV into OAT1- and OAT3-expressing HEK293T cells were approximately 83-fold and 8.4-fold, respectively, that into wild-type cells, and decreased in the presence of probenecid. The above results suggest that TFV is a substrate of OAT1 and OAT3, while TAF is not.

4.R Outline of the prior assessment conducted by PMDA

PMDA's view:

Although the submitted non-clinical pharmacokinetics data of TAF do not include study data on placental transfer or excretion in milk, cautionary statements regarding administration to pregnant, possibly pregnant, or lactating woman should be included in the package insert etc., since placental transfer and excretion in milk of TFV have been reported in animals.

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

The prior assessment requestor submitted the results from toxicity studies of TAF, namely single-dose toxicity, repeat-dose toxicity, genotoxicity, reproductive and developmental toxicity, local tolerance, and other toxicity studies (studies on mechanism of toxicity and study on impurities, etc.). Unless otherwise specified, water containing 0.1% (w/v) Tween 20 and 0.1% (w/v) hydroxypropylmethylcellulose (K100LV) was used as vehicle, and the dose levels are expressed as free base equivalents.

Although no toxicity studies of TAF in combination with the other 3 active ingredients (EVG, COBI, and FTC) were conducted, the prior assessment requestor explained that the E/C/F/TAF FDC tablet is unlikely to be associated with increased toxicological concerns compared with FTC, EVG, COBI, or TAF used as a single agent because they have no common main target organs of toxicity.

5.1 Single-dose toxicity (CTD 4.2.3.1-1, 4.2.3.1-3)

Rats (n = 5/sex/group) received a single oral dose of TAF 0 (vehicle[16)]), 80, 240, or 800 mg/kg, and dogs (n = 1/sex/group) received a single oral dose of TAF 0 (vehicle[16)]), 24, 72, or 216 mg/kg. No animals died, and the approximate lethal dose was determined to be >800 mg/kg in rats and >216 mg/kg in dogs.

5.2 Repeat-dose toxicity

The main studies included oral dose studies in mice (13 weeks), rats (4 weeks and 26 weeks), dogs (4 weeks and 39 weeks), and monkeys (4 weeks). The main target organs of TAF toxicity were the nasal mucosa in mice; the kidneys and bone in rats; and the kidneys, bone, and the cardiovascular system, etc., in dogs. The prior assessment requestor explained that the effect on the cardiovascular system observed in dogs is likely due to decreased T3 levels and TAF is unlikely to have a direct impact on the cardiovascular system for the following reasons: the electrocardiographic data from the safety

16) Water containing 25 mmol/L of citric acid

pharmacology study of TAF showed no abnormalities up to 80 mg/kg/day [see "3.3 Safety pharmacology"]; a long-term treatment of TAF decreased thyroid hormone (triiodothyronine [T3]) levels in 39-week repeated oral dose toxicity study in dogs and hypothyroidism has been known to be associated with a decreased heart rate and PR and QT interval prolongations (*Vet Clin North Am Small Anim Pract.* 1994;24:495-507, *Vascul Pharmacol.* 2010;52:102-112). No electrocardiographic abnormalities were found in the study evaluating the effect of the E/C/F/TAF FDC tablet on the cardiovascular system in humans [see "6.2.5 QT/QTc study"]. The plasma exposure[17] (steady-state AUC_{last} [18]) to TAF at the no observed adverse effect level (NOAEL) (<8 mg/kg/day in mice, 20 mg/kg/day in rats, 1.6 mg/kg/day in dogs, and ≥24 mg/kg/day in monkeys) was 0.08 μg·h/mL in dogs (CTD 4.2.3.2-6) and 1.0 μg·h/mL in monkeys (CTD 4.2.3.2-2), and that to TFV at the NOAEL was 0.213 μg·h/mL in mice (CTD 4.2.3.2-9), 3.8 μg·h/mL in rats (CTD 4.2.3.2-5), 1.2 μg·h/mL in dogs (CTD 4.2.3.2-6), and 5.9 μg·h/mL in monkeys (CTD 4.2.3.2-2), while the plasma exposures[19] (steady-state AUC_{tau}) to TAF and TFV in humans at the clinical dose (10 mg/day as TAF) were 0.206 and 0.293 μg·h/mL, respectively [see "6.2.2.2.2 PPK analysis"]. On the basis of these data, the plasma exposures to TAF in dogs and monkeys were found to be less than comparable to and ≥5-fold, respectively, that in humans, and they were not calculable in mice or rats.[20] The plasma exposures to TFV were less than comparable to in mice, approximately 13-fold in rats, approximately 4-fold in dogs, and ≥20-fold in monkeys.

5.2.1 Thirteen-week repeated oral dose toxicity study in mice (CTD 4.2.3.2-9)

Mice (n = 15/sex/group) received oral doses of TAF 0 (vehicle), 8, 24, or 80 mg/kg/day for 13 weeks. Neutrophil infiltration into respiratory and olfactory mucosa in the turbinate and degeneration of the olfactory epithelium were observed in the ≥8 mg/kg/day groups; exudate in the nasal cavity was observed in the ≥24 mg/kg/day groups; and apoptosis in the rectal epithelium was observed in the 80 mg/kg/day group. Consequently, the NOAEL was determined to be <8 mg/kg/day.

5.2.2 Four-week repeated oral dose toxicity study in rats (CTD 4.2.3.2-4)

Rats (n = 10/sex/group) received oral doses of TAF 0 (vehicle[21]), 1.2, 5, 20, 80, or 320 mg/kg/day for 4 weeks. Reduced body weight gain was observed in the ≥20 mg/kg/day groups; and effects on bone parameters (including decreased 1.25-dihydroxyvitamin D levels) were observed in the ≥80 mg/kg/day groups; and decreased food consumption, reddish dirty fur around nasal and oral cavities, effects on leukocytic parameters (decreases in leukocyte and lymphocyte counts), effects on erythroid parameters (including decreases in red blood cell count and hemoglobin levels), abnormal clinical chemistry values (including increases in serum urea nitrogen and serum cholesterol), increased liver weight, effects on the thymus (including decreased weight and atrophy), atrophy of trabecular bone of the front limbs, effects on the kidneys (basification and karyomegaly of the renal tubules), and decreased bone mineral density (BMD), etc., were observed in the 320 mg/kg/day group. Consequently, the NOAEL was determined to be 5 mg/kg/day.

5.2.3 Twenty-six-week repeated oral dose toxicity study in rats (CTD 4.2.3.2-5)

Rats (n = 15/sex/group) received oral doses of TAF 0 (vehicle[22]), 4, 20, or 80 mg/kg/day for 26 weeks. Karyomegaly of the renal tubules, atrophy of tibial trabecular bone, and effects on bone parameters (including decreased 1.25-dihydroxyvitamin D levels, increased C-telopeptide levels, decreased BMD, and decreased bone mineral content) were observed in the 80 mg/kg/day group. On the basis of the above results, the NOAEL was determined to be 20 mg/kg/day.

5.2.4 Four-week repeated oral dose toxicity study in dogs (CTD 4.2.3.2-1)

Dogs (n = 4/sex/group) received oral doses of TAF 0 (vehicle[21]), 0.08, 0.24, 0.8, 2.48, or 8 mg/kg/day for 4 weeks. Effects on the gastrointestinal tract (including dark reddish change of the large intestine) and effects on the kidneys (basification and karyomegaly of the renal tubules) were observed in the

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17) Plasma exposure to TAF could not be calculated in mice or rats because plasma TAF levels were too low due to fast conversion of TAF to TFV in plasma.

18) For rats, AUC_{tau} is presented.

19) AUCs of TAF and TFV were calculated from the pooled data from phase III studies of E/C/F/TAF FDC (Studies GS-US-292-0104 and GS-US-292-0111).

20) The human equivalent dose (on a mg/m^2 basis) of the mouse NOAEL was <3.8-fold the clinical dose, and that of the rat NOAEL was 19.1-fold the clinical dose.

21) Water containing 50 mmol/L of citric acid

22) 0.9% benzyl alcohol containing 0.5% polysorbate 20 (NF) and 0.5% carboxymethylcellulose

≥2.48 mg/kg/day groups; and increased serum aspartate aminotransferase (AST) was observed in the 8 mg/kg/day group. On the basis of the above results, the NOAEL was determined to be 0.8 mg/kg/day.

5.2.5 Thirty-nine-week repeated oral dose toxicity study in dogs (CTD 4.2.3.2-6)

Dogs (n = 2-4/sex/group) received oral doses of TAF 0 (vehicle[22]), 1.6, 4.8, or 14.4/9.6[23] mg/kg/day for 13 or 39 weeks (animals in the 14.4/9.6 mg/kg/day group [high dose group] had a 3-month recovery period to assess reversibility after the 39 weeks of treatment). One male in the high dose group was sacrificed moribund; this animal showed decreased body weight, decreased food consumption, abnormal hematology values (decreases in monocyte and platelet counts), abnormal clinical chemistry values (increases in serum AST and triglycerides, etc.), enlargement of the mandibular lymph nodes associated with inflammation and plasma cell infiltration, monocyte infiltration in the posterior uvea, renal tubular degeneration in the kidneys, atrophy of the mesenteric lymph nodes etc., mucosal atrophy of the fundic gland, and degeneration and regeneration of the cecum and colon. Among surviving animals, effects on the lungs (including macrophage infiltration and interstitial inflammation) were observed in the ≥1.6 mg/kg/day groups; effects on the cardiovascular system (PR and QT interval prolongations [the high dose group only] and a decreased heart rate [the high dose group only]), effects on the kidneys (including degeneration, regeneration, and/or karyomegaly of the renal tubules), and brown pigment deposits in the liver were observed in the ≥4.8 mg/kg/day groups; and a decreased body weight or reduced body weight gain, decreased food consumption, abnormal clinical chemistry values (including increased serum creatinine, decreased serum albumin, and decreased serum T3 levels), effects on bone parameters (including decreased 1.25-dihydroxyvitamin D levels and decreased BMD), increases in lung and spleen weights, monocyte infiltration in the posterior uvea, brown pigment deposits in the adrenal gland, and macrophage infiltration in the spleen were observed in animals in the high dose group. These findings were reversible after the recovery period. The prior assessment requestor explained that the effects on the lungs observed in the 1.6 mg/kg/day and 4.8 mg/kg/day groups are of limited toxicological significance because these effects were very mild and not dose-dependent in frequency or intensity. Consequently, the NOAEL was determined to be 1.6 mg/kg/day.

5.2.6 Four-week repeated oral dose toxicity study in monkeys (CTD 4.2.3.2-2)

Rhesus monkeys (n = 3/sex/group) received oral doses of TAF 0 (vehicle[21]), 2.4, or 24 mg/kg/day or TFV 15 mg/kg/day for 4 weeks. No abnormalities occurred, and the NOAEL of TAF was determined to be ≥24 mg/kg/day.

5.3 Genotoxicity (CTD 4.2.3.3.1-1, 4.2.3.3.1-2, 4.2.3.3.2-1)

Bacterial reverse mutation assay, mouse lymphoma TK assay, and bone marrow micronucleus assay were conducted. All assay results were negative, and TAF was determined to be non-genotoxic.

5.4 Carcinogenicity

Although no carcinogenicity studies of TAF have been conducted, the prior assessment requestor explained that TAF is unlikely to have carcinogenic potential and such study is of little significance for the following reasons:

- Plasma TAF exposure in rodents is limited because TAF is rapidly metabolized to TFV.
- The plasma TFV exposures[24] (steady-state $AUC_{0\text{-}24}$) at the non-carcinogenic dose of TDF (300 mg/kg/day) in mice and rats determined in carcinogenicity studies of TDF (Review Report for Viread Tab. 300 mg [February 6, 2004]) are estimated to be ≥50-fold the plasma TFV exposure[19] in humans at the clinical dose of E/C/F/TAF FDC (10 mg as TAF).
- Because of the minimal levels of exposure to the metabolites in humans that are formed during the metabolic process from TAF to TFV [see "6.2.1.1 TAF"], TAF is unlikely to be genotoxic in light of structure-activity relationships based evaluation.

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[23] In the 14.4 mg/kg/day group, due to decreased body weight and serious effects on clinical signs, the dose was reduced to 9.6 mg/kg/day on Day 45 in males and on Day 51 in females.

[24] On the assumption that plasma levels are proportionate to the dose, plasma exposure to TDF ($AUC_{ss\ 0\text{-}24}$) in the 300 mg/kg/day group was estimated to be 22 and 25 μg·h/mL in male and female mice, respectively, and 16.69 and 15.72 μg·h/mL in male and female rats, respectively, based on the plasma levels in the 600 mg/kg group in carcinogenicity studies of TDF in mice and rats.

5.5 Reproductive and developmental toxicity

Fertility and early embryonic development to implantation were studied in rats, and embryo-fetal development was studied in rats and rabbits. No effects were observed on reproductive functions or early embryonic development in rats, or on embryo-fetal development in rabbits. Effects on embryo-fetal development in rats included decreased body weight and skeletal variations. The plasma exposures to TAF and TFV at the NOAEL for embryo-fetal development (80 mg/kg/day in rats and ≥80 mg/kg/day in rabbits) were equal to and approximately 59-fold, respectively, in rats and approximately 53-fold and approximately 93-fold, respectively, in rabbits as compared with those in humans at the clinical dose (10 mg as TAF).

Although the effects of TAF on pre- and postnatal development and maternal function have not been studied, the prior assessment requestor explained that TAF is unlikely to affect pre- and postnatal development and such study is of little significance for the following reasons:

- Plasma TAF exposure in rodents is limited because TAF is rapidly metabolized to TFV.
- The levels of exposure to the metabolites are minimal in humans that are formed during the metabolic process from TAF to TFV.
- The effects of TFV on pre- and postnatal development and maternal function can be evaluated on the basis of studies of TDF, and the plasma exposure to TFV ($AUC_{0-\infty}$: 5.88 μg·h/mL on Lactation Day 20 in maternal animals in the 50 mg/kg/day group [CTD 4.2.3.2-9]; and 11.7 μg·h/mL on Lactation Day 20 in maternal animals in the 150 mg/kg/day group [CTD 4.2.3.2-9]) at the NOAEL for general toxicity in maternal animals and offspring (50 mg/kg/day) or the NOAEL for functional development of offspring (150 mg/kg/day) is ≥20-fold that[19)] in humans (AUC_{tau}, 0.293 μg·h/mL [see "6.2.2.2.2 PPK analysis"]) at the clinical dose (10 mg as TAF).

5.5.1 Fertility and early embryonic development to implantation (CTD 4.2.3.5.1-1)

TAF 0 (vehicle), 20, 80, or 160 mg/kg/day were administered orally to male rats (n = 22/group) from 4 weeks prior to mating and throughout the mating period until the day before necropsy for approximately 10 weeks in total, and to female rats (n = 22/group) from 14 days prior to mating and throughout the mating period until Gestation Day 7 for approximately 5 weeks in total. Reduced body weight gain and decreased food consumption were observed in parent animals of both sexes in the 160 mg/kg/day group. No effects were observed on reproductive functions or on early embryonic development. Consequently, the NOAEL was determined to be 80 mg/kg/day for paternal and maternal general toxicity, and 160 mg/kg/day for reproductive functions and early embryonic development.

5.5.2 Embryo-fetal development

5.5.2.1 Embryo-fetal development study in rat (CTD 4.2.3.5.2-2)

Pregnant rats (n = 22-25/group) received oral doses of TAF 0 (vehicle), 20, 80, or 200 mg/kg/day from Gestation Day 6 to 17. Total litter resorption, salivation, reduced body weight gain, and decreased food consumption were observed in maternal animals in the 200 mg/kg/day group, and decreased body weight and skeletal variations (including inadequate ossification of sternum) were observed in embryos/fetuses in the 200 mg/kg/day group. Consequently, the NOAEL was determined to be 80 mg/kg/day for both maternal animals and embryos/fetuses.

5.5.2.2 Embryo-fetal development study in rabbit (CTD 4.2.3.5.2-4)

Pregnant rabbits (n = 17-20/group) received oral doses of TAF 0 (vehicle), 8, 24, or 80 mg/kg/day from Gestation Day 7 to 20. Decreased stool output, reduced body weight gain, and decreased food consumption were observed in maternal animals in the 80 mg/kg/day group. No abnormalities were observed in embryos/fetuses. Consequently, the NOAEL was determined to be 24 mg/kg/day for maternal animals and 80 mg/kg/day for embryos/fetuses.

5.6 Local tolerance (CTD 4.2.3.6-1, 4.2.3.6-2)

Bovine corneal opacity and permeability were studied as a part of the evaluation of eye irritation. The results revealed no effects of TAF (20%)[25)] on corneal opacity and permeability, and TAF was

[25)] 0.9% sodium chloride solution containing 20% (w/w) of TAF

determined not to be corrosive or strongly irritating. In addition, skin irritation was studied in rabbits, and TAF (0.5 g/site)[26] was considered not to be skin-irritating.

5.7 Other studies

Other studies conducted included local lymph node assay in mice, mechanistic studies of toxicity in rats and dogs, and toxicity studies of impurities in rats. Although no studies on toxicity of metabolites have been conducted, the prior assessment requestor explained that E/C/F/TAF FDC is unlikely to raise safety concerns associated with TAF metabolites since the metabolites (M18 and M28) that could be formed during the metabolic process from TAF to TFV have not been detected in human plasma, urine, or feces [see "6.2.1.1 TAF"] and since TFV-derived metabolites are identical to those formed from TDF.

5.7.1 Local lymph node assay in mice (CTD 4.2.3.7.1-1)

TAF 0% (vehicle[27]), 10%, 25%, or 50% or positive control substance (hexylcinnamic aldehyde) was applied to the ear auricles of female mice (n = 5/group). The results showed no lymphocyte proliferation in the auricular lymph node of mice treated with TAF, and TAF was considered unlikely to be skin-sensitizing.

5.7.2 Mechanism of toxicity

5.7.2.1 Study on bone turnover (CTD 4.2.3.7.3-1)

Male dogs (n = 3/group) received oral doses of TAF 0 (vehicle[21]), 30, or 60 mg/kg/day for 5 days. Decreases in body weight and food consumption, changes in leukocytic parameters (decreases in total leukocyte count, neutrophil count, and lymphocyte count, etc.), abnormal clinical chemistry values (increases in serum ALP and AST, etc.), increased urinary phosphorus levels, effects on bone metabolic markers (including decreases in serum 25-hydroxyvitamin D and calcitriol levels), effects on the gastrointestinal tract (including necrosis of mucosal epithelium), decreased myeloid cell count, and effects on lymphoid tissues (including thymus atrophy) were observed in the ≥30 mg/kg/day groups.

5.7.2.2 Study on effects on the kidneys (CTD 4.2.3.7.3-3)

Male rats (n = 10/group) received a single dose of TAF 0 (vehicle[21]), 80, or 800 mg/kg. Increased urinary calcium levels were observed in the 800 mg/kg group. The prior assessment requestor explained that this is a change related to increased serum calcium levels.

5.7.3 Study on impurities

General toxicity studies were conducted on impurities with specifications exceeding the qualification thresholds specified in "Impurities in New Drug Substances (PMSB/ELD Notification No. 1216001, dated December 16, 2002)." The prior assessment requestor explained that the structure-activity relationships based evaluation of these impurities,[28] for which the maximum acceptable daily intake is considered to be <1 mg/day, was conducted as recommended by "Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (PSEHB/ELD Notification No. 1110-3, dated November 10, 2015)," and the results showed that these impurities are non-genotoxic.

5.7.3.1 Two-week repeated oral dose toxicity study in rats (CTD 4.2.3.7.6-1)

Male rats (n = 10/group) received oral doses of vehicle or TAF 4 or 40 mg/kg from 2 batches[29] with different impurity levels once daily for 14 days. No abnormalities were observed in any groups, and thus no new toxicological findings were found that were attributable to the difference in impurity level.

5.7.3.2 Four-week repeated oral dose toxicity study in rats (CTD 4.2.3.7.6-2)

Rats (n = 10/sex/group) received oral doses of vehicle or TAF 25 or 50 mg/kg from 3 batches[30] with different impurity levels once daily for 4 weeks. The results showed no new toxicity findings or change in the severity of existing toxicity findings attributed to the difference in impurity level.

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[26] Applied after being dampened with 0.5 to 0.6 mL of distilled water.
[27] Mixture of acetone and olive oil (4:1 v/v)
[28] Impurities A, B, and C, and GS-7339
[29] A product batch containing 0.15% Impurity A, 0.05% Impurity B, and 0.94% GS-7339, and a product batch containing 0.22% Impurity A, 0.41% Impurity B, 0.12% Impurity C, and 13.1% GS-7339 were used.
[30] A product batch containing 0.13% Impurity A, 0.16% Impurity C, and 0.35% GS-7339, a product batch containing 0.13% Impurity A and 0.15% Impurity C, and a product batch containing 0.13% Impurity A, 0.15% Impurity C, and other impurities were used.

5.R Outline of the prior assessment conducted by PMDA

PMDA's view:

Further studies are not needed from a toxicological viewpoint because (i) the nephrotoxicity and the effects on bone parameters[31)] associated with TAF seen in the repeat-dose toxicity studies, which were similar to those noted with TDF, are likely to be changes associated with plasma TFV exposure, and (ii) the plasma exposure[19)] to TFV in humans receiving the E/C/F/TAF FDC tablet is lower than that[32)] in humans receiving TDF products (containing 300 mg of TDF) that are approved in Japan. The nephrotoxicity and the effects on bone parameters associated with E/C/F/TAF FDC found in humans will be described in "7.R.2.1 Summary of safety of the E/C/F/TAF FDC tablet in adult HIV-1 patients." Although no toxicity studies of TAF in combination with each one of the other 3 active ingredients (EVG, COBI, and FTC) were conducted, the prior assessment requestor's following explanation is acceptable: E/C/F/TAF FDC is unlikely to be associated with increased toxicological concerns compared with FTC, EVG, COBI, or TAF used as a single agent because there is no overlap in the main target organs of toxicity between TAF, FTC, EVG, and COBI. On the other hand, the following reviews were conducted to examine new findings associated only with TAF and not with TDF (degeneration/inflammation of the nasal mucosa and monocyte infiltration into organs including the eyes) and the safety of E/C/F/TAF FDC in children.

5.R.1 Degeneration/inflammation of the turbinate mucosa

PMDA asked the prior assessment requestor to explain the mechanism of the effects on the nasal mucosa in mice and the related safety concerns in humans.

The prior assessment requestor's explanation:

In the 13-week repeated oral dose toxicity study in mice, findings including neutrophil infiltration into respiratory and olfactory mucosa in the turbinate and degeneration of the olfactory epithelium were observed even at the low dose (8 mg/kg/day). In addition, multiple turbinate-specific metabolites (M1, M2, M29, M30, and M34) were detected in the *in vivo* distribution study in mice (CTD 4.2.2.4-2). It has been reported that, in mice, some isoforms are expressed only in the nasal cavity or at higher levels in the nasal cavity than in the liver, kidneys, or lungs due to the presence of nasal mucosa-specific drug-metabolizing enzymes (*J Pharmacol Exp Ther.* 1998;285:1287-1295). The expression levels of CYPs in the nasal mucosa have been reported to be extremely low in humans compared with those in rodents (*Chem Biol Interact.* 2004;147:247-258). Although some compounds (e.g., acetaminophen or imidazoles) are considered to cause injurious changes mediated by active metabolites in the nasal cavity of rodents, they have not been reported to cause such injuries in humans; therefore such compound-related changes are reported to have limited relevance for humans (*Toxicol Pathol.* 2006;34:827-852). Although CYP isoforms involved in the metabolism of TAF that are localized in mouse turbinate or turbinate-specific metabolites in other animal species are unknown, the findings observed in mouse nasal mucosa are likely to be caused by turbinate-specific metabolites of TAF in light of a certain level of exposure to metabolites of TAF in mouse turbinate [see "4.3.3 *In vivo* metabolism"]. The effects on the nasal mucosa in mice are unlikely to raise safety concerns in humans because the incidence of adverse events (e.g., nasal congestion and rhinitis) possibly related to nasal mucosal toxicity in clinical studies were comparable between the E/C/F/TAF FDC and control groups.

PMDA's view:

The prior assessment requestor's explanation of the mechanism of the effects on the nasal mucosa in mice is not well justified because no investigation of CYP isoforms involved in the metabolism of TAF in the turbinate has been conducted. However, given that the incidence of adverse events possibly related to nasal mucosal toxicity in clinical studies was comparable between the E/C/F/TAF FDC and control groups, and that such findings can be monitored in clinical settings, the prior assessment requestor's explanation is acceptable in that these effects are unlikely to raise safety concerns associated with clinical use of E/C/F/TAF FDC.

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31) Viread Tab. 300 mg [package insert]. 9th ed.

32) AUC_{tau} = 4.4 μg·h/mL (Stribild Combination Tab. [package insert]. 6th ed.)

5.R.2 Monocyte infiltration in the eyes

PMDA asked the prior assessment requestor to explain the mechanism of the monocyte infiltration in the eyes in dogs and the related safety concerns in humans.

The prior assessment requestor's explanation:
In the high dose group of the 39-week repeated oral dose toxicity study in dogs, monocyte infiltration in the posterior uvea was observed in 2 of 2 males and 1 of 2 females at 3 months post-dose, and 3 of 4 males and 1 of 4 females at 9 months post-dose. These findings are considered not to suggest a direct effect of TAF on the eyes, but likely to be changes secondary to deterioration in general condition for the following reasons:

- All these findings were minimal to mild in severity, and deterioration due to prolonged treatment, abnormal ophthalmological findings during the treatment period, or similar findings in the recovery group were not observed.
- Animals in the high dose group showed deterioration in general condition accompanied by decreased body weight at Week 3 or later and inflammatory changes including macrophage infiltration were observed in the lungs and spleen.
- TAF has low affinity to melanin and showed little distribution to ocular tissues in dogs (CTD 4.2.2.3-3 and 4.2.2.3-5).
- Inflammatory changes of ocular tissues have been reported to develop secondary to deterioration in general condition (*City Med J.* 1962;11:105-117, *Japanese Journal of Clinical Ophthalmology.* 1960;14:1123-1130).

However, given the high permeability of choroidal microvascular endothelial cells that constitute the uvea (*Practical Ophthalmology 6, Anatomical Physiology Necessary for Ophthalmic Clinic.* Bunkodo, 2005:220-237) and the abundance of leucocytes in the choroid even under normal conditions (*Toxicol Pathol.* 2006;34:148-151), the above findings may be attributed to an enhanced permeability of choroidal microvessels caused by some factors. The plasma exposures to TAF and TFV in animals with the above findings ($AUC_{0\text{-}24}$ at Week 39 in the high dose group, 1.95 and 13.7 μg·h/mL, respectively) were approximately 9- and 47-fold, respectively, those in humans[19)] at the clinical dose (steady-state AUC_{tau}, 0.206 and 0.293 μg·h/mL, respectively [see "6.2.2.2.2 PPK analysis"]). In addition, no abnormal eye-related histopathological findings were found in the repeat-dose toxicity studies in mice, rats, or monkeys. Furthermore, although adverse events related to ocular functions in the phase II study[33)] included eye disorders reported by 8 subjects (7.1%), a causal relationship to E/C/F/TAF FDC could not be ruled out for photophobia in 1 subject, and all events of eye disorders resolved during the course of treatment. On the basis of the above, the inflammatory changes in the posterior uvea in the 39-week repeated oral dose toxicity study in dogs are unlikely to become safety concerns in humans receiving E/C/F/TAF FDC.

PMDA's view:
Since the above findings are not suggestive of tissue toxicity and a certain level of safety margin is secured for such findings, the prior assessment requestor's explanation is acceptable in that safety concerns in humans are limited, although the detailed mechanism is unclear for those findings.

5.R.3 Safety in pediatric patients

PMDA asked the prior assessment requestor to explain safety concerns in adolescents (aged ≥12 years) treated with E/C/F/TAF FDC in terms of the target organs of toxicity of each active ingredient.

The prior assessment requestor's explanation:
Among the active ingredients of E/C/F/TAF FDC, no target organs of toxicity were identified for FTC that potentially affect humans. In repeat-dose toxicity studies in adult animals, the cecum and upper small intestine were identified as the target organs of toxicity of EVG; the immune system, liver, and thyroid were identified as the target organs of toxicity of COBI; and TAF was shown to primarily affect the kidneys, bone, and nasal cavity.

33) Phase II study in treatment-naïve adult HIV-1 patients (Study GS-US-292-0102)

The repeat-dose toxicity studies of EVG and COBI conducted in juvenile rats showed no specific impact up to the maximum doses (2000 mg/kg/day for EVG, 75 mg/kg/day for COBI). Also, the effects on the gastrointestinal tract associated with EVG and the effects on the liver and thyroid associated with COBI in adult animals have limited relevance for humans (see Review Report for Stribild Combination Tab. [February 19, 2013]). Although COBI was found to affect the immune system (decrease in IgG levels), new concerns related to development of immune function associated with E/C/F/TAF FDC are unlikely to arise in adolescents compared with adults because immune function develops mainly during the embryonic stage in humans and antibody titer (including IgG) has been reported to reach the adult levels within approximately 5 years after birth (*Environ Health Perspect.* 2000;108:463-473).

Although no studies of TAF were conducted in juvenile animals, the effects on the bone and kidneys noted in the repeat-dose toxicity studies in adult animals are considered to be caused by TFV. On the basis of the reported data on the subcutaneous dose toxicity study of TFV in newborn or juvenile monkeys, repeated doses of 10 mg/kg/day for ≥5 years to newborn monkeys 1 to 23 days of age did not reveal bone or renal toxicity, and the plasma exposure to the above TFV dose (after a 30-month subcutaneous administration to juvenile monkeys aged 30 months; AUC, 18 μg·h/mL; *Antimicrob Agents Chemother.* 2004;48:1469-1487) in juvenile monkeys was approximately 64-fold that (AUC, 283 ng·h/mL) in pediatric patients receiving 10 mg/day of TAF. Bone development, as measured by the length to distal epiphysis of femur, has been reported to continue until the age of 14 to 19 years in humans, the age of 15 to 17 weeks in rats, and the age of 8 to 11 months in dogs (*Birth Defects Res B Dev Reprod Toxicol.* 2003;68:86-110). Thus, the age of animals at the start of treatment in the 26-week repeated oral dose toxicity study of TAF in rats (6 weeks of age) and that in the 39-week repeated oral dose toxicity study of TAF in dogs (5 to 6 months of age) were adequate to evaluate the effects of TAF on bone development in the long-term toxicity study. In addition, given that anatomical and functional development of human kidneys completes within 180 days after birth (*Guidance for Industry Nonclinical Safety Evaluation of Pediatric Drug Products, 2006*), olfactory development within several days (Abman. In: Drs. Polin et al, eds. *Fetal and Neonatal Physiology* 2010:1899-1907), and ocular development within 4 months to 10 years (*Practical Ophthalmology 6, Anatomical Physiology Necessary for Clinical Ophthalmology* [in Japanese]. Bunkodo, 2005:306-313, *Vision Res.* 1986;26:847-855), new safety concerns due to TAF-related toxicity are unlikely to arise in adolescents compared with adults.

PMDA has concluded that the prior assessment requestor's explanation is acceptable from a toxicological viewpoint. The safety of E/C/F/TAF FDC in pediatric patients will be discussed in "7.R.2.2 Safety in pediatric HIV-1 patients."

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 the results from biopharmaceutic studies, namely 2 relative BA studies and 2 food effect studies (including 1 study in healthy adult Japanese subjects).

The following Formulations 1 and 2[34)] were used during clinical development of TAF as a single drug; Formulations 3, 4, 5, and 6[35)] during clinical development of E/C/F/TAF FDC; and Formulation 6 was selected as the commercial formulation.

- Formulation 1 contains 25 mg of TAF as TAF monofumarate (TAF:fumarate = 1:1).
- Formulation 2 contains 25 mg of TAF as TAF hemifumarate (TAF:fumarate = 2:1).
- Formulation 3 contains 25 or 40 mg of TAF as TAF monofumarate in the form of monolayer formulation.
- Formulation 4 contains 25 or 40 mg of TAF as TAF monofumarate in the form of bilayer formulation.
- Formulation 5 contains 10 mg of TAF as TAF hemifumarate.
- Formulation 6 is identical to Formulation 5 except for the film-coating color.

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34) TAF hemifumarate was selected to ensure removal of impurities during manufacturing process and for its thermal stability. Main clinical studies in which Formulation 1 was used were Studies GS-US-120-0104 and GS-US-292-0101, and Formulation 2, Study GS-US-292-0103.

35) The main clinical study in which Formulations 3 and 4 were used was Study GS-US-292-0101; Formulation 5, Studies GS-US-292-0102, GS-US-292-0103, and GS-US-292-0108; and Formulation 6, Studies GS-US-292-0104, GS-US-292-0106, GS-US-292-0109, GS-US-292-0110, GS-US-292-0111, GS-US-292-0112, GS-US-292-1316, GS-US-342-1167, and SBX5-1.

Concentrations of TAF, TFV, EVG, COBI, and FTC in human plasma were measured by LC/tandem mass spectrometry (LLOQ: 1 ng/mL for TAF, 0.3 or 5 ng/mL for TFV, 20 ng/mL for EVG and GS-9200, and 5 ng/mL for COBI and FTC). Concentrations of TAF and TFV in human urine were measured by LC/tandem mass spectrometry (LLOQ: 2 ng/mL for TAF and 10 ng/mL for TFV). Unless otherwise specified, PK parameters are presented as mean values, and the dose and concentration of TAF are expressed as free base equivalents.

6.1.1 Relative BA

6.1.1.1 Phase I study (CTD 5.3.3.1-2, Study GS-US-292-0101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The relative BAs of STB (EVG/COBI/FTC/TDF = 150/150/200/300 mg) QD and Formulation 1 (TAF 25 mg tablet) QD administered orally for 12 days were compared with that of Formulation 3 (E/C/F/TAF = 150/150/200/25 mg) QD administered orally for 12 days in healthy adult non-Japanese subjects (37 in PK evaluation).[36] The data obtained on Day 12 are shown in Table 13. After administration of Formulation 3, the exposures to TAF and TFV were higher than those after administration of Formulation 1 (TAF 25 mg tablet), while the exposure to TFV was lower than that after administration of STB. The exposures to EVG, COBI, and FTC after administration of Formulation 3 were comparable to those after administration of STB.

Table 13. Ratio of least-square geometric means of PK parameters of the active ingredients (Formulation 3/STB, or Formulation 3/Formulation 1)

		N	Ratio of least-square geometric means [90% confidence interval]		
			AUC[a)]	C_{max}	C_{tau}
TAF	Formulation 3/ Formulation 1	19	2.22 [2.00, 2.46]	2.23 [1.87, 2.65]	-
TFV	Formulation 3/ Formulation 1	19	3.07 [2.90, 3.24]	3.68 [3.20, 4.23]	3.02 [2.83, 3.21]
	Formulation 3/STB		0.23 [0.21, 0.24]	0.14 [0.12, 0.16]	0.39 [0.37, 0.41]
EVG	Formulation 3/STB	19	1.11 [1.04, 1.19]	1.13 [1.04, 1.23]	1.02 [0.94, 1.12]
COBI	Formulation 3/STB	19	1.09 [1.04, 1.13]	1.10 [1.04, 1.17]	1.02 [0.88, 1.18]
FTC	Formulation 3/STB	19	0.99 [0.96, 1.03]	1.04 [0.97, 1.10]	1.00 [0.92, 1.08]

-, Not evaluated

a) AUC_{last} is presented for TAF, and AUC_{tau} is presented for TFV, EVG, COBI, and FTC.

6.1.1.2 Phase I study (CTD 5.3.1.2-1, Study GS-US-292-0103 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The relative BAs of combination treatment with EVG 150 mg and COBI 150 mg QD and combination treatment with FTC 200 mg and Formulation 2 (TAF 25 mg tablet) QD administered orally for 12 days were compared with that of Formulation 5 (E/C/F/TAF = 150/150/200/10 mg) QD administered orally for 12 days in healthy adult non-Japanese subjects (33 in PK evaluation).[37] The data obtained after the last dose are shown in Table 14.

Table 14. Ratio of least-square geometric means of PK parameters of the active ingredients (Formulation 5/EVG + COBI, or Formulation 5/FTC + Formulation 2)

		n	Ratio of least-square geometric means [90% CI]		
			AUC[a)]	C_{max}	C_{tau}
TAF	Formulation 5/ FTC + Formulation 2	19	0.91 [0.84, 0.99]	0.99 [0.85, 1.15]	-
TFV	Formulation 5/ FTC + Formulation 2	19	1.24 [1.17, 1.31]	1.14 [0.98, 1.34]	1.25 [1.18, 1.34]
EVG	Formulation 5/ EVG + COBI	14	0.95 [0.92, 0.98]	0.90 [0.85, 0.96]	0.98 [0.88, 1.08]
COBI	Formulation 5/ EVG + COBI	14	1.02 [0.98, 1.06]	1.04 [0.99, 1.09]	1.16 [1.02, 1.33]
FTC	Formulation 5/ FTC + Formulation 2	19	1.18 [1.14, 1.22]	1.09 [1.03, 1.16]	1.21 [1.15, 1.28]

-, Not evaluated

a) AUC_{last} is presented for TAF, and AUC_{tau} is presented for TFV, EVG, COBI, and FTC.

[36] A four-treatment, four-period crossover study was conducted with a 2-day washout period between each treatment period. A formulation containing 40 mg of TAF was also administered in a study, but the results are not presented here.

[37] A two-treatment, two-period crossover study was conducted in 2 cohorts (Formulation 5 or EVG + COBI in Cohort 1, and Formulation 5 or FTC + Formulation 2 in Cohort 2).

6.1.2 Food effect study (CTD 5.3.3.1-4, Study SBX5-1 [20 to 20])

The food effect was evaluated in healthy adult Japanese subjects (12 in PK evaluation), who received a single oral dose of E/C/F/TAF FDC under fasted conditions, within 5 minutes after a light meal (approximately 250 kcal, containing approximately 30% fat), and within 5 minutes after an ordinary meal (approximately 400 kcal, containing approximately 20% fat).[38] The results are shown in Table 15. C_{max} and AUC_{inf} of EVG were higher in the immediate postprandial group than in the fasted group. However, C_{max} and AUC_{inf} of EVG were comparable between the ordinary meal and light meal groups, and those of TAF, TFV, COBI, and FTC were comparable between the fasted, light meal, and ordinary meal groups.

Table 15. PK parameters of the active ingredients after administration of E/C/F/TAF FDC in the fasted, light meal, and ordinary meal groups

		N	Immediately after ordinary meal	Immediately after light meal	Fasted
EVG	AUC_{inf} (ng·h/mL)	12	32,267 (24)	33,020 (28)	17,111 (47)
	C_{max} (ng/mL)		2488 (17)	2817 (23)	1166 (51)
	t_{max} (h)[a]		4.0 [3.0-5.0]	4.0 [3.0-5.0]	4.0 [3.0-8.0]
	$t_{1/2}$ (h)[a]		5.9 [3.9-8.0]	5.6 [4.1-7.1]	6.4 [4.9-9.8]
COBI	AUC_{inf} (ng·h/mL)	12	6851 (42)	7810 (39)	7715 (39)
	C_{max} (ng/mL)		1081 (29)	1120 (21)	1043 (23)
	t_{max} (h)[a]		2.5 [2.0-5.0]	3.0 [2.0-5.0]	4.0 [2.0-5.0]
	$t_{1/2}$ (h)[a]		3.1 [1.8-4.4]	3.1 [1.9-4.5]	3.3 [2.7-4.6]
FTC	AUC_{inf} (ng·h/mL)	12	14,193 (19)	13,894 (16)	14,295 (20)
	C_{max} (ng/mL)		2759 (27)	2858 (24)	2562 (29)
	t_{max} (h)[a]		2.0 [1.0-4.0]	2.0 [1.0-3.0]	1.5 [1.0-3.0]
	$t_{1/2}$ (h)[a]		12.7 [8.9-20.9]	12.9 [11.5-19.6]	12.8 [7.4-23.3]
TAF	AUC_{inf} (ng·h/mL)	12	154 (22)	153 (31)	141 (30)
	C_{max} (ng/mL)		163.2 (46)	165.2 (48)	159.6 (61)
	t_{max} (h)[a]		1.0 [0.3-2.0]	1.0 [0.5-2.0]	0.5 [0.5-1.0]
	$t_{1/2}$ (h)[a]		0.4 [0.4-0.5]	0.5 [0.4-1.0]	0.5 [0.4-0.7]
TFV	AUC_{inf} (ng·h/mL)	12	288 (17)	294 (12)	279 (19)
	C_{max} (ng/mL)		8.04 (22)	8.31 (20)	8.49 (30)
	t_{max} (h)[a]		2.0 [1.0-3.0]	2.0 [1.0-3.0]	2.0 [1.0-3.0]
	$t_{1/2}$ (h)[a]		44.1 [33.4-48.7]	42.8 [35.7-49.7]	39.3 [35.4-45.7]

Mean (CV%)
a) Median [range]

6.2 Clinical pharmacology

The prior assessment requestor submitted the results from phase I studies in healthy adult subjects and HIV-1 patients to evaluate TAF as a single drug; and from a phase I study in healthy adult subjects and phase II and III studies in HIV-1 patients to evaluate E/C/F/TAF FDC. In addition, the prior assessment requestor submitted the results from phase I studies of: combination administration of EVG and COBI, and combination administration of FTC and TAF in healthy adult subjects. Unless otherwise specified, PK parameters are presented as mean values.

6.2.1 Studies in healthy adult subjects

6.2.1.1 TAF

Mass balance study (CTD 5.3.3.1-1, Study GS-US-120-0109 [20 to 20])

The mass balance of TAF (containing 3.7 MBq of ^{14}C-TAF) administered as a single oral dose of 25 mg was evaluated in healthy adult non-Japanese subjects (8 in PK evaluation). A total of 84.4% of the administered radioactivity was recovered within 504 hours post-dose (36.2% in urine and 47.2% in feces). Uric acid, TAF, and TFV accounted for 73.9%, 1.8%, and 1.5%, respectively, of the radioactivity AUC from 1 to 96 hours post-dose. In urine and feces, TFV accounted for 22.2% and 31.4%, respectively, of the administered radioactivity, and no other metabolites were detected that accounted for >2% of the administered radioactivity.

6.2.1.2 E/C/F/TAF

Phase I study (CTD 5.3.3.1-3, Study GS-US-292-0108 [20 to 20])

[38] This study was conducted as a three-treatment, three -period crossover study with a ≥10-day washout period between each treatment period.

The PK of E/C/F/TAF FDC (150/150/200/10 mg) administered orally as a single dose or once daily for 12 days were evaluated for each active ingredient in healthy adult Japanese and Caucasian subjects (20 in PK evaluation), yielding the results shown in Table 16. The prior assessment requestor explained that the exposures to individual active ingredients are comparable and no substantial ethnic differences exist.

Table 16. PK parameters of the active ingredients in Japanese and Caucasian subjects receiving a single oral dose or multiple oral doses of E/C/F/TAF FDC

	Single dose administration		Multiple dose administration for 12 days	
	Japanese (n = 10)	Caucasian (n = 10)	Japanese (n = 9)	Caucasian (n = 8)
TAF				
AUC (ng·h/mL)[a)]	242 (22)	236 (30)	254 (26)	292 (28)
C_{max} (ng/mL)	360 (29)	259 (39)	317 (19)	319 (45)
C_{last} (ng/mL)	-	-	2.1 (46)	2.4 (63)
TFV				
AUC (ng·h/mL)[a)]	339 (19)	338 (16)	331 (12)	412 (37)
C_{max} (ng/mL)	20.3 (55)	11.5 (39)	24.5 (32)	23.1 (31)
C_{tau} (ng/mL)	-	-	11.1 (16)	14.9 (29)
EVG				
AUC (ng·h/mL)[a)]	24,629 (19)	31,144 (41)	31,195 (38)	35,804 (29)
C_{max} (ng/mL)	2143 (16)	2496 (43)	2964 (33)	3698 (32)
C_{tau} (ng/mL)	-	-	380 (64)	558 (40)
COBI				
AUC (ng·h/mL)[a)]	6273 (38)	5680 (56)	8228 (19)	10,644 (39)
C_{max} (ng/mL)	958 (37)	810 (44)	1293 (17)	1457 (35)
C_{tau} (ng/mL)	-	-	17.8 (28)	28.5 (47)
FTC				
AUC (ng·h/mL)[a)]	12,020 (13)	12,647 (17)	13,142 (12)	14,827 (23)
C_{max} (ng/mL)	2652 (21)	2381 (21)	2945 (12)	2744 (15)
C_{tau} (ng/mL)	-	-	75.4 (29)	102 (44)

Mean (CV%); -, Not evaluated

a) AUC_{inf} is presented for single administration, AUC_{tau} is presented for multiple dose administration, and AUC_{last} is presented for multiple dose administration of TAF.

6.2.2 Studies in patients

6.2.2.1 TAF

Phase I study (CTD 5.3.4.2-2, Study GS-US-120-0104 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Concentrations of TAF and TFV in plasma and of TFV-DP in PBMCs in non-Japanese HIV-1 patients (31 in PK evaluation) were evaluated after multiple oral doses of TAF 8, 25, or 40 mg QD or TDF 300 mg QD for 10 days, yielding the results shown in Table 17.

Table 17. PK parameters of TAF and TFV in plasma and of TFV-DP in PBMCs

	Day 1				Day 10			
	TAF 8 mg	TAF 25 mg	TAF 40 mg	TDF 300 mg	TAF 8 mg	TAF 25 mg	TAF 40 mg	TDF 300 mg
TAF								
n	9	8	8		9	8	8	
AUC_{last} (ng·h/mL)	38.4 (80.6)	140 (57.8)	322 (42.0)		54.7 (92.6)	115 (33.4)	309 (33.6)	
C_{max} (ng/mL)	58.3 (61.1)	232 (76.8)	599 (50.4)		85.8 (116.3)	224 (58.8)	630 (57.0)	
t_{max} (h)[a)]	0.5 [0.3-1.0]	0.5 [0.3-1.5]	0.4 [0.3-0.5]		0.5 [0.3-1.0]	0.5 [0.5-1.0]	0.5 [0.3-1.0]	
$t_{1/2}$ (h)[a)]	0.3 [0.2-0.6)	0.4 [0.2-0.7]	0.4 [0.3-0.7]		0.4 [0.2-0.8][c)]	0.4 [0.3-0.8]	0.4 [0.3-0.7]	
TFV								
n	9	8	8	6	9	8	8	6
AUC (ng·h/mL)[b)]	49.4 (30.3)	196 (27.2)	287 (33.7)	1,719 (57.9)	65.5 (23.5)	268 (26.7)	406 (12.7)	1,918 (39.4)
C_{max} (ng/mL)	2.0 (31.1)	6.5 (40.1)	14.0 (20.3)	181 (50.5)	4.2 (24.7)	15.7 (22.1)	28.3 (8.7)	252 (36.6)
C_{tau} (ng/mL)	0.7 (19.8)	2.4 (23.5)	4.0 (27.2)	23.9 (57.5)	2.1 (33.8)	9.2 (26.1)	13.3 (16.0)[d)]	38.7 (44.7)
t_{max} (h)[a)]	1.0 [1.0-2.0]	1.5 [1.0-3.0]	1.0 [0.5-8.0]	1.3 [0.5-2.0]	1.5 [1.0-3.0]	1.5 [1.0-2.0]	1.3 [0.5-2.0]	1.3 [0.5-2.0]
$t_{1/2}$ (h)[a)]	23.9 [17.6-49.5][d)]	29.8 [20.9-46.4]	24.6 [11.1-31.7]	15.6 [12.0-17.9]	30.8 [11.5-88.2][c)]	40.2 [28.6-62.3][d)]	36.0 [23.8-67.4][d)]	14.9 [8.9-17.4]
TFV-DP								
n	-	-	-	-	6	4	7	4
AUC_{tau} (μmol·h/L)	-	-	-	-	3.5 (77.6)	21.4 (76.8)	74.5 (92.7)	3.0 (118)

Mean (CV%); -, Not evaluated

a) Median [range]; b) AUC_{inf} is presented for Day 1 and AUC_{tau} is presented for Day 10; c) n = 8; d) n = 7

6.2.2.2 E/C/F//TAF

6.2.2.2.1 Phase III study (Studies GS-US-292-0104 and GS-US-292-0111) (CTD 5.3.5.1-3, 5.3.5.1-7)

Concentrations of TFV in plasma and of TFV-DP in PBMCs were evaluated in HIV-1 patients (66 in plasma PK evaluation, 35 in PBMC PK evaluation) at Weeks 2 to 8 of 48-week treatment with E/C/F/TAF FDC QD or STB QD administered orally, yielding the results shown in Table 18.[39)]

Table 18. PK parameters of TFV in plasma and of TFV-DP in PBMCs in subjects receiving E/C/F/TAF FDC or STB

	E/C/F/TAF FDC	STB	Ratio of least-square geometric means [90% CI]
TFV (in plasma)			
n	36	30	
AUC_{tau} (ng·h/mL)	297 (20)	3410 (25)[a)]	8.8 [7.9, 9.7]
C_{max} (ng/mL)	17 (22)	416 (29)[a)]	4.1 [3.7, 4.6]
C_{tau} (ng/mL)	10 (23)[b)]	69 (32)	14.8 [13.1, 16.7]
TFV-DP (in PBMCs)			
n	21	14	
AUC_{tau} (ng·h/mL)	16 (62)	4.9 (98)	411 [234, 722]

Mean (CV%); a) n = 29; b) n = 35

6.2.2.2.2 PPK analysis (CTD 5.3.3.5-1)

The population pharmacokinetic (PPK) analysis (NONMEM ver. 7.3.0) was performed on PK data of healthy adult subjects and HIV-1 patients obtained from phase I, II, and III studies[40)] (1191 subjects and 3960 time points for TAF; 1557 subjects and 10,186 time points for TFV). A 2-compartment model with absorption lag and zero- and first-order absorption was selected as the final model to describe the PK of

39) The plasma AUC_{last} and C_{max} of TAF at Weeks 2 to 8 were 230 ng·h/mL and 259 ng/mL, respectively, in Study GS-US-292-0104 and 259 ng·h/mL and 202 ng/mL, respectively, in Study GS-US-292-0111.

40) Three phase I studies (Studies GS-US-292-0103, GS-US-292-0108, and GS-US-292-0110), 1 phase II study (Study GS-US-292-0102), and 5 phase III studies (Studies GS-US-292-0106, GS-US-292-0104, GS-US-292-0109, GS-US-292-0111, and GS-US-292-0112)

TAF. No significant covariates were identified for CL/F or Vc/F of TAF.[41)] A 2-compartment model with zero- and first-order absorption was selected as the final model to describe the PK of TFV. Creatinine clearance (CL_{cr}), sex, and race were identified as significant covariates for CL/F of TFV, and CL_{cr} and subject type (HIV-1 patients/healthy adult subjects) were identified as covariates for Vc/F and Vp/F of TFV.[41)] The following were the final model-derived steady-state PK parameter values after administration of E/C/F/TAF FDC determined based on the data from phase III studies (Studies GS-US-292-0104 and GS-US-292-0111): AUC_{tau} of TAF, 206.4 ng·h/mL; C_{max} of TAF, 162.2 ng/mL; AUC of TFV, 292.6 ng·h/mL; C_{max} of TFV, 15.2 ng/mL; and C_{min} of TFV, 10.6 ng/mL. The prior assessment requestor explained that the effect of covariates related to TFV is not clinically significant because the exposure to TFV after administration of E/C/F/TAF FDC was approximately 10% of that after administration of STB (AUC_{tau} and C_{max} of TFV after administration of STB were 3410 ng·h/mL and 416 ng/mL, respectively [see "6.2.2.2.1 Phase III study"]).

The final model-derived estimated PK parameter values after multiple oral doses of E/C/F/TAF FDC QD in HIV-1 patients determined on the basis of the data from phase II and III studies[42)] are shown in Table 19 by renal function category.

Table 19. Estimated PK parameters in HIV-1 patients after multiple oral doses of E/C/F/TAF FDC QD by renal function category

	CL_{cr} ≥30 and <60 mL/min	CL_{cr} ≥60 and <90 mL/min	CL_{cr} >90 mL/min
TAF			
n	133	204	769
AUC_{tau} (ng·h/mL)	305 (113)	224 (86.8)	210 (94.1)
C_{max} (ng/mL)	209 (53.0)	166 (43.7)	159 (57.1)
TFV			
n	155	264	1053
AUC_{tau} (ng·h/mL)	670 (29.2)	421 (30.2)	286 (27.1)
C_{max} (ng/mL)	33.2 (28.7)	21.6 (33.4)	14.9 (25.4)
C_{min} (ng/mL)	24.2 (29.4)	15.3 (30.6)	10.4 (28.6)

Mean (CV%)

6.2.2.2.3 Phase II/III study in HIV-1 infected adolescents with body weight ≥35 kg (CTD 5.3.5.2-2, Study GS-US-292-0106 [May 2013 to ongoing])

The PK was evaluated at Week 4 of 48-week treatment with E/C/F/TAF FDC QD administered orally in HIV-1 patients aged ≥12 and <18 years with body weight ≥35 kg (PK evaluation, n = 24), yielding the results shown in Table 20.

Table 20. PK parameters at Week 4 of treatment with multiple oral doses of E/C/F/TAF FDC QD

	TAF (n = 24)	TFV (n = 24)	EVG (n = 24)	COBI (n = 24)	FTC (n = 24)
AUC (ng·h/mL)[a)]	189 (55.8)	288 (18.8)	23,840 (25.5)	8241 (36.1)	14,424 (23.9)
C_{max} (ng/mL)	167 (64.4)	17.6 (23.7)	2230 (19.2)	1202 (35.0)	2265 (22.5)
C_{tau} (ng/mL)	-	10.0 (21.4)	301 (81.0)	25.0 (180)	102 (38.9)

Mean (CV%); -, Not evaluated

a) AUC_{tau} is presented for EVG, COBI, FTC, and TFV; and AUC_{last}, for TAF.

6.2.3 Intrinsic factor studies

6.2.3.1 PK study in subjects with hepatic impairment (CTD 5.3.3.3-2, Study GS-US-120-0114 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK of TAF and TFV was evaluated after a single oral dose of TAF 25 mg in subjects with mild (Child-Pugh-Turcotte class A) and moderate (class B) hepatic impairment (n = 10/class) and 20 subjects with normal hepatic function. On the basis of the results shown in Table 21,[43)] the prior assessment requestor explained that dose adjustment is not required for patients with mild or moderate hepatic impairment. In addition, the prior assessment requestor explained that careful administration of E/C/F/TAF FDC will be recommended in patients with severe hepatic impairment as in the case of STB,

41) All potential covariates (body weight, CL_{cr}, healthy adult subjects/ HIV-1 patients, age, sex, and race) were examined for association with Vp/F (only of TFV), CL/F, and Vc/F.

42) Studies GS-US-292-0102, GS-US-292-0104, GS-US-292-0106, GS-US-292-0109, GS-US-292-0111, and GS-US-292-0112

43) The protein-unbound fraction of TAF in subjects with mild or moderate hepatic impairment (16%-19% and 21%-23%, respectively) did not apparently differ from that in subjects with normal hepatic function (14%-18%). The protein-unbound fraction of TFV was comparable also between subjects with mild or moderate hepatic impairment and subjects with normal hepatic function (≥99% in all subject populations).

which may cause increasing exposure to EVG (an active ingredient) in patients with severe hepatic impairment, although no studies in subjects with severe hepatic impairment were conducted.

Table 21. PK parameters of TAF and TFV after a single dose of TAF 25 mg in subjects with hepatic impairment and with normal hepatic function

	Subjects with hepatic impairment (n = 10)	Subjects with normal hepatic function (n = 10)	Ratio of least-square geometric means [90% CI]
TAF	Mild	Normal	
AUC_{inf} (ng·h/mL)	228 (47.7)	239 (39.8)	92.5 [66.3, 129]
C_{max} (ng/mL)	171 (55.5)	181 (54.2)	89.0 [57.7, 137]
TAF	Moderate	Normal	
AUC_{inf} (ng·h/mL)	206 (37.8)	181 (30.8)	113 [87.3, 145]
C_{max} (ng/mL)	133 (37.1)	124 (64.2)	119 [78.9, 178]
TFV	Mild	Normal	
AUC_{inf} (ng·h/mL)	276 (37.8)	307 (36.9)	89.2 [67.2, 118]
C_{max} (ng/mL)	8.2 (31.3)	8.4 (27.9)	97.0 [75.9, 124]
TFV	Moderate	Normal	
AUC_{inf} (ng·h/mL)	248 (38.0)	241 (15.1)	97.2 [77.0, 123]
C_{max} (ng/mL)	7.3 (24.2)	8.4 (30.4)	87.6 [70.5, 109]

Mean (CV%)

6.2.3.2 PK study in subjects with renal impairment (CTD 5.3.3.3-1, Study GS-US-120-0108 [[redacted] 20[redacted] to [redacted] 20[redacted]])

Concentrations of TAF and TFV in plasma and urine were evaluated after a single oral dose of TAF 25 mg in 14 subjects with severe renal impairment (CL_{cr} ≥15 and ≤29 mL/min) and 13 subjects with normal renal function (CL_{cr} ≥90 mL/min), yielding the results shown in Table 22.[44)]

Table 22. PK parameters of TAF and TFV after a single dose of TAF 25 mg in subjects with severe renal impairment and with normal renal function

	Subjects with severe renal impairment (n = 14)	Subjects with normal renal function (n = 13)	Ratio of least-square geometric means [90% CI]
TAF			
AUC_{inf} (ng·h/mL)	513 (47.3)	267 (49.2)	192 [138, 267]
C_{max} (ng/mL)	364 (65.7)	199 (62.1)	179 [124, 260]
$t_{1/2}$ (h)	0.75 (51.8)	0.53 (22.8)	-
CL_r (mL/min)	4.2 (77.6)	35.8 (51.7)	-
TFV			
AUC_{inf} (ng·h/mL)	2074 (47.1)	343 (27.2)	574 [457, 720]
C_{max} (ng/mL)	26.4 (32.4)	9.5 (36.5)	279 [231, 337]
$t_{1/2}$ (h)	56.5 (19.6)	51.3 (12.2)	-
CL_r (mL/min)	51.4 (40.1)	209 (24.6)	-

Mean (CV%); -, Not evaluated

6.2.3.3 Effect of UGT1A1 activity (CTD 5.3.3.3-3, Study GS-US-183-1004 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK of EVG was evaluated after oral administration of (EVG 150 mg + COBI 150 mg) QD for 10 days in 18 subjects with decreased UGT1A1 activity and 18 subjects with normal UGT1A1 activity,[45)] yielding the results shown in Table 23.

[44)] The prior assessment requestor explained that the protein-unbound fractions of TAF and TFV in subjects with severe renal impairment (14%-20% and 99%, respectively) were comparable to those in subjects with normal renal function (14%-20% and 97%-99%, respectively).

[45)] Subjects with decreased UGT1A1 activity were defined as subjects with UGT1A1*28, and subjects with normal UGT1A1 activity were defined as subjects with UGT1A1*1.

Table 23. PK parameters of EVG after oral administration of (EVG + COBI) QD for 10 days in subjects with decreased UGT1A1 activity and with normal UGT1A1 activity

	Subjects with decreased UGT1A1 activity (n = 18)	Subjects with normal UGT1A1 activity (n = 18)	Ratio of least-square geometric means [90% CI]
AUC_{tau} (ng·h/mL)	27,833 (35.5)	24,743 (22.8)	104 [79.9, 134]
C_{max} (ng/mL)	2205 (35.3)	2202 (32.2)	97.6 [78.4, 122]
C_{tau} (ng/mL)	589 (60.8)	507 (36.6)	121 [95.5, 152]

Mean (CV%)

6.2.4 Drug interaction studies

6.2.4.1 Study on interaction of E/C/F//TAF with sertraline (CTD 5.3.3.4-3, Study GS-US-292-1316 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK of each component of E/C/F/TAF FDC in concomitant use with sertraline 50 mg was evaluated in healthy adult non-Japanese subjects (19 in PK evaluation), yielding the results shown in Table 24.

Table 24. Ratio of least-square geometric means of PK parameters of TAF, TFV, EVG, COBI, FTC, and sertraline (combination therapy/non-combination therapy)

	Ratio of least-square geometric means [90% CI]					
	TAF (n = 19)	TFV (n = 19)	EVG (n = 19)	COBI (n = 19)	FTC (n = 19)	Sertraline (n = 19)
AUC[a] (ng·h/mL)	95.6 [89.2, 103]	102 [100, 104]	93.5 [89.5, 97.8]	99.9 [97.0, 103]	84.4 [81.1, 87.7]	93.3 [77.0, 113]
C_{max} (ng/mL)	100 [86.5, 116]	110 [100, 121]	87.5 [82.3, 93.1]	106 [101, 110]	89.6 [82.0, 97.9]	114 [93.7, 138]
C_{tau} (ng/mL)	-	101 [98.9, 103]	99.2 [93.5, 105]	86.8 [79.4, 94.9]	94.2 [89.9, 98.6]	-

-, Not evaluated

a) AUC_{last} is presented for TAF, AUC_{tau} is presented for TFV, EVG, COBI, and FTC, and AUC_{inf} is presented for sertraline.

6.2.4.2 Study on interaction of FTC/TAF in combination with EFV or with DRV and COBI (CTD 5.3.3.4-4, Study GS-US-311-0101 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK of each component was evaluated in healthy adult non-Japanese subjects (48 in PK evaluation) receiving the following regimens, yielding the results shown in Table 25: (a) FTC/TAF (200/40 mg) QD administered orally for 12 days, and then in combination with EFV 600 mg QD for another 14 days, (b) FTC/TAF (200/25 mg) QD administered orally for 12 days, and then in combination with DRV800 mg + COBI 150 mg QD for another 10 days, (c) (DRV800 mg + COBI 150 mg) QD administered orally for 10 days, and then in combination with FTC/TAF (200/25 mg) QD for another 12 days, or (d) TAF8 mg QD administered orally for 12 days, and then in combination with COBI 150 mg QD for another 10 days.

Table 25. Ratio of least-square geometric means of PK parameters of TAF, TFV, COBI, FTC, and DRV (combination therapy/non-combination therapy)

	Ratio of least-square geometric means [90% CI]				
	TAF	TFV	COBI	FTC	DRV
(a): FTC/TAF (200/40 mg) and EFV (n = 11)					
AUC[a] (ng·h/mL)	85.5 [72.1, 102]	79.7 [73.3, 86.7]	-	91.6 [87.4, 96.1]	-
C_{max} (ng/mL)	77.9 [57.7, 105]	75.5 [66.7, 85.5]	-	89.7 [81.3, 98.9]	-
C_{tau} (ng/mL)	-	81.6 [74.7, 89.1]	-	91.9 [86.1, 98.2]	-
(b) and (c): FTC/TAF (200/25 mg), DRV and COBI ([b] n = 11, [c] n = 14)[b]					
AUC[a] (ng·h/mL)	97.6 [80.4, 119]	324 [302, 347]	109 [103, 115]	124 [117, 131]	99.1 [91.5, 107]
C_{max} (ng/mL)	93.4 [72.2, 121]	316 [300, 333]	106 [100, 112]	113 [102, 124]	102 [95.6, 109]
C_{tau} (ng/mL)	-	321 [290, 354]	111 [98.0, 125]	131 [124, 138]	96.8 [81.5, 115]
(d): TAF (8 mg) and COBI (n = 12)					
AUC[a] (ng·h/mL)	265 [229, 307]	331 [310, 353]	-	-	-
C_{max} (ng/mL)	283 [220, 365]	334 [302, 370]	-	-	-
C_{tau} (ng/mL)	-	335 [312, 359]	-	-	-

-, Not evaluated

a) AUC_{last} is presented for TAF and AUC_{tau} is presented for TFV, COBI, FTC, and DRV;

b) Data for TAF, TFV, and FTC are from regimen (b), and data for COBI and DRV are from regimen (c).

6.2.4.3 Study on interaction of EVG + COBI combination with ledipasvir acetonate/sofosbuvir combination tablet (5.3.3.4-5, Study GS-US-344-0102 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK of EVG 150 mg + COBI 150 mg in combination with ledipasvir acetonate/sofosbuvir combination tablet (90/400 mg) was evaluated for each component in healthy adult non-Japanese subjects (29 in PK evaluation), yielding the results shown in Table 26.

Table 26. Ratio of least-square geometric means of PK parameters of each component (combination administration/single-agent administration)

	N	Ratio of least-square geometric means [90% CI]		
		C_{max}	AUC_{tau}	C_{tau}
EVG	29	0.88 [0.82, 0.95]	1.02 [0.95, 1.09]	1.36 [1.23, 1.49]
COBI		1.25 [1.18, 1.32]	1.59 [1.49, 1.70]	4.25 [3.47, 5.22]
Ledipasvir		1.63 [1.51, 1.75]	1.78 [1.64, 1.94]	1.91 [1.76, 2.08]
Sofosbuvir		1.33 [1.14, 1.56]	1.36 [1.21, 1.52]	-
GS-331007		1.33 [1.22, 1.44]	1.44 [1.41, 1.48]	1.53 [1.47, 1.59]

-, Not evaluated; GS-331007, a metabolite of sofosbuvir

6.2.5 QT/QTc study (CTD 5.3.4.1-1, Study GS-US-120-0107 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A four-treatment, four-period crossover study was conducted in 59 healthy adult non-Japanese subjects to evaluate the effects of a single oral dose of placebo or TAF 25 or 125 mg on the QT/QTc interval with a single oral dose of moxifloxacin 400 mg as the positive control.[46)] The mean difference in the change in QTc (corrected by Fridericia formula) from baseline between the TAF 125 mg and placebo groups peaked at 12 hours post-dose, the mean difference [90% confidence interval (CI)] was 0.9 [-1.0, 2.8] ms, and the upper bound of the 90% CI was below 10 ms for both dose groups. On the basis of these results, the prior assessment requestor explained that TAF does not prolong the QTc interval at exposures up to 125 mg.[47)] C_{max} of TAF and TFV in the QT/QTc study after administration of TAF 125 mg were 859 and 50.8 ng/mL, respectively, and AUC_{inf} were 1228 and 1543 ng·h/mL, respectively.[48)]

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46) Subjects had an 11-day washout period between each treatment period.

47) Three subjects receiving TAF 25 mg and 1 subject receiving TAF 125 mg had an absolute QTcB interval (corrected by Bazett formula) of >450 ms, and 1 subject receiving TAF 25 mg had an absolute QTcI interval (individually corrected QT interval) of >450 ms. The difference in the change in QTcF (corrected by Fridericia formula) from baseline between moxifloxacin and placebo groups reached the peak value [90% CI] of 11.5 [9.6, 13.5] ms at 3 hours post-dose.

48) A PPK analysis was performed on data from phase III studies (Studies GS-US-292-0104 and GS-US-292-0111) to estimate the PK parameters of TAF and TFV in HIV-1 patients receiving the E/C/F/TAF FDC tablet, revealing that C_{max} was 162.2 and 15.2 ng/mL, respectively, and AUC was 206.4 and 292.6 ng·h/mL, respectively [see "6.2.2.2.2 PPK analysis"].

6.R Outline of the prior assessment conducted by PMDA

6.R.1 Appropriateness of dose selection (combination ratio)

The prior assessment requestor's rationale for the proposed dose from a pharmacokinetic viewpoint:
The E/C/F/TAF FDC tablet was developed from STB by replacing TDF, an active ingredient, with TAF fumarate. TAF is stable in plasma and is converted to TFV through metabolism by cathepsin A in PBMCs. Therefore, a lower dose level of TAF than that of TDF can exert an antiviral activity higher than or comparable to that of TDF.

In a phase I study in HIV-1 patients (Study GS-US-120-0104), the time-weighted average change from baseline in plasma HIV-1 RNA level to Day 11 ($DAVG_{11}$) were -0.67, -0.94, -1.14, -0.45, and 0.13 log_{10} copies/mL, respectively, in the TAF 8, 25, and 40 mg groups, the TDF 300 mg group, and the placebo group. On the basis of the above, the dose of TAF as a single agent expected to achieve maximum antiviral activity was considered to be 25 mg.

Taking also into consideration that AUC_{last} and C_{max} of TAF after E/C/F/TAF (150/150/200/25 mg) administration were 2.2-fold those after TAF 25 mg administration alone [see "6.1.1.1 Phase I study"],[49] 10 mg was selected as the dose of TAF in E/C/F/TAF FDC. After E/C/F/TAF (150/150/200/10 mg) administration, AUC_{tau} and C_{max} of TFV in plasma were approximately 90% lower than those after STB administration, and AUC_{tau} of TFV-DP in PBMCs was ≥4-fold that after STB administration [see "6.2.2.2.1 Phase III study"]).

In the same way as STB, 150, 150, and 200 mg were selected as the dose of EVG, COBI, and FTC, respectively, and the exposures to EVG, COBI, and FTC in subjects receiving E/C/F/TAF (150/150/200/25 mg) in phase I study (Study GS-US-292-0101) were comparable to those seen in subjects receiving STB [see "6.1.1.1 Phase I study"].

Consequently, 150, 150, 200, and 10 mg were selected as the dose of EVG, COBI, FTC, and TAF in the E/C/F/TAF FDC tablet, respectively.

PMDA has concluded that the prior assessment requestor's explanation on the selection of the doses of EVG, COBI, FTC, and TAF is acceptable from a pharmacokinetic viewpoint.

6.R.2 Effects of meal timing

PMDA asked the prior assessment requestor to explain the appropriateness of administration after a meal specified in the proposed dosage and administration since the E/C/F/TAF FDC tablet was developed from STB by replacing the active ingredient TDF with TAF fumarate, and the approved dosage and administration for STB mandates administration during or immediately after a meal.

The prior assessment requestor's explanation:
The exposure to EVG has been known to be affected by food (see Review Report for Stribild Combination Tab. [February 19, 2013]). In the food effect study (Study SBX5-1), EVG was found to be the only active ingredient affected by food in the E/C/F/TAF FDC; AUC_{inf} of EVG after administration under fasted conditions was 50% lower than that after administration immediately after a meal [see "6.1.2 Food effect study"]. Concerning the food effect on EVG, E/C/F/TAF FDC in phase III studies (Studies GS-US-292-0104 and GS-US-292-0111) mandated administration "with food", but no detailed statement on the timing of administration in relation to meal was included in the protocols. Therefore, Japanese protocol of phase III study (Study GS-US-292-0104) adopted a requirement that E/C/F/TAF FDC should be administered after a meal, and the efficacy and safety in Japanese HIV-1 patients were evaluated under such protocol.

On the basis of the above, the recommended timing of the E/C/F/TAF FDC tablet administration in relation to meal may be "after a meal".

PMDA's view:
Recommendation of administer of the E/C/F/TAF FDC tablet after a meal is acceptable because Japanese HIV-1 patients received the E/C/F/TAF FDC tablet after a meal according to the protocol in

[49] The prior assessment requestor explained that inhibition of P-gp by COBI is involved in the increased exposure to TAF, a substrate of P-gp.

phase III studies (Studies GS-US-292-0104 and GS-US-292-0111). The efficacy and safety in Japanese HIV-1 patients who participated in phase III study (Study GS-US-292-0104) will be reviewed in "7.R.1 efficacy" and 7.R.2 Safety."

6.R.3 Differences in the PK of the E/C/F/TAF FDC tablet between HIV-1 infected adolescents with body weight ≥35 kg and adult HIV-1 patients

The prior assessment requestor's explanation on the PK of E/C/F/TAF FDC among adolescent HIV-1 patients (aged ≥12 and <18 years) with body weight ≥35 kg and adult HIV-1 patients:

The PK parameters of each active ingredient obtained in phase II/III study in adolescent HIV-1 patients with body weight ≥35 kg (Study GS-US-292-0106) [see "6.2.2.2.3 Phase II/III study in HIV-1 infected adolescents with body weight ≥35 kg"] were compared with those in studies in adult patients. The ratio of least-square geometric means [90% CI] of the PK parameters in adolescent HIV-1 patients with body weight ≥35 kg to that in adult patients (pooled data from Studies GS-US-292-0102 and GS-US-292-0103) is shown in Table 27. AUC_{last} of TAF tended to be lower in adolescent HIV-1 patients with body weight ≥35 kg. However, the minimum AUC_{tau} of TAF in responders[50] in phase III studies of E/C/F/TAF FDC in adult HIV-1 patients (Studies GS-US-292-0104 and GS-US-292-0111) was 47.2 ng·h/mL, which was lower than all of AUC (median [range], 199 [55.5, 646.3] ng·h/mL) in pediatric HIV-1 patients in phase II/III study (Study GS-US-292-0106). Therefore, the difference in AUC_{last} of TAF between adolescent HIV-1 patients with body weight ≥35 kg and adult patients is not clinically significant from a pharmacokinetic viewpoint.

Table 27. Ratio of least-square geometric means of PK parameters (Adolescent HIV-1 patients with body weight ≥35 kg/adult patients)

	Ratio of least-square geometric means [90% CI]				
	TAF	TFV	EVG	COBI	FTC
AUC[a] (ng·h/mL)	70.7 [56.1, 89.1]	87.6 [81.2, 94.5]	106 [94.7, 118]	79.0 [68.7, 90.8]	117 [107, 128]
C_{max} (ng/mL)	77.7 [59.9, 101]	91.5 [83.9, 99.8]	108 [97.9, 119]	78.6 [69.7, 88.6]	113 [103, 124]
C_{tau} (ng/mL)	-	86.9 [79.7, 94.8]	69.3 [52.8, 91.0]	60.4 [39.1, 93.3]	97.5 [83.4, 114]

-, Not evaluated

a) AUC_{tau} is presented for EVG, COBI, FTC, and TFV, and AUC_{last} is presented for TAF.

PMDA has concluded that the prior assessment requestor's explanation is acceptable from a pharmacokinetic viewpoint. The efficacy in adolescent HIV-1 patients with body weight ≥35 kg will be reviewed in "7.R.1.3 Efficacy of E/C/F/TAF FDC in pediatric HIV-1 patients."

6.R.4 PK in subjects with renal impairment

The prior assessment requestor's explanation on the PK of E/C/F/TAF FDC in subjects with renal impairment:

In a phase I study (Study GS-US-120-0108), AUC_{inf} of TAF after a single oral dose[51] of TAF 25 mg in subjects with severe renal impairment was 1.9-fold that in subjects with normal renal function. However, since the median AUC_{inf} of TAF [range] was 495.2 [165.5-1093.6] ng·h/mL, which fell within the range of steady-state AUC_{tau} (median [range], 184.9 [47.2-1869.3] ng·h/mL)[52] estimated from the data in phase III studies of E/C/F/TAF FDC (Studies GS-US-292-0104 and GS-US-292-0111), the above difference is not clinically significant. On the other hand, AUC_{inf} of TFV in subjects with severe renal impairment was 6.1-fold that in subjects with normal renal function [see "6.2.3.2 PK study in subjects with renal impairment"]. The PPK analysis revealed that AUC of TAF in HIV-1 patients with mild or moderate renal impairment was 1.5-fold that in HIV-1 patients with normal renal function, but, as in the case of subjects with severe renal impairment, fell within the range of steady-state AUC_{tau} estimated from the data in phase III studies (Studies GS-US-292-0104 and GS-US-292-0111). There was approximately a 2-fold difference in AUC of TFV [see "6.2.2.2.2 PPK analysis"]. These exposures to TFV in HIV-1 patients with mild or moderate renal impairment and subjects with severe renal

50) Defined as subjects with HIV-1 RNA levels of <50 copies/mL at Week 48.

51) The exposures to TAF and TFV were comparable between subjects receiving TAF 25 mg as a single drug and subjects receiving TAF 10 mg as E/C/F/TAF FDC [see "6.1.1.2 Phase I study"].

52) Estimated based on the final PPK model

impairment fell within the range of AUC_{tau} of TFV in healthy adult subjects with normal renal function or HIV-1 patients with normal renal function receiving TDF 300 mg[53)]

On the basis of the PK data obtained from subjects with normal renal function and subjects with severe renal impairment receiving EVG 150 mg QD and COBI 150 mg QD orally for 7 days, there were no substantial differences in the exposures to EVG and COBI.[54)] In phase III study (Study GS-US-292-0112), AUC_{tau} of FTC in HIV-1 patients with mild and moderate renal impairment receiving E/C/F/TAF FDC were 19,379.7 and 25,139.5 ng·h/mL, respectively, and C_{max} were 2500.9 and 3042.5 ng/mL, respectively. The exposure to FTC in subjects with moderate renal impairment receiving E/C/F/TAF FDC was comparable to that in subjects with mild renal impairment, for whom dose adjustment of FTC monotherapy is not required.

Consequently, dose adjustment is not required in subjects with mild or moderate renal impairment (CL_{cr} ≥30 mL/min) from a pharmacokinetic viewpoint. However, it is necessary to confirm that patients have CL_{cr} ≥30 mL/min at the start of treatment with E/C/F/TAF FDC, given the facts that dosing interval of FTC should be adjusted in patients with severe renal impairment (CL_{cr} <30 mL/min) unlike in patients with mild or moderate renal impairment (see Emtriva Capsules 200 mg [package insert]. 6th ed.) and that E/C/F/TAF FDC has never been used in patients with CL_{cr} <30 mL/min [see "7.2.4 Foreign phase III study"].

PMDA's view:
The prior assessment requestor's explanation on the PK of subjects with renal impairment treated with E/C/F/TAF FDC is acceptable from a pharmacokinetic viewpoint.

The safety of E/C/F/TAF FDC in HIV-1 patients with mild or moderate renal impairment, and the appropriateness of cautionary statements regarding use of E/C/F/TAF FDC in such patients will be reviewed in "7.R.2.1.1 Renal impairment."

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

The prior assessment requestor submitted the results from efficacy and safety studies of E/C/F/TAF FDC in HIV-1 patients, namely 1 phase II study (Study GS-US-292-0102), 1 phase II/III study (Study GS-US-292-0106), and 4 phase III studies (Studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0109, and GS-US-292-0112). These studies are summarized in Table 28. This section summarizes data from studies other than the phase II study (Study GS-US-292-0102).

53) AUC_{tau} of TFV in healthy adult subjects with normal renal function who received an oral dose of TDF 300 mg was 2197 ng·h/mL (Viread Tab. 300 mg [package insert]. 9th ed.). AUC_{tau} of TFV in HIV-1 patients with normal renal function who received an oral regimen containing TDF 300 mg was 2270 to 4630 ng·h/mL (CTD 5.3.3.3-1).

54) See "4.(i).A.(5) Effect of renal function on pharmacokinetics of EVG and COBI concomitantly administered" of Prior Assessment Report (1) in Review Report for Stribild Combination Tab. (February 19, 2013).

Table 28. Summary of main efficacy and safety studies of E/C/F/TAF FDC in HIV-1 patients

Study (phase)	Study design	Subjects	Dosage and administration (N)	Primary endpoint	Proportion of subjects who achieved the primary endpoint[a)]
GS-US-292-0102 (II)	Randomized, double-blind, comparative	Treatment-naïve adult HIV-1 patients	(a) E/C/F/TAF FDC QD (112) (b) STB QD (58)	Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24	(a) 88.4 (99) (b) 89.7 (52)
GS-US-292-0106 (II/III)	Open-label, uncontrolled	Treatment-naïve HIV-1 patients aged ≥12 and <18 years with body weight ≥35 kg	E/C/F/TAF FDC QD (50)	Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24[b)]	90.0 (45)
GS-US-292-0104 (III)	Randomized, double-blind, comparative	Treatment-naïve adult HIV-1 patients	(a) E/C/F/TAF FDC QD (435) (b) STB QD (432)	Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48	(a) 93.1 (405) (b) 92.4 (399)
GS-US-292-0111 (III)	Randomized, double-blind, comparative	Treatment-naïve adult HIV-1 patients	(a) E/C/F/TAF FDC QD (431) (b) STB QD (435)	Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48	(a) 91.6 (395) (b) 88.5 (385)
GS-US-292-0109 (III)	Randomized, open-label, comparative	Adult HIV-1 patients on an anti-HIV therapy containing TDF	(a) Switching to E/C/F/TAF FDC QD (959) (b) Continued FTC/TDF + 3rd agent (477)	Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48	(a) 97.2 (932) (b) 93.1 (444)
GS-US-292-0112 (III)	Open-label, uncontrolled	Treatment-naïve or on-treatment adult HIV-1 patients with mild or moderate renal impairment	(a) E/C/F/TAF FDCE QD (6, treatment-naïve) (b) E/C/F/TAF FDC QD (242, on-treatment)	Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24	(a) 83.3 (5) (b) 95.0 (230)
Study GS-US-292-1249 (III)	Open-label, uncontrolled study	Treatment-naïve or on-treatment adult HIV-1 patients superinfected with HBV	(a) E/C/F/TAF FDC QD (3, treatment-naïve) (b) E/C/F/TAF FDC QD (72, on-treatment)	A: Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 B: Proportion of subjects with HBV DNA <29 IU/mL at Week 24	A: (a) 100 (3), (b) 94.4 (68) B: (a) 33.3 (1), (b) 86.1 (62)

a) % (n); b) a secondary endpoint

7.1 Foreign phase II/III study (CTD 5.3.5.2-2, Study GS-US-292-0106 [May 2013 to ongoing])

An open-label, uncontrolled study was conducted to evaluate the PK, safety, and efficacy of E/C/F/TAF FDC in adolescent HIV-1 patients who were not previously treated with anti-HIV drugs[55)] (target sample size, 50 patients) at 9 study sites in 4 countries including the U.S.

Subjects received oral doses of E/C/F/TAF FDC QD during or immediately after a meal for 48 weeks.

All 50 subjects treated with E/C/F/TAF FDC were included in the full analysis set (FAS) and safety analysis set. The FAS was also for the efficacy analysis.

Regarding efficacy, the proportion of subjects with HIV-1 RNA levels <50 copies/mL[56)] at Week 24[57)] (the efficacy analysis set) was 90.0% (45 of 50) of subjects.

Adverse events (including abnormal changes in laboratory values) were reported by 42 of 50 subjects (84.0%) and, of these, adverse events considered related to the study drug by the (sub-)investigator (adverse drug reactions) (including abnormal changes in laboratory values) were reported by 18 of 50 subjects (36.0%). Adverse events with an incidence of ≥5% included respiratory tract infection (16 of 50 subjects [32.0%]); diarrhoea and upper respiratory tract infection (13 of 50 subjects [26.0%] each);

55) Inclusion criteria: aged ≥12 and <18 years; body weight ≥35 kg; HIV-1 RNA levels ≥1000 copies/mL; CD4-positive cell counts >100 cells/μL; and CL_{cr} ≥90 mL/min, at screening

56) FDA snapshot algorithm

57) The time point of efficacy evaluation was selected according to CHMP guideline (CHMP, EMA. *Guideline on the clinical development of medicinal products for the treatment of HIV infection Rev 3 [Draft]*, 19 Sep 2013).

nausea (12 of 50 subjects [24.0%]); headache (10 of 50 subjects [20.0%]); abdominal pain (8 of 50 subjects [16.0%]); vomiting (7 of 50 subjects [14.0%]); dizziness, body tinea, bronchopneumonia, and seborrhoeic dermatitis (6 of 50 subjects [12.0%] each); abdominal pain upper, vitamin D deficiency, urinary tract infection, rash papular, and cough (5 of 50 subjects [10.0%] each); vulvovaginal candidiasis and acne (4 of 50 subjects [8.0%] each); and somnolence, iron deficiency anaemia, constipation, conjunctivitis, folliculitis, malaria, nasopharyngitis, rhinitis, rhinorrhoea, and skin papilloma (3 of 50 subjects [6.0%] each). Adverse drug reactions with an incidence of ≥5% included nausea (10 of 50 subjects [20.0%]); abdominal pain (6 of 50 subjects [12.0%]); vomiting (5 of 50 subjects [10.0%]); and diarrhoea, abdominal pain upper, and somnolence (3 of 50 subjects [6.0%] each).

No deaths were reported. Serious adverse events were reported by 6 subjects (suicide attempt in 2 subjects; and urinary retention, neuralgia, constipation, bipolar I disorder, conduct disorder, substance abuse, visual impairment, autoimmune uveitis, drug abuse, subcutaneous tumor, radius fracture, ulna fracture, agitation, and suicidal ideation in 1 subject each [includes duplicate counting]); and a causal relationship to the study drug was ruled out for all events except visual impairment and autoimmune uveitis. Among serious adverse events, the outcomes of bipolar I disorder, conduct disorder, substance abuse, and drug abuse were reported not recovered/not resolved and all the remaining events were reported recovered/resolved. No adverse events led to treatment discontinuation.

7.2 Phase III studies

7.2.1 Global phase III study (CTD 5.3.5.1-3, Study GS-US-292-0104 [December 2012 to ongoing] [data cutoff, [redacted] 20[redacted]])

A randomized, double-blind, STB-controlled, parallel-group, comparative study was conducted to evaluate the efficacy and safety of E/C/F/TAF FDC in treatment-naïve non-Japanese and Japanese adult HIV-1 patients (target sample size, 840 [n = 420/group]) at 120 study sites in 11 countries including Japan and the U.S.

E/C/F/TAF FDC or STB QD was administered orally to subjects during or immediately after a meal for 96 weeks.

Among 872 randomized subjects (438 in the E/C/F/TAF FDC group, 434 in the STB group), all 867 subjects who received the study drug (435 in the E/C/F/TAF FDC group, 432 in the STB group)[58] were included in the FAS and safety analysis set, and the FAS was also for the efficacy analysis.

The proportion of subjects with an HIV-1 RNA level of <50 copies/mL at Week 48,[56] the primary endpoint, was as shown in Table 29. The between-group difference [95.002% CI] was 1.0% [-2.6%, 4.5%]; therefore, the non-inferiority of E/C/F/TAF FDC to STB was demonstrated because the lower bound of the 95.002% CI exceeded the predefined non-inferiority margin (-12%).

Table 29. Proportion of subjects with an HIV-1 RNA level of <50 copies/mL at Week 48

	E/C/F/TAF FDC	STB
Proportion of subjects with an HIV-1 RNA level of <50 copies/mL at Week 48	405/435 (93.1)	399/432 (92.4)
Between-group difference [95.002% CI]	1.0% [-2.6%, 4.5%]	

n/N (%)

Between-group difference was stratified by baseline HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL) and geographic region (in or out of the U.S.) and adjusted by the Mantel-Haenszel method. A total of 2 interim analyses were planned and performed, with α of 0.00001 being consumed in each analysis, leading to a calculated significance level of 0.04998 (two-sided) (Haybittle procedure).

Adverse events (including abnormal changes in laboratory values) were reported by 396 of 435 subjects (91.0%) in the E/C/F/TAF FDC group and 392 of 432 subjects (90.7%) in the STB group, and adverse drug reactions (including abnormal changes in laboratory values) were reported by 182 of 435 subjects (41.8%) in the E/C/F/TAF FDC group and 196 of 432 subjects (45.4%) in the STB group. Adverse events and adverse drug reactions with an incidence of ≥5% in any group are shown in Table 30.

[58] In Japan, 10 subjects (4 in the E/C/F/TAF FDC group, 6 in the STB group) received the study drug at 1 study site.

Table 30. Adverse events and adverse drug reactions with an incidence of ≥5% in any group

Event	Adverse events		Adverse drug reactions	
	E/C/F/TAF FDC	STB	E/C/F/TAF FDC	STB
N	435	432	435	432
Total	396 (91.0)	392 (90.7)	182 (41.8)	196 (45.4)
Diarrhoea	78 (17.9)	81 (18.8)	37 (8.5)	41 (9.5)
Nausea	62 (14.3)	75 (17.4)	49 (11.3)	55 (12.7)
Headache	50 (11.5)	51 (11.8)	28 (6.4)	28 (6.5)
Fatigue	33 (7.6)	37 (8.6)	24 (5.5)	19 (4.4)
Insomnia	27 (6.2)	23 (5.3)	8 (1.8)	9 (2.1)
Rash	25 (5.7)	18 (4.2)	5 (1.1)	2 (0.5)
Vomiting	23 (5.3)	20 (4.6)	5 (1.1)	11 (2.5)
Upper respiratory tract infection	50 (11.5)	64 (14.8)	0	1 (0.2)
Cough	37 (8.5)	31 (7.2)	0	0
Nasopharyngitis	35 (8.0)	31 (7.2)	1 (0.2)	0
Back pain	27 (6.2)	25 (5.8)	0	0
Arthralgia	26 (6.0)	17 (3.9)	1 (0.2)	2 (0.5)
Bronchitis	25 (5.7)	17 (3.9)	0	0
Syphilis	20 (4.6)	24 (5.6)	0	0
Pyrexia	18 (4.1)	23 (5.3)	2 (0.5)	0
Osteopenia	11 (2.5)	23 (5.3)	3 (0.7)	10 (2.3)

n (%)

Death occurred in 1 subject receiving E/C/F/TAF FDC (embolic stroke) and 1 subject receiving STB group (cardiac arrest); a causal relationship to the study drug was ruled out for both events.

Serious adverse events were reported by 37 of 435 subjects (8.5%) in the E/C/F/TAF FDC group and 29 of 432 subjects (6.7%) in the STB group; of these, events assessed as causally related to the study drug were reported by 3 subjects receiving E/C/F/TAF FDC (staphylococcal skin infection, rash erythematous, and hypovolaemic shock in 1 subject each) and by 1 subject receiving STB (immune reconstitution inflammatory syndrome). Among serious adverse events, the outcomes of headache, staphylococcal skin infection, mycobacterium avium complex infection, Burkitt's lymphoma, cerebral infarction, haemorrhagic transformation stroke, bacterial sepsis, and sleep apnoea syndrome in the E/C/F/TAF FDC group and the outcomes of cardiac failure congestive, anal squamous cell carcinoma, ligament rupture, meniscus injury, and eye infection syphilitic in the STB group were reported not recovered/not resolved, and all the remaining events were reported recovered/resolved.

Adverse events leading to treatment discontinuation were reported by 4 subjects receiving E/C/F/TAF FDC (dysphagia, proctalgia, pharyngitis, cerebral infarction, haemorrhagic transformation stroke, penile pain, and rash erythematous in 1 subject each [includes duplicate counting]) and by 6 subjects receiving STB (cardiac arrest, abdominal pain, immune reconstitution inflammatory syndrome, glomerular filtration rate decreased, temporomandibular joint syndrome, headache, depression, nephropathy, and renal failure in 1 subject each [includes duplicate counting]); and all events were assessed as causally related to the study drug except cardiac arrest, cerebral infarction, and haemorrhagic transformation stroke. Among adverse events leading to treatment discontinuation, the outcomes of renal failure, abdominal pain, temporomandibular joint syndrome, headache, depression, cerebral infarction, haemorrhagic transformation stroke, and nephropathy were reported not recovered/not resolved, and all the remaining events were reported recovered/resolved.

7.2.2 Foreign phase III study (CTD 5.3.5.1-7, Study GS-US-292-0111 [March 2013 to ongoing] [data cutoff, [redacted] 20[redacted]])

A randomized, double-blind, STB-controlled, parallel-group, comparative study was conducted to evaluate the efficacy and safety of E/C/F/TAF FDC in treatment-naïve non-Japanese adult HIV-1 patients (target sample size, 840 [n = 420/group]) at 121 study sites in 10 countries including the U.S.

Subjects received oral doses of E/C/F/TAF FDC or STB QD during or immediately after a meal for 96 weeks.

Among 872 randomized subjects (435 in the E/C/F/TAF FDC group, 437 in the STB group), all 866 subjects who received the study drug (431 in the E/C/F/TAF FDC group, 435, in the STB group) were included in the FAS and safety analysis set, and the FAS was also for the efficacy analysis.

The proportion of subjects with HIV-1 RNA levels <50 copies/mL at Week 48,[56] the primary endpoint, was as shown in Table 31. The between-group difference [95.002% CI] was 3.1% [-1.0%, 7.1%]; therefore, the non-inferiority of E/C/F/TAF FDC to STB was demonstrated because the lower bound of the 95.002% confidence interval exceeded the predefined non-inferiority margin (-12%).

Table 31. Proportion of subjects with an HIV-1 RNA level of <50 copies/mL at Week 48

	E/C/F/TAF FDC	STB
Proportion of subjects with an HIV-1 RNA level of <50 copies/mL at Week 48	395/431 (91.6)	385/435 (88.5)
Between-group difference [95.002% CI]	3.1% [-1.0%, 7.1%]	

n/N (%)

Between-group difference was stratified by baseline HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL) and geographic region (in or out of the U.S.) and adjusted by the Mantel-Haenszel method. A total of 2 interim analyses were planned and performed, with α of 0.00001 being consumed in each analysis, leading to a calculated significance level of 0.04998 (two-sided) (Haybittle procedure).

Adverse events (including abnormal changes in laboratory values) were reported by 382 of 431 subjects (88.6%) in the E/C/F/TAF FDC group and 390 of 435 subjects (89.7%) in the STB group; and adverse drug reactions (including abnormal changes in laboratory values) were reported by 160 of 431 subjects (37.1%) in the E/C/F/TAF FDC group and 168 of 435 subjects (38.6%) in the STB group. Adverse events and adverse drug reactions with an incidence of ≥5% in any group are shown in Table 32.

Table 32. Adverse events and adverse drug reactions with an incidence of ≥5% in any group

Event	Adverse events		Adverse drug reactions	
	E/C/F/TAF FDC	STB	E/C/F/TAF FDC	STB
N	431	435	431	435
Total	382 (88.6)	390 (89.7)	160 (37.1)	168 (38.6)
Headache	74 (17.2)	57 (13.1)	24 (5.6)	19 (4.4)
Nausea	70 (16.2)	76 (17.5)	41 (9.5)	58 (13.3)
Diarrhoea	69 (16.0)	83 (19.1)	25 (5.8)	33 (7.6)
Vomiting	39 (9.0)	34 (7.8)	11 (2.6)	16 (3.7)
Fatigue	38 (8.8)	34 (7.8)	19 (4.4)	16 (3.7)
Rash	30 (7.0)	28 (6.4)	8 (1.9)	9 (2.1)
Insomnia	30 (7.0)	25 (5.7)	9 (2.1)	5 (1.1)
Dizziness	23 (5.3)	19 (4.4)	12 (2.8)	10 (2.3)
Upper respiratory tract infection	49 (11.4)	45 (10.3)	1 (0.2)	0
Nasopharyngitis	43 (10.0)	49 (11.3)	1 (0.2)	0
Arthralgia	35 (8.1)	22 (5.1)	2 (0.5)	1 (0.2)
Back pain	33 (7.7)	32 (7.4)	2 (0.5)	2 (0.5)
Cough	30 (7.0)	29 (6.7)	0	0
Pyrexia	27 (6.3)	18 (4.1)	3 (0.7)	2 (0.5)
Lymphadenopathy	23 (5.3)	19 (4.4)	4 (0.9)	0
Syphilis	22 (5.1)	16 (3.7)	1 (0.2)	0
Oropharyngeal pain	18 (4.2)	29 (6.7)	0	2 (0.5)
Anxiety	12 (2.8)	23 (5.3)	1 (0.2)	1 (0.2)
Constipation	9 (2.1)	22 (5.1)	4 (0.9)	4 (0.9)

n (%)

Death occurred in 1 subject receiving E/C/F/TAF FDC (alcohol poisoning) and 2 subjects receiving STB (overdose of drugs and alcohol, and acute myocardial infarction); a causal relationship to the study drug was ruled out for all these events.

Serious adverse events were reported by 33 of 431 subjects (7.7%) in the E/C/F/TAF FDC group and 30 of 435 subjects (6.9%) in the STB group; of these, 1 subject receiving STB (cholelithiasis) was assessed as causally related to the study drug. Among serious adverse events, the outcomes of depression, cellulitis, chorioretinitis, staphylococcal bacteraemia, and hidradenitis in the E/C/F/TAF FDC group and the outcomes of cerebrovascular accident, iridocyclitis, meningioma, West Nile viral infection, and immune reconstitution inflammatory syndrome in the STB group were reported not recovered/not resolved, and all the remaining events were reported recovered/resolved.

Adverse events leading to treatment discontinuation were reported by 4 subjects receiving E/C/F/TAF FDC (eye irritation, eye pain, eye pruritus, abdominal distension, abdominal pain, blood triglycerides increased, back pain, erectile dysfunction, dyspnoea, hyperkeratosis, and lipodystrophy acquired in 1 subject each [includes duplicate counting]) and 7 subjects receiving STB (vomiting in 2 subjects, and iridocyclitis, dysphagia, nausea, pyrexia, arthropod bite, hyperamylasaemia, myalgia, headache, bladder spasm, renal failure, dermatitis, rash generalised, and rash maculo-papular in 1 subject each [includes duplicate counting]); and all events were assessed as causally related to the study drug except iridocyclitis and arthropod bite. Among adverse events leading to treatment discontinuation, the outcomes of dyspnoea, renal failure, iridocyclitis, hyperamylasaemia, and blood triglycerides increased were reported not recovered/not resolved, and all the remaining events were reported recovered/resolved.

7.2.3 Foreign phase III study (CTD 5.3.5.1-6, Study GS-US-292-0109 [March 2013 to ongoing] [data cutoff, [redacted] 20[redacted]])

A randomized, open-label, parallel-group, comparative study with anti-HIV drug containing TDF as the comparator was conducted to evaluate the efficacy and safety of E/C/F/TAF FDC in non-Japanese adult patients[59] with HIV-1 infection who achieved virologic suppression with an anti-HIV drug containing TDF[60] (target sample size, 1500 patients [1000 in the E/C/F/TAF FDC group, 500 in the continued treatment group, in which the previous anti-HIV therapy was continued without modification]) at 168 study sites in 20 countries including the U.S.

Subjects received oral doses of E/C/F/TAF FDC or the previous anti-HIV drug containing TDF QD during or immediately after a meal for 96 weeks.[61]

Among 1443 randomized subjects (963 in the E/C/F/TAF FDC group, 480 in the continued treatment group), all 1436 subjects who received the study drug (959 in the E/C/F/TAF FDC group, 477 in the continued treatment group) were included in the FAS and safety analysis set, and the FAS was also for the efficacy analysis.

The proportion of subjects with an HIV-1 RNA level of <50 copies/mL at Week 48[56], the primary endpoint, was as shown in Table 33. The between-group difference [95% CI] was 4.1% [1.6%, 6.7%]; therefore, the non-inferiority of E/C/F/TAF FDC to anti-HIV drugs containing TDF was demonstrated because the lower bound of the 95% CI exceeded the predefined non-inferiority margin (-12%).

Table 33. Proportion of subjects with an HIV-1 RNA level of <50 copies/mL at Week 48

	E/C/F/TAF FDC	Continued treatment
Proportion of subjects with an HIV-1 RNA of <50 copies/mL at Week 48	932/959 (97.2)	444/477 (93.1)
Between-group difference [95% CI]	4.1% [1.6%, 6.7%]	

n/N (%)
Between-group difference was stratified by prior therapy (STB, EFV/FTC/TDF, ATV/COBI/FTC/TDF, or ATV/RTV/FTC/TDF) and adjusted using the Mantel-Haenszel method.

Adverse events (including abnormal changes in laboratory values) were reported by 828 of 959 subjects (86.3%) in the E/C/F/TAF FDC group and 399 of 477 subjects (83.6%) in the continued treatment group. Adverse drug reactions (including abnormal changes in laboratory values) were reported by 204 of 959 subjects (21.3%) in the E/C/F/TAF FDC group and 76 of 477 subjects (15.9%) in the continued treatment group. Adverse events and adverse drug reactions with an incidence of ≥5% in any group are shown in Table 34.

59) Patients who received ≥6 months of anti-HIV therapy containing TDF and had HIV-1 RNA levels <50 copies/mL for ≥6 months at screening.
60) Any one of the following anti-HIV drugs containing TDF:
(a) STB, (b) EFV/FTC/TDF (Atripla; not approved in Japan), (c) ATV/COBI/FTC/TDF, or (d) ATV/RTV/FTC/TDF
61) Patients in the continued treatment group were allowed to be switched to E/C/F/TAF FDC after completion of the 96-week treatment.

Table 34. Adverse events and adverse drug reactions with an incidence of ≥5% in any group

Event	Adverse events		Adverse drug reactions	
	E/C/F/TAF FDC	Continued treatment	E/C/F/TAF FDC	Continued treatment
N	959	477	959	477
Total	828 (86.3)	399 (83.6)	204 (21.3)	76 (15.9)
Upper respiratory tract infection	151 (15.7)	54 (11.3)	0	0
Diarrhoea	96 (10.0)	42 (8.8)	24 (2.5)	6 (1.3)
Nasopharyngitis	88 (9.2)	39 (8.2)	1 (0.1)	0
Headache	69 (7.2)	20 (4.2)	17 (1.8)	1 (0.2)
Cough	64 (6.7)	25 (5.2)	1 (0.1)	0
Syphilis	46 (4.8)	30 (6.3)	0	0
Insomnia	50 (5.2)	30 (6.3)	10 (1.0)	7 (1.5)
Depression	42 (4.4)	30 (6.3)	3 (0.3)	3 (0.6)
Arthralgia	59 (6.2)	24 (5.0)	2 (0.2)	1 (0.2)
Bronchitis	58 (6.0)	26 (5.5)	0	0
Osteopenia	56 (5.8)	22 (4.6)	11 (1.1)	7 (1.5)
Back pain	52 (5.4)	25 (5.2)	1 (0.1)	0
Sinusitis	48 (5.0)	25 (5.2)	0	0
Nausea	50 (5.2)	16 (3.4)	22 (2.3)	2 (0.4)

n (%)

Four deaths occurred in the E/C/F/TAF FDC group (septic shock, lung adenocarcinoma, sudden death, and methamphetamine-related myocarditis); a causal relationship to the study drug was ruled out for all these events.

Serious adverse events were reported by 65 of 959 subjects (6.8%) in the E/C/F/TAF FDC group and 35 of 477 subjects (7.3%) in the continued treatment group; of these, 2 events in the continued treatment group (Fanconi syndrome and cholecystitis acute) were assessed as causally related to the study drug. Among serious adverse events, the outcomes of Hodgkin's disease, sleep apnoea syndrome, acute psychosis, coronary artery disease, general physical health deterioration, radius fracture, Reiter's syndrome, lung adenocarcinoma, chest pain, acute hepatitis C, prostate cancer, inappropriate antidiuretic hormone secretion, and drug-induced liver injury in 1 subject each in the E/C/F/TAF FDC group and the outcomes of cardiac failure congestive, depression, Hodgkin's disease, drug abuse, abscess limb, cellulitis, osteomyelitis, Fanconi syndrome acquired, hypertension, and appendiceal abscess in 1 subject each in the continued treatment group were reported not recovered/not resolved and all the remaining events were reported recovered/resolved.

Adverse events leading to treatment discontinuation were reported by 9 subjects receiving E/C/F/TAF FDC (nausea, vomiting, local swelling, Reiter's syndrome, amnesia, disturbance in attention, headache, speech disorder, depression, apathy, panic attack, suicide attempt, renal failure acute, and tubulointerstitial nephritis in 1 subject each [includes duplicate counting]) and 12 subjects receiving the continued treatment (jaundice in 3 subjects, blood creatinine increased, depression, and insomnia in 2 subjects each, and blood bilirubin increased, memory impairment, abnormal dreams, irritability, nightmare and Fanconi syndrome acquired, renal colic, and chronic kidney disease in 1 subject each [includes duplicate counting]); and all events were assessed as causally related to the study drug except renal failure acute, Reiter's syndrome, suicide attempt, abnormal dreams, and tubulointerstitial nephritis. Among adverse events leading to treatment discontinuation, the outcomes of panic attack, amnesia, speech disorder, apathy, Reiter's syndrome, and tubulointerstitial nephritis in the E/C/F/TAF FDC group and the outcomes of insomnia, nightmare, memory impairment, blood creatinine increased, renal failure chronic, Fanconi syndrome acquired, and blood bilirubin increased in the continued treatment group were reported not recovered/not resolved, and all the remaining events were reported recovered/resolved.

7.2.4 Foreign phase III study (CTD 5.3.5.2-3, Study GS-US-292-0112 [March 2013 to ongoing] [data cutoff, [redacted] 20[redacted]])

An open-label, non-controlled study was conducted to evaluate the safety and efficacy of E/C/F/TAF FDC in non-Japanese adult HIV-1 patients with mild or moderate renal impairment[62)] who were

62) Patients with CL_{cr} of 30 to 69 mL/min at baseline.

treatment-naïve or achieved virologic suppression[63] with an anti-HIV drug (target sample size, 260 patients[64]) at 70 study sites in 9 countries including the U.S.

Subjects received oral doses of E/C/F/TAF FDC QD during or immediately after a meal for 96 weeks.

A total of 248 subjects (6, treatment-naïve; 242, switched from the previous anti-HIV drug to E/C/F/TAF FDC [80 with CL_{cr} <50 mL/min; 162 with CL_{cr} ≥50 mL/min]) who received the study drug were included in the FAS and safety analysis set, and the FAS was also for the efficacy analysis.

The proportion of subjects with an HIV-1 RNA level of <50 copies/mL at Week 24,[56] the primary endpoint, was 83.3% (5 of 6) of treatment-naïve subjects and 95.0% (230 of 242) of previously treated subjects (95.0% [76 of 80] of subjects with CL_{cr} <50 mL/min, 95.1% [154 of 162] of subjects with CL_{cr} ≥50 mL/min).

Adverse events (including abnormal changes in laboratory values) were reported by 5 of 6 treatment-naïve subjects (83.3%) and 209 of 242 previously treated subjects (86.4%) (67 of 80 subjects with CL_{cr} <50 mL/min [83.8%], 142 of 162 subjects with CL_{cr} ≥50 mL/min [87.7%]), and adverse drug reactions (including abnormal changes in laboratory values) were reported by 1 of 6 treatment-naïve subjects (16.7%) and 62 of 242 previously treated subjects (25.6%) (21 of 80 subjects with CL_{cr} <50 mL/min [26.3%], 41 of 162 subjects with CL_{cr} ≥50 mL/min [25.3%]). Adverse events and adverse drug reactions with an incidence of ≥5% in any group are shown in Table 35.

Table 35. Adverse events and adverse drug reactions with an incidence of ≥5% in any group

Event	Adverse events				Adverse drug reactions			
	Previously treated subjects			Untreated subjects	Previously treated subjects			Untreated subjects
	CL_{cr}		Total	Total	CL_{cr}		Total	Total
	<50 mL/min	≥50 mL/min			<50 mL/min	≥50 mL/min		
N	80	162	242	6	80	162	242	6
Total	67 (83.8)	142 (87.7)	209 (86.4)	5 (83.3)	21 (26.3)	41 (25.3)	62 (25.6)	1 (16.7)
Diarrhoea	8 (10.0)	13 (8.0)	21 (8.7)	1 (16.7)	1 (1.3)	5 (3.1)	6 (2.5)	0
Osteopenia	8 (10.0)	11 (6.8)	19 (7.9)	0	0	0	0	0
Bronchitis	7 (8.8)	12 (7.4)	19 (7.9)	0	0	0	0	0
Dizziness	7 (8.8)	7 (4.3)	14 (5.8)	0	4 (5.0)	3 (1.9)	7 (2.9)	0
Arthralgia	6 (7.5)	14 (8.6)	20 (8.3)	1 (16.7)	0	0	0	0
Nausea	5 (6.3)	12 (7.4)	17 (7.0)	0	1 (1.3)	3 (1.9)	4 (1.7)	0
Renal cyst	5 (6.3)	8 (4.9)	13 (5.4)	0	0	0	0	0
Fatigue	4 (5.0)	10 (6.2)	14 (5.8)	1 (16.7)	0	2 (1.2)	2 (0.8)	0
Cough	4 (5.0)	8 (4.9)	12 (5.0)	0	0	0	0	0
Pain in extremity	3 (3.8)	13 (8.0)	16 (6.6)	1 (16.7)	0	0	0	0
Headache	2 (2.5)	15 (9.3)	17 (7.0)	0	1 (1.3)	4 (2.5)	5 (2.1)	0
Back pain	2 (2.5)	13 (8.0)	15 (6.2)	0	0	2 (1.2)	2 (0.8)	0
Upper respiratory tract infection	1 (1.3)	16 (9.9)	17 (7.0)	1 (16.7)	0	0	0	0

n (%)

No deaths were reported. Serious adverse events were reported by 26 previously treated subjects (9 subjects with CL_{cr} <50 mL/min, 17 subjects with CL_{cr} ≥50 mL/min); a causal relationship to E/C/F/TAF FDC was ruled out for all these events. Among serious adverse events, the outcomes of prostatomegaly, acute myocardial infarction, osteonecrosis, type 2 diabetes mellitus, transitional cell carcinoma, ophthalmic herpes zoster, radiculitis cervical, arthralgia, malignant neoplasm of unknown primary site, and bladder transitional cell carcinoma were reported not recovered/not resolved, and all the remaining events were reported recovered/resolved.

Adverse events leading to treatment discontinuation were reported by 8 previously treated subjects including 6 subjects with CL_{cr} <50 mL/min (diarrhoea, dry mouth, fatigue, pain, arthralgia, joint swelling, sleep disorder, renal failure, chronic kidney disease, and pruritus generalised in 1 subject each

[63] Patients who had HIV-1 RNA levels below the detection limit for ≥6 months at screening and had HIV-1 RNA levels <50 copies/mL at screening.

[64] A total of 30 patients or more with CL_{cr} of 30 to 49 mL/min were intended to be enrolled in the treatment-naïve group or the previously treated group.

[includes duplicate counting]) and 2 subjects with CL_{cr} ≥50 mL/min (bladder transitional cell carcinoma and choking in 1 subject each). A causal relationship to E/C/F/TAF FDC was ruled out for all remaining events except choking, sleep disorder, and renal failure. Among adverse events leading to treatment discontinuation, the outcomes of choking and renal failure were reported recovered/resolved, and all the remaining events were reported not recovered/not resolved.

7.2.5 Global phase III study (CTD 5.3.3.3-4, Study GS-US-292-1249 [February 2014 to ongoing] [data cutoff, [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to evaluate the efficacy and safety of E/C/F/TAF FDC in non-Japanese adult patients with HIV-1 and hepatitis B virus (HBV) superinfection who were treatment-naïve[65)] or achieved virologic suppression[66)] with an anti-HIV drug (target sample size, 125 patients [50 treatment-naïve patients, 75 previously treated patients]) at 24 study sites in Japan, the U.S., and Canada.

Subjects received oral doses of the E/C/F/TAF FDC tablet QD during or immediately after a meal for 48 weeks.

A total of 77 subjects (3, treatment-naïve; 74, treated previously) who received the E/C/F/TAF FDC tablet were included in the safety analysis set; of these, 75 subjects (3, treatment-naïve; 72, treated previously) were included in the FAS excluding 2 subjects with no post-dose HBV DNA or HIV-1 RNA data or with protocol deviation. The FAS was also for the efficacy analysis.

The proportion of subjects with HIV-1 RNA levels <50 copies/mL at Week 24,[56)] the primary endpoint, was 100% (3 of 3) of treatment-naïve subjects and 94.4% (68 of 72) of previously treated subjects. The proportion of subjects with HBV DNA level <29 IU/mL at Week 24 was 33.3% (1 of 3) of treatment-naïve subjects and 86.1% (62 of 72) of previously treated subjects.

Adverse events (including abnormal changes in laboratory values) were reported by 2 of 3 treatment-naïve subjects (66.7%) and 61 of 74 previously treated subjects (82.4%), and adverse drug reactions (including abnormal changes in laboratory values) were not reported by treatment-naïve subjects while reported by 12 of 74 previously treated subjects (16.2%). Adverse events and adverse drug reactions with an incidence of ≥5% in any group are shown in Table 36.

Table 36. Adverse events and adverse drug reactions with an incidence of ≥5% in any group

Event	Adverse events		Adverse drug reactions	
	Treatment-naïve subjects	Previously treated subjects	Treatment-naïve subjects	Previously treated subjects
N	3	74	3	74
Total	2 (66.7)	61 (82.4)	0	12 (16.2)
Diarrhoea	1 (33.3)	5 (6.8)	0	3 (4.1)
Gastrooesophageal reflux disease	0	5 (6.8)	0	1 (1.4)
Pyrexia	0	4 (5.4)	0	0
Upper respiratory tract infection	1 (33.3)	12 (16.2)	0	0
Nasopharyngitis	0	6 (8.1)	0	0
Back pain	0	5 (6.8)	0	0
Rhinitis allergic	0	4 (5.4)	0	0

n (%)

No deaths were reported. Serious adverse events were not reported by treatment-naïve subjects while reported by 6 previously treated subjects (abscess limb, appendicitis, meningitis pneumococcal, pneumococcal bacteraemia, pneumonia, pneumonia pneumococcal, diabetes mellitus, benign prostatic hyperplasia, prostatitis, and acute myocardial infarction in 1 subject each [includes duplicate counting]); a causal relationship to E/C/F/TAF FDC was ruled out for all these events. Among serious adverse

65) Patients who had received neither anti-HIV drugs nor anti-HBV therapies

66) Patients who had received an anti-HIV drug for ≥6 months and had HIV-1 RNA levels <50 copies/mL for ≥6 months at screening. Patients receiving or with a history of anti-HBV therapy containing 3 agents (e.g., TDF/FTC/entecavir or TDF/lamivudine/entecavir) were excluded, and patients receiving anti-HBV therapy containing 2 agents including entecavir were to discontinue treatment with entecavir and be switched to treatment with E/C/F/TAF FDC.

events, the outcomes of appendicitis and benign prostatic hyperplasia were reported not recovered/not resolved, and all the remaining events were reported recovered/resolved.

Adverse events leading to treatment discontinuation were not reported by treatment-naïve subjects while reported by 1 previously treated subject (weight increased and increased appetite in 1 subject each [includes duplicate counting]); all these events were assessed as causally related to E/C/F/TAF FDC. Among adverse events leading to treatment discontinuation, the outcome of increased appetite was reported recovered/resolved, and the outcome of weight increased was reported not recovered/not resolved.

7.R Outline of the prior assessment conducted by PMDA

7.R.1 Efficacy

As a result of the following reviews, PMDA concluded that E/C/F/TAF FDC is expected to be effective in adult or adolescent (aged ≥12 years with body weight ≥35 kg) HIV-1 patients who are treatment-naïve or have achieved virologic suppression with an anti-HIV drug. However, given the limited treatment experience with E/C/F/TAF FDC in Japanese HIV-1 patients, information on the efficacy of E/C/F/TAF FDC should be collected continuously after market launch and should be appropriately provided to healthcare professionals in clinical settings.

The above conclusion by PMDA will be discussed at the Prior Assessment Meeting.

7.R.1.1 Efficacy of E/C/F/TAF FDC in treatment-naïve adult HIV-1 patients

The prior assessment requestor's explanation on the efficacy of E/C/F/TAF FDC in treatment-naïve adult HIV-1 patients:

The percentages of subjects with HIV-1 RNA levels <50 copies/mL at Week 48, the primary endpoint, and of patients who experienced virologic failure at Week 48 in phase III studies in treatment-naïve adult HIV-1 patients (Studies GS-US-292-0104 and GS-US-292-0111) are shown in Table 37. Because the lower bound of the 95.002% confidence interval of the between-group difference between the E/C/F/TAF FDC and STB groups exceeded the predefined non-inferiority margin (-12%), the non-inferiority of E/C/F/TAF FDC to STB was evaluated and the efficacy of E/C/F/TAF FDC in the selected patients were demonstrated. The proportion of subjects with HIV-1 RNA levels <50 copies/mL at Week 48 among the 10 Japanese HIV-1 patients (4 in the E/C/F/TAF FDC group, 6 in the STB group) who participated in phase III study (Study 0104) was 100% in both groups.

Table 37. Efficacy at Week 48 in phase III studies (Studies 0104 and 0111) (FAS)

	Study 0104		Study 0111	
	E/C/F/TAF FDC	STB	E/C/F/TAF FDC	STB
N	435	432	431	435
Subjects with HIV-1 RNA <50 copies/mL	405 (93.1)	399 (92.4)	395 (91.6)	385 (88.5)
Between-group difference [95.002% CI][a)]	1.0% [-2.6%, 4.5%]		3.1% [-1.0%, 7.1%]	
Subjects with virologic failure[b)]	13 (3.0)	11 (2.5)	18 (4.2)	24 (5.5)

n (%)

a) Between-group difference was stratified by baseline HIV-1 RNA level (≤100,000 copies/mL or >100,000 copies/mL) and geographic region (in or out of the U.S.) and adjusted using the Mantel-Haenszel method.

b) Subjects who met any of the following:
(a) Subjects with HIV-1 RNA levels ≥50 copies/mL; (b) withdrawals due to lack of efficacy; (c) subjects who were withdrawn due to other reasons and showed an HIV-1 RNA level of ≥50 copies/mL at the last measurement; or (d) subjects who received treatment with an additional anti-HIV drug.

The proportion of subjects with HIV-1 RNA levels <50 copies/mL at Week 96 in phase III studies (Studies 0104 and 0111) was 89.2% (388 of 435) of subjects receiving E/C/F/TAF FDC and 88.2% (381 of 432) of subjects receiving STB in Study 0104; and 84.0% (362 of 431) of subjects receiving E/C/F/TAF FDC and 82.3% (358 of 435) of subjects receiving STB in Study 0111.

PMDA's view:

Because the non-inferiority of E/C/F/TAF FDC to STB was demonstrated in terms of the proportion of subjects with HIV-1 RNA levels <50 copies/mL at Week 48, the primary endpoint of phase III studies in treatment-naïve adult HIV-1 patients (Studies 0104 and 0111), E/C/F/TAF FDC is expected to be effective in treatment-naïve adult HIV-1 patients. Although E/C/F/TAF FDC was effective in Japanese

patients with HIV-1 infection as evidenced by the fact that all 4 Japanese HIV-1 patients who received E/C/F/TAF FDC in phase III study (Study 0104) achieved HIV-1 RNA levels <50 copies/mL at Week 48, information on the efficacy of E/C/F/TAF FDC should be collected continuously after market launch and should be provided appropriately to healthcare professionals in clinical settings, given the limited treatment experience with E/C/F/TAF FDC in Japanese HIV-1 patients.

7.R.1.2 Efficacy of E/C/F/TAF FDC in adult HIV-1 patients who have achieved virologic suppression with an anti-HIV drug

The prior assessment requestor's explanation on the efficacy of E/C/F/TAF FDC in adult HIV-1 patients who have achieved virologic suppression with an anti-HIV drug containing TDF:

In a phase III study in adult HIV-1 patients[59] who achieved virologic suppression with an anti-HIV drug containing TDF[60] (Study GS-US-292-0109), the percentages of subjects with HIV-1 RNA levels <50 copies/mL at Week 48, the primary endpoint, and of subjects who experienced virologic failure[67] at Week 48 were 97.2% (932 of 959) of subjects and 1.0% (10 of 959) of subjects, respectively, in the E/C/F/TAF FDC group and 93.1% (444 of 477) of subjects and 1.3% (6 of 477) of subjects, respectively, in the continued treatment group, resulting in a between-group difference [95% CI] of 4.1% [1.6%, 6.7%] [see "7.2.3 Foreign phase III study"]. In terms of the proportion of subjects with HIV-1 RNA levels <50 copies/mL at Week 48, the lower bound of the 95% confidence interval of the between-group difference and STB groups exceeded the predefined non-inferiority margin (-12%). Therefore, the non-inferiority of E/C/F/TAF FDC to anti-HIV drugs containing TDF was evaluated and the efficacy of E/C/F/TAF FDC in adult HIV-1 patients who have achieved virologic suppression with an anti-HIV drug containing TDF were demonstrated. In addition, given the results of phase III study (Study 0109) (Table 38), virologic suppression is expected to be maintained also in adult HIV-1 patients without EVG-, FTC-, or TFV-resistant mutation who have achieved virologic suppression with an anti-HIV drug not containing TDF.

Table 38. Efficacy at Week 48 in phase III study (Study 0109) by patient treatment history (FAS)

	STB		EFV/FTC/TDF		ATV/COBI/FTC/TDF		ATV/RTV/FTC/TDF	
	E/C/F/TAF FDC	Continued treatment	E/C/F/TAF FDC	Continued treatment	E/C/F/TAF FDC	Continued treatment	E/C/F/TAF FDC	Continued treatment
N	306	153	251	125	147	69	255	130
Subjects with HIV-1 RNA <50 copies/mL	301 (98.4)	149 (97.4)	241 (96.0)	112 (89.6)	145 (98.6)	65 (94.2)	245 (96.1)	118 (90.8)
Subjects with virologic failure[a]	2 (0.7)	1 (0.7)	3 (1.2)	1 (0.8)	1 (0.7)	3 (4.4)	4 (1.6)	1 (0.8)

n (%)

a) Subjects who met any one of the following:
(a) those with HIV-1 RNA levels ≥50 copies/mL; (b) those withdrawn due to a lack of efficacy; (c) those withdrawn due to other reasons and with HIV-1 RNA levels ≥50 copies/mL at the last measurement; or (d) those receiving an additional anti-HIV drug.

PMDA's view:

Because the non-inferiority of E/C/F/TAF FDC to anti-HIV drugs containing TDF was demonstrated in terms of the proportion of subjects with HIV-1 RNA levels <50 copies/mL at Week 48, which was the primary endpoint of phase III study in adult HIV-1 patients who achieved virologic suppression with an anti-HIV drug containing TDF (Study 0109), E/C/F/TAF FDC is expected to be effective in adult HIV-1 patients who have achieved virologic suppression with an anti-HIV drug. However, given that patients who had no history of virologic failure and had maintained virologic suppression with the previous therapy for at least 6 months prior to switching therapy were selected for a phase III study (Study 0109), information on selecting candidates for switching therapy should be appropriately provided by the package insert, etc. Taking account of the data from Study 0109, a phase III study, the prior assessment requestor's explanation that E/C/F/TAF FDC can be expected to maintain virologic suppression after switching therapy also in patients who have achieved virologic suppression with a treatment history is acceptable, although Study 0109 was conducted only in HIV-1 patients who achieved virologic

[67] Subjects who met any one of the following:
(a) those with HIV-1 RNA levels ≥50 copies/mL; (b) those withdrawn due to a lack of efficacy; (c) those withdrawn due to other reasons and with HIV-1 RNA levels ≥50 copies/mL at the last measurement; or (d) those receiving an additional anti-HIV drug.

suppression with an anti-HIV drug containing TDF. However, since treatment experience is limited in Japanese HIV-1 patients who have achieved virologic suppression with another anti-HIV drug switching to E/C/F/TAF FDC, information on the efficacy of switching to E/C/F/TAF FDC should be collected continuously after market launch and provided appropriately to healthcare professionals in clinical settings.

7.R.1.3 Efficacy of E/C/F/TAF FDC in pediatric HIV-1 patients

The prior assessment requestor's explanation on the efficacy of E/C/F/TAF FDC in pediatric HIV-1 patients:

In a phase II/III study in treatment-naïve HIV-1 infected adolescents (aged ≥12 and <18 years) with body weight ≥35 kg (Study GS-US-292-0106), the proportions of subjects with an HIV-1 RNA level of <50 copies/mL and of those who experienced virologic failure[67)] at Week 24 were 90.0% (45 of 50) and 8.0% (4 of 50), respectively, and the proportions at Week 48 were 92.0% (46 of 50) and 6.0% (3 of 50), respectively. Although treatment experience was limited, the proportion of subjects with HIV-1 RNA levels <50 copies/mL at Week 48 was comparable to that in adult HIV-1 patients. Thus, the efficacy of E/C/F/TAF FDC in treatment-naïve HIV-1 infected adolescents with body weight ≥35 kg was demonstrated. Moreover, no clinical studies were conducted in pediatric HIV-1 patients aged ≥12 years with body weight ≥35 kg who achieved virologic suppression with an anti-HIV drug, but a comparable efficacy was seen between treatment-naïve adult HIV-1 patients [see "7.2.1 Global phase III study" and "7.2.2 Foreign phase III study"] and adult HIV-1 patients who achieved virologic suppression [see "7.2.3 Foreign phase III study"], and no clinically significant difference in the exposure to individual active ingredients was seen between adult HIV-1 patients and HIV-1 infected adolescents with body weight ≥35 kg receiving E/C/F/TAF FDC [see "6.R.3 Differences in PK of E/C/F/TAF FDC between HIV-1 infected adolescents with body weight ≥35 kg and adult HIV-1 patients"]. Thus, E/C/F/TAF FDC is expected to be effective in HIV-1 patients aged ≥12 years with body weight ≥35 kg who have achieved virologic suppression with an anti-HIV drug.

PMDA's view:

There was no clinically significant difference in the exposure to individual active ingredients between adult HIV-1 patients and HIV-1 infected adolescents with body weight ≥35 kg receiving E/C/F/TAF FDC [see "6.R.3 Differences in PK of E/C/F/TAF FDC between HIV-1 infected adolescents with body weight ≥35 kg and adult HIV-1 patients"]. On the basis of the above and the data from phase II/III study (Study 0106), the efficacy of E/C/F/TAF FDC was suggested in HIV-1 patients aged ≥12 years with body weight ≥35 kg. However, a phase II/III study (Study 0106) was conducted only in treatment-naïve patients, and no efficacy data with E/C/F/TAF FDC have been obtained in HIV-1 patients aged ≥12 years with body weight ≥35 kg who have achieved virologic suppression with an anti-HIV drug. Therefore, information on the efficacy of E/C/F/TAF FDC in these patients should be collected continuously after market launch and provided appropriately to healthcare professionals in clinical settings.

7.R.1.4 Emergence of resistance mutations and its impact on the efficacy

The prior assessment requestor's explanation on the emergence of resistance mutations in a phase II study (Study GS-US-292-0102) and phase III studies (Studies 0104 and 0111) conducted in treatment-naïve adult HIV-1 patients:

A pooled analysis of a phase II study (Study 0102) and phase III studies (Studies 0104 and 0111) revealed that 19 of 978 subjects (1.9%) in the E/C/F/TAF FDC group and 22 of 925 subjects (2.4%) in the STB group underwent resistance testing[68)] by Week 48 due to virologic failure; and resistance mutations were found in 4 of 19 subjects (21.1%) in the E/C/F/TAF FDC group and 7 of 22 subjects (31.8%) in the STB group. Resistance mutations in reverse transcriptase region found in the E/C/F/TAF FDC group included K65R (1 subject) and M184V (4 subjects), and those found in the STB group included E44E/D (1 subject), K65R (2 subjects), K70K/E (1 subject), M184V (4 subjects), M184M/V

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68) Subjects underwent resistance testing if they received at least 1 dose of the study drug, and met any one of the following criteria for virologic failure within 72 hours after completion, interruption, or treatment discontinuation:
- Inadequate virologic suppression: Decrease in HIV-1 RNA levels from baseline or cutoff to Week 8 was <1 $\log_{10}$, and HIV-1 RNA was detected 2 weeks later.
- Virologic rebound: A consecutive occurrence of elevated HIV-1 RNA levels beyond the cutoff from below, or an elevation from the nadir HIV-1 RNA level by ≥1 $\log_{10}$.
- Viremia at the end of the study: None of the above is applicable, and HIV-1 RNA levels were ≥400 copies/mL at the end of the study or at study interruption.

(2 subjects), and M184M/I/V (1 subject). Resistance mutations in integrase region found in the E/C/F/TAF FDC group included T66A (1 subject), E92Q (2 subjects), and N155H (1 subject), and those found in the STB group included E92Q (2 subjects), E92E/Q (1 subject), and Q148R (2 subjects). Resistance mutations M184V and K65R in the reverse transcriptase region were frequently detected and M184V was detected in all subjects tested. No apparent differences were found in the type or frequency of resistance mutation between the E/C/F/TAF FDC and STB groups. In a phase III study in adult HIV-1 patients who achieved virologic suppression with an anti-HIV drug containing TDF (Study 0109), no mutations resistant to individual study drugs were detected.

PMDA's view:
No apparent differences were found in the type or frequency of resistance mutation in treatment-naïve adult HIV-1 patients between E/C/F/TAF FDC treatment and STB treatment, and no mutations resistant to individual study drugs were detected among adult HIV-1 patients who had achieved virologic suppression with an anti-HIV drug containing TDF. Thus, there are no new concerns specific to E/C/F/TAF FDC regarding the emergence of resistance mutations compared with those specific to STB. However, given that resistance mutations were actually detected in a small number of adult HIV-1 patients who experienced virologic failure after receiving E/C/F/TAF FDC, and that only limited data is available on resistance mutations in HIV-1 patients who are treatment-naïve or have switched from another anti-HIV drug to E/C/F/TAF FDC, information on the emergence of resistance mutations in patients receiving E/C/F/TAF FDC should be collected continuously after market launch and provided appropriately to healthcare professionals in clinical settings.

7.R.2 Safety

As a result of the following reviews, PMDA has concluded that the safety of E/C/F/TAF FDC is acceptable in adult HIV-1 patients and HIV-1 infected adolescents with body weight ≥35 kg who are treatment-naïve or have achieved virologic suppression with an anti-HIV drug. However, as in the case of STB, a cautionary statement should be provided regarding the effects on renal impairment and on BMD. Moreover, the limited treatment experience with E/C/F/TAF FDC in Japanese HIV-1 patients, and information on the safety of E/C/F/TAF FDC should be collected continuously after market launch and provided appropriately to healthcare professionals in clinical settings.

The above conclusion by PMDA will be discussed at the Prior Assessment Meeting.

7.R.2.1 Summary of safety of E/C/F/TAF FDC in adult HIV-1 patients

The prior assessment requestor's explanation on the summary of safety of E/C/F/TAF FDC in adult HIV-1 patients:
Table 39 lists adverse events and adverse drug reactions (including abnormal changes in laboratory values) with an incidence of ≥5% in any group by Week 48 identified in a pooled analysis[69] of phase III studies in treatment-naïve HIV-1 patients (Studies 0104 and 0111). No particular differences were found in the nature and incidence of adverse events and adverse drug reactions between the E/C/F/TAF FDC and STB groups, and most of the events were Grade[70] 1 or 2. The incidence of deaths was 0.2% (2 of 866) of subjects receiving E/C/F/TAF FDC and 0.3% (3 of 867) of subjects receiving STB, the incidence of serious adverse events was 8.1% (70 of 866) of subjects receiving E/C/F/TAF FDC and 6.8% (59 of 867) of subjects receiving STB, and the incidence of adverse events leading to treatment discontinuation was 0.9% (8 of 866) of subjects receiving E/C/F/TAF FDC and 1.5% (13 of 867) of subjects receiving STB.

Within the period up to Week 96, the incidence of adverse events was 93.2% (807 of 866) of subjects receiving E/C/F/TAF FDC and 94.9% (823 of 867) of subjects receiving STB, the incidence of adverse drug reactions was 42.4% (367 of 866) of subjects receiving E/C/F/TAF FDC and 45.9% (398 of 867) of subjects receiving STB, the incidence of deaths was 0.2% (2 of 866) of subjects receiving E/C/F/TAF FDC and 0.3% (3 of 867) of subjects receiving STB, the incidence of serious adverse events was 11.2% (97 of 866) of subjects receiving E/C/F/TAF FDC and 10.0% (87 of 867) of subjects receiving STB, and the incidence of adverse events leading to treatment discontinuation was 1.2% (10 of 866) of subjects

[69] The pooled analysis was performed on the data of phase III studies (Studies 0104 and 0111), whose cutoff dates were [redacted] 20[redacted] and [redacted] 20[redacted], respectively.
[70] Severities of adverse events and adverse drug reactions were evaluated based on the severity grading scale for adverse events and laboratory test abnormal established by Gilead Sciences, Inc.

receiving E/C/F/TAF FDC and 2.3% (20 of 867) of subjects receiving STB. At Week 96, no particular differences were noted in the nature and incidence of adverse events and adverse drug reactions between E/C/F/TAF FDC and STB groups.

Table 39. Adverse events and adverse drug reactions with an incidence of ≥5% in any group in phase III studies (Studies 0104 and 0111)

Event	Adverse events		Adverse drug reactions	
	E/C/F/TAF FDC	STB	E/C/F/TAF FDC	STB
N	866	867	866	867
Total	778 (89.8)	782 (90.2)	342 (39.5)	364 (42.0)
Diarrhoea	147 (17.0)	164 (18.9)	62 (7.2)	74 (8.5)
Nausea	132 (15.2)	151 (17.4)	90 (10.4)	113 (13.0)
Headache	124 (14.3)	108 (12.5)	52 (6.0)	47 (5.4)
Upper respiratory tract infection	99 (11.4)	109 (12.6)	1 (0.1)	1 (0.1)
Nasopharyngitis	78 (9.0)	80 (9.2)	2 (0.2)	0
Fatigue	71 (8.2)	71 (8.2)	43 (5.0)	35 (4.0)
Cough	67 (7.7)	60 (6.9)	0	0
Vomiting	62 (7.2)	54 (6.2)	16 (1.8)	27 (3.1)
Arthralgia	61 (7.0)	39 (4.5)	3 (0.3)	3 (0.3)
Back pain	60 (6.9)	57 (6.6)	2 (0.2)	2 (0.2)
Insomnia	57 (6.6)	48 (5.5)	17 (2.0)	14 (1.6)
Rash	55 (6.4)	46 (5.3)	13 (1.5)	11 (1.3)
Pyrexia	45 (5.2)	41 (4.7)	5 (0.6)	2 (0.2)
Dizziness	44 (5.1)	37 (4.3)	26 (3.0)	19 (2.2)
Oropharyngeal pain	39 (4.5)	47 (5.4)	0	3 (0.3)
Osteopenia	32 (3.7)	44 (5.1)	8 (0.9)	17 (2.0)

n (%)

Table 40 shows summary of safety from phase III study in adult HIV-1 patients who achieved virologic suppression with an anti-HIV drug containing TDF (Study 0109) and from phase III study in adult patients with HIV-1 and HBV superinfection who were treatment-naïve or achieved virologic suppression with an anti-HIV drug (Study GS-US-292-1249). There were no substantial differences in the nature and incidence of adverse events and adverse drug reactions between the E/C/F/TAF FDC and continued treatment groups in phase III study (Study 0109). In phase III study (Study 1249), no specific trends of patients superinfected with HBV were observed in the occurrence of adverse events, although the number of studied subjects was limited.

Table 40. Summary of safety in phase III studies (safety analysis set)

	Study 0109		Study 1249	
	E/C/F/TAF FDC	Continued treatment	Treatment-naïve	Previously treated
N	959	477	3	74
All adverse events	828 (86.3)	399 (83.6)	2 (66.7)	61 (82.4)
Grade 3 or worse adverse events	84 (8.8)	54 (11.3)	0	4 (5.4)
Serious adverse events	65 (6.8)	35 (7.3)	0	6 (8.1)
Deaths	4 (0.4)	0	0	0
Adverse events leading to treatment discontinuation	9 (0.9)	12 (2.5)	0	1 (1.4)

n (%)

In phase III studies (Studies 0104 and 1249), the incidence of adverse events among Japanese adult HIV-1 patients within the period up to Week 48[71)] was 87.5% (7 of 8) of subjects receiving E/C/F/TAF FDC and 100.0% (6 of 6) of subjects receiving STB, and the incidence of adverse drug reactions was 12.5% (1 of 8) of subjects receiving E/C/F/TAF FDC and 33.3% (2 of 6) of subjects receiving STB; the incidence was comparable to that among the whole population of these phase III studies. In Study 0104, a serious adverse event was reported by 1 subject receiving E/C/F/TAF FDC (retinal detachment), but its causal relationship to E/C/F/TAF FDC was ruled out, and the outcome of the event was reported recovered/resolved. No deaths or adverse events leading to treatment discontinuation occurred.

71) Data cutoff dates of phase III Studies 0104 and 1249 were [redacted] 20[redacted] and [redacted] 20[redacted], respectively.

PMDA's view:
The safety of E/C/F/TAF FDC is acceptable for the following reasons: No particular differences were found in the incidences of adverse events and adverse drug reactions between the E/C/F/TAF FDC and STB groups in the treatment-naïve adult HIV-1 patients of phase III studies (Studies 0104 and 0111); and no substantial differences were noted in the incidences of adverse events and adverse drug reactions between patients who switched to E/C/F/TAF FDC treatment and patients who continued their previous treatment in the adult HIV-1 patients of a phase III study who achieved virologic suppression with an anti-HIV drug containing TDF (Study 0109). Moreover, PMDA confirmed that there are no particular problems based on available safety data, although treatment experience is limited in Japanese adult HIV-1 patients.

The following sections describe the effects of E/C/F/TAF FDC on renal impairment and BMD associated particularly with TDF-containing drugs.

7.R.2.1.1 Renal impairment

The prior assessment requestor's explanation on renal impairment induced by E/C/F/TAF FDC:
Table 41 shows the incidence of adverse events related to renal function[72)] in treatment-naïve adult HIV-1 patients of phase III studies (Studies 0104 and 0111) and in adult HIV-1 patients of a phase III study who achieved virologic suppression with an anti-HIV drug containing TDF (Study 0109).

Table 41. Incidence of kidney-related adverse events in phase III studies

	Studies 0104 and 0111		Study 0109	
	E/C/F/TAF FDC	STB	E/C/F/TAF FDC	Continued treatment
N	867	866	959	477
Total	52 (6.0)	80 (9.2)	75 (7.8)	36 (7.5)
Serious adverse events	2 (0.2)	1 (0.1)	2 (0.2)	2 (0.4)
Adverse events leading to treatment discontinuation	0	5 (0.6)	2 (0.2)	5 (0.5)

n (%)

A causal relationship to the study drug was ruled out for all serious adverse events in the E/C/F/TAF FDC group in phase III studies (Studies 0104 and 0111) in treatment-naïve adult HIV-1 patients. A causal relationship to the study drug was ruled out for all of the adverse events leading to treatment discontinuation in the E/C/F/TAF FDC group in a phase III study (Study 0109) in adult HIV-1 patients who achieved virologic suppression with an anti-HIV drug containing TDF.

As shown above, the incidence of adverse events related to renal function were different between the E/C/F/TAF FDC and STB groups.

In addition, in phase III studies (Studies 0104 and 0111), the changes in CL_{cr} from baseline to Weeks 24 and 48 were smaller in the E/C/F/TAF FDC group than in the STB group, as shown in Table 42.

Table 42. Changes in CL_{cr} from baseline to Weeks 24 and 48

	E/C/F/TAF FDC	STB
Baseline		
N	866	867
CL_{cr} at baseline	120.8 ± 30.9	118.7 ± 30.7
Week 24		
N	836	833
Change in CL_{cr} from baseline	-6.3 ± 14.6	-10.2 ± 14.3
Week 48		
N	821	806
Change in CL_{cr} from baseline	-6.5 ± 15.3	-11.2 ± 15.0

Mean ± standard deviation

In a phase III study in adult HIV-1 patients with mild or moderate renal impairment (Study GS-US-292-0112), serious adverse event related to renal function was reported by only 1 subject in the previously treated group, and adverse events related to renal function that led to treatment discontinuation were

72) Defined as adverse events that correspond to either of the following:
• Adverse events of MedDRA Preferred Terms (PTs) within System Organ Class (SOC) "renal and urinary disorders."
• Adverse events of MedDRA PTs within SOC "investigations" and also within its High Level Term "renal function analyses."

reported by only 2 subjects in the previously treated group. Laboratory parameter values related to renal function at baseline and at Week 24 are shown in Table 43. At Week 24, all laboratory parameters showed similar changes from baseline, and no particular trends were observed in patients with CL_{cr} of ≥30 and <50 mL/min.

Table 43. Change in laboratory parameters related to renal function

	CL_{cr} ≥30 and <50 mL/min		CL_{cr} ≥50 mL/min	
	Baseline	Week 24	Baseline	Week 24
n	77	77	166	166
Serum creatinine (mg/dL)	1.68 ± 0.46	1.67 ± 0.50	1.34 ± 0.26	1.39 ± 0.31
CL_{cr} (mL/min)	42.26 ± 4.97	43.86 ± 8.78	61.36 ± 7.30	60.61 ± 9.66
UPCR (mg/g)	573.82 ± 915.80	477.28 ± 922.33	253.07 ± 399.53	145.32 ± 398.34
UACR (mg/g)	272.77 ± 568.43	254.49 ± 628.27	93.16 ± 355.72	60.15 ± 331.29
Urinary β2-microglobulin/ creatinine ratio (μg/g)	20,923.58 ± 37,185.83	6815.02 ± 14,351.31	8610.21 ± 19,435.18	1266.58 ± 3191.48
Urinary β2-microglobulin (μg/mL)	16.58 ± 29.84	5.21 ± 9.64	9.51 ± 24.00	1.45 ± 3.75

Mean ± standard deviation
UPCR, Urinary protein/creatinine ratio; UACR, Urinary albumin/creatinine ratio

The safety of E/C/F/TAF FDC in HIV-1 patients with renal impairment (CL_{cr} <30 mL/min) at baseline was not evaluated and E/C/F/TAF FDC is a combination drug containing a fixed dose of FTC, which requires a different dosing interval when used as a single agent drug in patients with severe renal impairment (CL_{cr} <30 mL/min) than in patients with mild or moderate renal impairment (CL_{cr} ≥30 mL/min) (see Emtriva Capsules 200 mg [package insert]. 6th ed.). Consequently, all patients should be confirmed to have CL_{cr} value of ≥30 mL/min at the start of treatment with E/C/F/TAF FDC.

PMDA's view:
In light of the incidence of adverse events related to renal function in Studies 0104, 0111, and 0109, no new concerns arose from E/C/F/TAF FDC compared to STB. Although an evaluation of the change in CL_{cr} from baseline to Week 48 among treatment-naïve adult HIV-1 patients revealed a smaller change in the E/C/F/TAF FDC group than in the STB group, clinical relevance of the difference in the change in CL_{cr} between the two groups is not clear at present, and the incidence of adverse events related to renal function did not differ greatly between the two groups. Taking account of the above findings, nephrotoxicity risk associated with E/C/F/TAF FDC cannot be ruled out. Therefore, a cautionary statement should be provided regarding renal impairment induced by E/C/F/TAF FDC as in the case of TDF-containing drugs, and renal function tests should be performed before and during treatment with E/C/F/TAF FDC.

Because neither apparent changes in serum creatinine or CL_{cr} at Week 24 nor particular safety problems were observed in a phase III study in adult HIV-1 patients with mild or moderate renal impairment at baseline (Study 0112), the safety of E/C/F/TAF FDC in patients with mild or moderate renal impairment is acceptable. Taking also into consideration that no major difference was noted in the exposure between patients with mild and moderate renal impairment [see "6.R.4 PK in subjects with renal impairment"], dose adjustment of E/C/F/TAF FDC, which contains a fixed dose of FTC, is not required in patients with mild or moderate renal impairment (CL_{cr} ≥30 mL/min), although the package insert of single-agent FTC product states that dose adjustment is required for patients with renal impairment with CL_{cr} value of <50 mL/min (see Emtriva Capsules 200 mg [package insert]. 6th ed.). Therefore, the prior assessment requestor's explanation is acceptable in that patients are required to have CL_{cr} value of ≥30 mL/min before the start of treatment with E/C/F/TAF FDC. However, available safety information is extremely limited on continued use of E/C/F/TAF FDC in patients with CL_{cr} being <30 mL/min, and the package insert of single-agent FTC product states that a different dosing interval of FTC is necessary in patients with severe renal impairment (CL_{cr} <30 mL/min) than that in patients with mild or moderate renal impairment (CL_{cr} ≥30 mL/min) (see Emtriva Capsules 200 mg [package insert]. 6th ed.). Consequently, a cautionary statement should be provided for patients with CL_{cr} being <30 mL/min to consider discontinuation of E/C/F/TAF FDC.

After market launch, information on the emergence and worsening of renal impairment associated with E/C/F/TAF FDC should be collected and provided appropriately to healthcare professionals in clinical settings.

7.R.2.1.2 Effect on BMD

The prior assessment requestor's explanation on the effect of E/C/F/TAF FDC on BMD:
The change in BMD at Week 48 in phase III studies in treatment-naïve adult HIV-1 patients (Studies 0104 and 0111) was as shown in Table 44. The changes in BMD at the proximal femur and lumbar spine were smaller in the E/C/F/TAF FDC group than in the STB group. However, enhancement of bone turnover was suggested by a decrease in BMD and an increase in bone turnover biomarkers observed in non-clinical studies of E/C/F/TAF FDC [see "5.2 Repeat-dose toxicity" and "5.7.2.1 Study on bone turnover"], and a decrease in the mean BMD from baseline was observed at Week 48 in phase III studies (Studies 0104 and 0111). In addition, because of the paucity of information on the impact of long-term treatment with E/C/F/TAF FDC on the bone, information on the decreases in BMD observed in non-clinical and clinical studies will be provided to healthcare professionals in clinical settings, and the following cautionary statements will be included in the package insert, etc.: Patients with a history of pathological fracture should be carefully monitored and appropriate measures should be taken if any abnormalities are observed.

Table 44. Change in BMD from baseline to Week 48 in phase III studies (Studies 0104 and 0111)

	E/C/F/TAF FDC	STB
DXA analysis of proximal femur		
N	780	767
BMD at baseline (g/cm^2)	1.041 ± 0.157	1.029 ± 0.150
BMD at Week 48 (g/cm^2)	1.034 ± 0.159	0.999 ± 0.152
Change in BMD (g/cm^2)	-0.007 ± 0.034	-0.030 ± 0.036
DXA analysis of lumbar spine		
N	784	773
BMD at baseline (g/cm^2)	1.136 ± 0.177	1.114 ± 0.165
BMD at Week 48 (g/cm^2)	1.120 ± 0.173	1.082 ± 0.126
Change in BMD (g/cm^2)	-0.016 ± 0.036	-0.032 ± 0.037

Mean ± standard deviation

PMDA's view:
The prior assessment requestor's explanation is acceptable.

Information on the impact of long-term treatment and treatment experience in patients with different baseline BMD should be collected continuously after market launch and provided appropriately to healthcare professionals in clinical settings.

7.R.2.2 Safety in HIV-1 infected adolescents

The prior assessment requestor's explanation on the safety in HIV-1 infected adolescents (including the effects of E/C/F/TAF FDC on bone formation in adolescents):
In a phase II/III study in HIV-1 infected adolescents with body weight ≥35 kg (Study 0106), the incidence of adverse events was 84.0% (42 of 50) of subjects and the incidence of adverse drug reactions was 36.0% (18 of 50) of subjects. Adverse events with an incidence of ≥10% included respiratory tract infection (32.0% [16 of 50] of subjects); diarrhoea and upper respiratory tract infection (26.0% [13 of 50] of subjects each); nausea (24.0% [12 of 50] of subjects); headache (20.0% [10 of 50] of subjects); abdominal pain (16.0% [8 of 50] of subjects); vomiting (14.0% [7 of 50] of subjects); body tinea, bronchopneumonia, dizziness, and seborrhoeic dermatitis (12.0% [6 of 50] of subjects each); and abdominal pain upper, urinary tract infection, vitamin D deficiency, cough, and rash papular (10.0% [5 of 50] of subjects each). A comparison of safety (considering also serious adverse events) between adolescent and adult HIV-1 patients revealed no particular differences.

The lumbar spine BMD-Z score and total body less head BMD-Z score (adjusted by height and age) at Week 48 obtained in a phase II/III study (Study 0106) are shown in Table 45. No substantial changes were observed in the BMD-Z scores, indicating that E/C/F/TAF FDC does not impact on the mineral apposition rate.

Table 45. Changes in lumbar spine BMD-Z score and total body less head BMD Z score at Week 48

	Lumbar spine BMD-Z score	Total body less head BMD Z-score
N	47	45
Baseline	-0.73 ± 1.37	-0.33 ± 1.03
Change from baseline	-0.00 ± 0.40	-0.15 ± 0.31

Mean ± standard deviation (adjusted by height and age)

PMDA's view:
No new safety concerns arose from HIV-1 infected adolescents with body weight ≥35 kg compared with adult HIV-1 patients. Since treatment duration and experience with E/C/F/TAF FDC in HIV-1 infected adolescents with body weight ≥35 kg are limited, a cautionary statement should be provided regarding the effect of E/C/F/TAF FDC on the bone, as in the case of adult HIV-1 patients, although no apparent decrease in BMD-Z score was observed. Moreover, after market launch, information on the impact on the bone in HIV-1 infected adolescents with body weight ≥35 kg should be collected and provided appropriately to healthcare professionals in clinical settings.

7.R.3 Clinical positioning of E/C/F/TAF FDC and its significance

The prior assessment requestor's explanation on the clinical positioning of E/C/F/TAF FDC and the significance of this combination (including comparison with STB):
An analysis of renal function-related parameters conducted in phase III studies in treatment-naïve adult HIV-1 patients (Studies 0104 and 0111) revealed that the changes in serum creatinine and CL_{cr} from baseline were smaller in the E/C/F/TAF FDC group than in the STB group. In addition, an analysis of proximal femur and lumbar spine BMD conducted in phase III studies (Studies 0104 and 0111) revealed that the change in BMD from baseline was smaller in the E/C/F/TAF FDC group than in the STB group. Consequently, the effects of E/C/F/TAF FDC on the kidneys and bone are expected to be lower than STB, which contains TDF.

In treating HIV-1 patients, it is important to continuously suppress the level of HIV-1 RNA below the detection limit over a long period of time, and a combination regimen with multiple drugs with different mechanisms of action should be used in order to prevent rebound of HIV-1 RNA and induction of drug-resistant virus (Research Group for Conquering HIV Infection and Complications. *Guideline for anti-HIV treatment* [in Japanese]. the Research Project on HIV/AIDS funded by the FY 2014 Health and Labour Sciences Research Grants; March, 2015); therefore, maintaining high adherence to anti-HIV drug therapy is essential. E/C/F/TAF FDC, like STB, is a combination drug of multiple active ingredients with different mechanisms of action in 1 tablet with smaller diameters than STB (major and minor diameters: STB, approximately 20.0 and 10.0 mm, respectively; E/C/F/TAF FDC, approximately 19.2 and 8.7 mm, respectively) to be administered once daily, and therefore, may improve medication adherence.

Consequently, E/C/F/TAF FDC can provide a new therapeutic option for HIV-1 patients.

PMDA's view:
E/C/F/TAF FDC, as a combination drug containing a new active ingredient TAF, can provide a new therapeutic option for HIV-1 patients. However, because clinical significance of the above improvement in laboratory parameters related to renal function and bone turnover has not been clearly shown (including long-term prognosis), and because the impacts on renal function and bone turnover were also observed with TAF [see "5.2 Repeat-dose toxicity," "5.7.2 Mechanism of toxicity," "7.R.2.1.1 Renal impairment," and "7.R.2.1.2 Effect on BMD"], the same cautions as for conventional TFV-containing preparations such as STB and TDF should be provided.

7.R.4 Indication

Because the efficacy of E/C/F/TAF FDC is expected in the treatment of HIV-1 infection and no particular safety concerns are posed on the basis of results from phase III studies (Studies 0104, 0111, 0109, 0112, and 1249) and phase II/III study (Study 0106) [see "7.R.1 Efficacy" and "7.R.2 Safety"], PMDA concluded that the indication for E/C/F/TAF FDC should be "HIV-1 infection" as proposed by the prior assessment requestor. However, an appropriate cautionary statement should be provided to ensure that E/C/F/TAF FDC should be used only in HIV-1 patients who had not been previously treated with anti-HIV drugs or who have achieved virologic suppression.

The above conclusion by PMDA will be discussed at the Prior Assessment Meeting.

7.R.5 Dosage and administration

PMDA's view on the following proposed dosage and administration for E/C/F/TAF FDC:
The usual adult dosage is 1 tablet (containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide) administered orally once daily after a meal.
For adolescents (aged ≥12 years) with body weight ≥35 kg, 1 tablet may be administered orally once daily after a meal.

On the basis of the data from phase III studies (Studies 0104, 0111, and 0109) conducted in adult patients with the dosage regimen established from the data of phase I studies (Studies GS-US-120-0104 and GS-US-292-0101) [see "6.R.1 Appropriateness of dose selection (combination ratio)" and "6.R.2 Timing of dosing relative to meals"], efficacy in E/C/F/TAF FDC can be expected [see "7.R.1 Efficacy"] and its safety can be accepted [see "7.R.2 Safety"]. Therefore, the proposed dosage and administration is acceptable.

Moreover, although adequate information were not available on the efficacy and safety of E/C/F/TAF FDC in HIV-1 infected adolescents with body weight ≥35 kg, no clinically significant difference was noted between the PK of HIV-1 infected adolescents with body weight ≥35 kg and adult HIV-1 patients [see "6.R.3 Differences in PK of E/C/F/TAF FDC between HIV-1 infected adolescents with body weight ≥35 kg and adult HIV-1 patients"]. Also, the efficacy of E/C/F/TAF FDC was suggested with no particular safety concerns in HIV-1 infected adolescents with body weight ≥35 kg. On the basis of the above findings, a dosage regimen for HIV-1 infected adolescents with body weight ≥35 kg may be established in Japan, as in the U.S.

Since an identical dosage regimen will be used for both adult patients and pediatric patients aged ≥12 years with body weight ≥35 kg, the statement of dosage and administration of E/C/F/TAF FDC should be modified as shown below:

The usual dosage for adults and adolescents (aged ≥12 years) with body weight ≥35 kg is one tablet (containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide) administered orally once daily after a meal.

Available information on the use of E/C/F/TAF FDC in HIV-1 infected adolescents with body weight ≥35 kg is limited at present, and its safety in such patients should be evaluated after market launch. The product for pediatric HIV-1 patients aged <12 years or with body weight <35 kg should be developed based on the data from ongoing foreign clinical studies and the use status in Japanese children.

The above conclusion by PMDA will be discussed at the Prior Assessment Meeting.

7.R.6 Post-marketing investigations

The prior assessment requestor plans to conduct an all-case post-marketing surveillance by participating in the Joint Investigation Consortium of HIV related drugs (HRD)[73] as described below:

- Objective: To collect information on the safety and efficacy in routine clinical practice
- Target sample size: All available patients

  Survey period: Starting from the date of initial marketing, all patients registered within 5 years from the date of approval will be surveyed until 8 years after approval. Information on pregnant women enrolled in this drug use-results survey will also be collected.

PMDA has concluded that the following information should be continuously collected by post-marketing surveillance:

- The safety and efficacy of E/C/F/TAF FDC in Japanese HIV-1 patients (including efficacy by patient characteristics)
- Emergence of resistance mutations associated with E/C/F/TAF FDC

[73] A post-marketing surveillance of the safety and efficacy of anti-HIV drugs

- The incidence of adverse events and laboratory test abnormal related to renal impairment or BMD decrease associated with long-term use of E/C/F/TAF FDC
- The safety and efficacy in patients superinfected with hepatitis virus

The above conclusion by 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, the efficacy of E/C/F/TAF FDC in HIV-1 patients can be expected and its safety is acceptable in view of its observed benefits. E/C/F/TAF FDC, a combination product containing a new (TAF fumarate) and approved (EVG, COBI, and FTC) active ingredients, provides a new therapeutic option for HIV-1 patients and, thus, is considered clinically significant.

PMDA has concluded that E/C/F/TAF FDC may be approved if no particular problems arise on the basis of the comments from the Prior Assessment Meeting.

Review Report (1)

May 18, 2016

Product Submitted for Registration

Brand Name	Genvoya Combination Tablets
Non-proprietary Name	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate
Applicant	Japan Tobacco Inc.
Date of Application	March 4, 2016

1. Content of the Review

Comments made during the Prior Assessment Meeting and Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors for the Prior Assessment Meeting and Expert Discussion were nominated based on their declarations etc., concerning the product submitted for registration, 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).

The conclusions of PMDA regarding issues described in the Prior Assessment Report (1) [see "7.R.1 Efficacy," "7.R.2 Safety," "7.R.4 Indications," "7.R.5 Dosage and administration," and "7.R.6 Post-marketing investigations"] were supported by the expert advisors at the Prior Assessment Meeting and Expert Discussion.

PMDA also discussed the following points and took action as necessary.

1.1 Cautionary statement regarding renal impairment and BMD decrease

PMDA concluded that nephrotoxicity risk associated with Genvoya Combination Tablets cannot be ruled out in light of the following points:

- Genvoya Combination Tablets contain tenofovir alafenamide fumarate, a prodrug of tenofovir, and therefore have a nephrotoxicity risk.
- The incidence of adverse events related to renal function[74)] in phase III studies in treatment-naïve adult patients with human immunodeficiency virus type 1 (HIV-1) infection (Studies GS-US-292-0104 and GS-US-292-0111) did not seem to be substantially different between the Genvoya Combination Tablets group and Stribild Combination Tab. group.
- An adverse drug reaction of renal failure that led to treatment discontinuation was reported in a foreign phase III study of non-Japanese adult HIV-1 patients with mild or moderate renal impairment (Study GS-US-292-0112).

Therefore, PMDA instructed the applicant to include a cautionary statement in the package insert etc., regarding renal impairment occurring after administration of Genvoya Combination Tablets and necessity of renal function testing, in a similar manner as in tenofovir disoproxil fumarate-containing products. The applicant agreed to the above instructions.

1.2 Risk management plan (draft)

In view of the discussion presented in "7.R.6 Post-marketing investigations" in the Prior Assessment Report (1) and comments from the expert advisors, PMDA considers that post-marketing surveillance should also cover the following issues.

- The safety and efficacy of Genvoya Combination Tablets in Japanese HIV-1 patients (including efficacy by patient characteristics)

74) Defined as adverse events that met either of the following criteria:
- Adverse events of MedDRA PTs within the SOC "renal and urinary disorders"
- Adverse events of MedDRA PTs within the SOC "investigations" and also within its High Level Term "renal function analyses"

- Emergence of resistance mutations associated with Genvoya Combination Tablets
- The incidence of adverse events and laboratory test abnormal related to renal impairment or BMD decrease associated with long-term use of Genvoya Combination Tablets
- The safety and efficacy in patients superinfected with hepatitis virus

PMDA requested that the applicant investigate the issues above during post-marketing surveillance. The applicant agreed to take such action.

In view of the discussions above, PMDA has concluded that the risk management plan (draft) for Genvoya Combination Tablets should include the safety and efficacy specifications presented in Table 46, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 47, and accepted the outline of use-results survey (draft) described in Table 48.

Table 46. Safety and efficacy specifications in the risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Nephrotoxicity • Bone-related events/BMD decrease • Relapse of hepatitis in patients with HIV-1 and HBV superinfection after discontinuing Genvoya Combination Tablets • Lactic acidosis and severe hepatomegaly (hepatic steatosis) • Lipodystrophy • Immune reconstitution inflammatory syndrome	• Pancreatitis	• Safety in Japanese HIV-1 patients • Long-term treatment • Use during pregnancy • Use in patients with severe hepatic impairment
Efficacy specifications		
• Efficacy in Japanese HIV-1 patients • Efficacy of long-term treatment (including emergence of drug resistance and/or cross-resistance)		

Table 47. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing clinical study[a)] • Drug use-results survey • Specified use-results surveys (pregnant and nursing women)	• Early post-marketing phase vigilance

a) After approval of Genvoya Combination Tablets, ongoing global phase III studies (Studies GS-US-292-0104 and GS-US-292-1249) will be continued as post-marketing clinical studies until the drug will be commercially available at each study site.

Table 48. Outline of post-marketing surveillance plan (draft)

Drug use-results survey	
Objective	To collect information on the safety and efficacy in routine clinical settings
Survey method	All-case surveillance will be conducted by participating in the Joint Investigation Consortium of HIV related drugs (HRD).
Population	Japanese HIV-1 patients
Observation period	The survey will be initiated on the launch date of Genvoya Combination Tablets and continued until the end of March of the 8th year of approval of Genvoya, according to the HRD joint survey procedure, covering all patients registered on and after the approval of Genvoya.
Planned sample size	All available patients
Main survey items	Patient characteristics, use status of Genvoya Combination Tablets, adverse events, plasma HIV-1 RNA levels, etc.
Specified use-results survey (pregnant and nursing women)	
Objective	To collect information on the safety in pregnant women and newborns in routine clinical settings
Survey method	Conducted by participating in a HRD joint survey
Population	Pregnant Japanese HIV-1 patients
Observation period	The survey will be initiated on the launch date of Genvoya Combination Tablets, and continued until the expiration of the re-examination period according to the HRD joint survey procedure, covering all patients registered on and after the launch date.
Planned sample size	All patients for whom the outcome of pregnancy will be available
Main survey items	Patient characteristics, use status of Genvoya Combination Tablets, adverse events, plasma HIV-1 RNA levels, effects on the newborns, etc.

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

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspection and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and 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. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (5.3.3.3-4, 5.3.5.1-4) were subjected to an on-site GCP inspection, 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. PMDA concluded that the conducted clinical studies were generally in compliance with GCP and that there were no obstacles to conduct its review based on the application documents submitted. The following was noted in the works done by the sponsor although they did not significantly affect the overall evaluation of the study. These were notified to the applicant (sponsor) for improvement.

[Matters to be improved]
Sponsor
- Delay in annual safety reporting to investigators and the head of the study sites

3. Overall Evaluation

As a result of the above review, PMDA has concluded that this product may be approved for the indication and dosage and administration as shown below with the following conditions for approval. Since Genvoya is an orphan drug, the re-examination period is 10 years. Tenofovir alafenamide fumarate, among the drug substances, as well as the drug product, are classified as powerful drugs, and the drug product is not classified as a biological product or a specified biological product.

Indication
HIV-1 infection

Dosage and Administration
The usual dosage for adults and adolescents (aged ≥12 years) with body weight ≥35 kg is 1 tablet (containing 150 mg of elvitegravir, 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide) administered orally once daily after a meal.

Conditions for Approval
The applicant is required to:
1. Develop and appropriately implement a risk management plan;

2. Request physicians to obtain patients' informed consent to the use of the product after having thoroughly informed them that the collection of additional data on the efficacy and safety of the product is still ongoing;

3. Submit the results and analyses of ongoing or planned clinical studies promptly after the study completion; and

4. Conduct a post-marketing surveillance which must, as a general rule, cover all patients treated with the product in Japan, until the expiration of the re-examination period; collect information on the use status of the product (patient characteristics, efficacy and safety [including the efficacy and safety of the product in concomitant use with other drugs], data on drug-drug interactions); then submit periodical reports thereof; and finally results of the surveillance should be submitted when applying re-examination.