Report on the Deliberation Results

November 16, 2016

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

Brand Name	Vemlidy Tablets 25 mg
Non-proprietary Name	Tenofovir Alafenamide Fumarate (JAN*)
Applicant	Gilead Sciences K.K.
Date of Application	March 31, 2016

Results of deliberation

In the meeting held on November 11, 2016, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 5 years and 10 months. The drug product is classified as a powerful drug.

Condition of Approval

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

**Japanese Accepted Name (modified INN)*

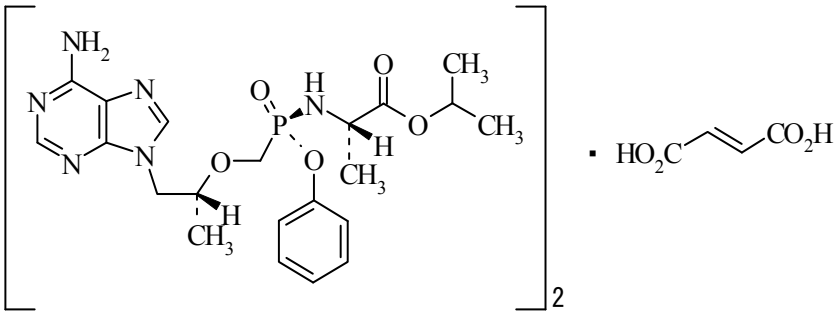
Review Report

October 18, 2016
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

Brand name	Vemlidy Tablets 25 mg
Non-proprietary Name	Tenofovir Alafenamide Fumarate
Applicant	Gilead Sciences K.K.
Date of Application	March 31, 2016
Dosage form/Strength	Each tablet contains 28 mg of Tenofovir Alafenamide Fumarate (equivalent to 25 mg of Tenofovir Alafenamide).
Application Cclassification	Prescription drug, (1) Drug with a new active ingredient

Chemical structure



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

Priority review (Notification No. 0412-2, dated April 12, 2016, issued by the Evaluation and Licensing Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug IV

Results of Review

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the submitted data demonstrate the efficacy of the product in the treatment of chronic hepatitis B and acceptable safety in view of the observed benefits, as shown in the Attachment.

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

Indication

Suppression of hepatitis B virus replication in chronic hepatitis B patients with evidence of viral replication and abnormal liver function

Dosage and Administration

The usual adult dosage is 25 mg of Tenofovir Alafenamide administered orally once daily.

Condition of Approval

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

Attachment

Review Report (1)

September 6, 2016

The data submitted in the application and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA), etc. are summarized below.

Product Submitted for Approval

Brand Name	Vemlidy Tablets 25 mg
Non-proprietary Name	Tenofovir Alafenamide Fumarate
Applicant	Gilead Sciences K.K.
Date of Application	March 31, 2016
Dosage form/Strength	Each tablet contains 28 mg of Tenofovir Alafenamide Fumarate (equivalent to 25 mg of Tenofovir Alafenamide).
Proposed Indication	Suppression of hepatitis B virus replication in chronic hepatitis B patients with evidence of viral replication and abnormal liver function
Proposed Dosage and Administration	The usual adult dosage is 25 mg of Tenofovir Alafenamide (equivalent to 28 mg of Tenofovir Alafenamide Fumarate) administered orally once daily.

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List of Abbreviations

ADV	Adefovir pivoxil
ALT	Alanine aminotransferase
ATV	Atazanavir
AUC	Area under the plasma concentration versus time curve
AUC_{inf}	AUC extrapolated to infinite time
AUC_{last}	AUC from time of administration up to the last time point with a measurable concentration after dosing
AUC_{tau}	AUC over the dosing interval
BCRP	Breast Cancer Resistance Protein
BID	bis in die
CC_{50}	Drug concentration that results in a 50% reduction in cell viability
CL_{cr}	Creatinine clearance
CL/F	Apparent clearance
CL_r	Renal clearance
C_{max}	Maximum plasma concentration
COBI	Cobicistat
C_{tau}	Observed drug concentration at the end of the dosing interval
CYP	Cytochrome P450
CV	Coefficient of variation
DRV	Darunavir
DTG	Dolutegravir
EC_{50}	50% effective concentration
Efflux ratio	Basal-to-apical versus apical-to-basal ratio
$eGFR_{CG}$	Estimated glomerular filtration rate calculated using the Cockcroft-Gault equation
ETV	Entecavir
EVG	Elvitegravir
FAS	Full analysis set
Guidelines for the Management of Hepatitis B Virus Infection, 2.2nd ed.	Guidelines for the Management of Hepatitis B Virus Infection, 2.2nd ed. Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology, ed. May 2016
HBV	Hepatitis B virus
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
LAM	Lamivudine
LPV	Lopinavir
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
P-gp	P-glycoprotein
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
QD	quaque die
RPV	Rilpivirine
RT	Reverse transcriptase
RTV	Ritonavir
Study 0108	Study GS-US-320-0108

Study 0110	Study GS-US-320-0110
t_{max}	Time to maximum plasma concentration
$t_{1/2}$	Estimate of the terminal elimination half-life
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir
Vemlidy	Vemlidy Tablets 25 mg
V_c/F	Apparent volume of distribution (central compartment)
V_d/F	Apparent volume of distribution
V_p/F	Apparent volume of distribution (peripheral compartment)

1. Origin or history of discovery, use in foreign countries, and other information

Tenofovir alafenamide (TAF) fumarate is an oral prodrug of tenofovir (TFV), a nucleotide analog, developed by Gilead Sciences, Inc. (the US). TAF fumarate is a selective inhibitor of HBV DNA polymerase and HIV-1 reverse transcriptase. Other oral prodrugs of TFV include Tenozet Tablets 300 mg containing tenofovir disoproxil fumarate (TDF) as the active substance and Complera Combination Tablets containing TDF as an active substance. In Japan, Tenozet Tablets 300 mg has been approved for the indication of chronic hepatitis B (CHB), and Complera Combination Tablets for the indication of HIV-1 infection.

The putative intracellar activation pathway for metabolism of TAF to TFV diphosphate (the active metabolite) are shown in Figure 1.

Since TAF is metabolized to TFV by carboxylesterase 1 (CES1) in hepatocytes, and by cathepsin A (CatA) in peripheral blood mononuclear cells, the plasma concentration of TFV can be reduced after administration of TAF compared to that of previously approved TDF.[1)]

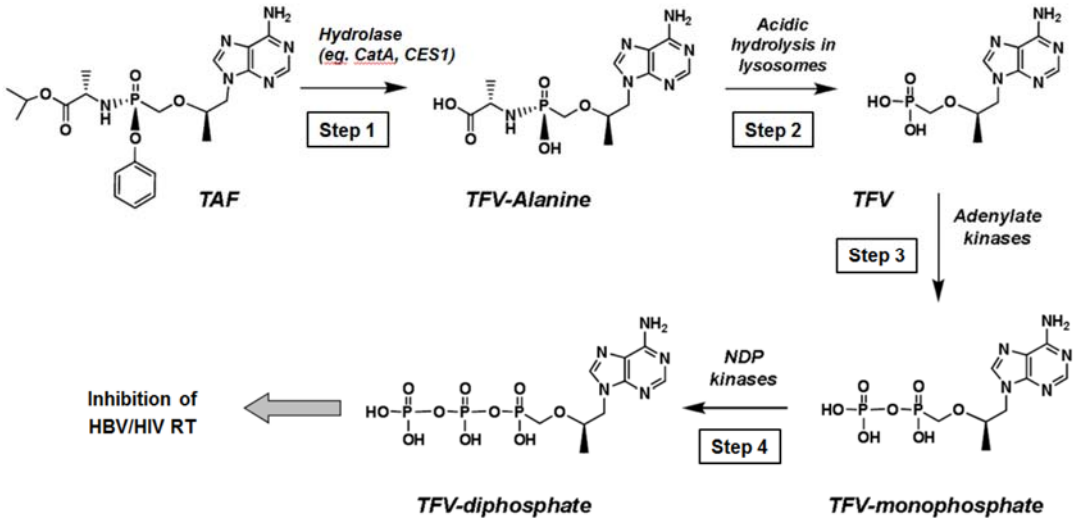

Figure 1. Putative intracellar activation pathways for metabolism of TAF to TFV diphosphate (the active metabolite)

An estimated 250 million individuals have chronic HBV infection around the world. An estimated 1.5 million persons have HBV infection in Japan, and approximately 10% of those infected with HBV become chronically infected with HBV (*Lancet.* 2015; 386: 1546-55, *Hepatol Res.* 2011;41: 1-21, etc.). The absence of effective treatment leads to the development of cirrhosis, hepatic decompensation, or hepatocellular carcinoma in 15% to 40% of persons with chronic HBV infection (Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection, WHO, 2015, *Am J Gastroenterol*. 2006; 101: S1-S6).

Based on the data including results from multi-regional clinical studies of TAF (Vemlidy) in treatment-naïve or treatment-experienced CHB patients with or without compensated cirrhosis, the applicant has filed a marketing application for Vemlidy.

[1)] Systemic exposure to TFV was reduced by approximately 92% after oral administration of Vemlidy (containing TAF 25 mg) compared to Tenozet Tablets 300 mg (containing TDF 300 mg) [see Section 6.2.2.1].

Outside Japan, regulatory applications for Vemlidy for the treatment of CHB were submitted in the US and the EU in January 2016.

In Japan, Genvoya Combination Tablets containing TAF fumarate as an active substance was approved for the indication of HIV-1 infection in June 2016. The data package for the present application included the data that had been submitted for marketing applications for "Tenozet Tablets 300 mg," "Complera Combination Tablets," and "Genvoya Combination Tablets." Because these data had previously been evaluated by PMDA, the newly submitted data were mainly evaluated in the present review.

2. Data relating to quality and outline of the review conducted by PMDA

2.1 Drug substance

The drug substance, tenofovir alafenamide fumarate, is registered in a Master File (MF) (MF Registration Number: 227MF10232). The drug substance manufacturing process and its control are the same as those used for the approved drug product.

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is a tablet containing 28.04 mg of tenofovir alafenamide fumarate (equivalent to 25 mg of tenofovir alafenamide). The excipients used in the drug product include lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and Opadry II Yellow 85F120028.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of [redacted], [redacted], [redacted], tableting, film-coating, packaging, labeling, testing, and storage. Of these steps, [redacted] and [redacted] have been defined as critical steps, and process control parameters and limits have been established for [redacted], [redacted], and [redacted].

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identification (ultraviolet-visible absorption spectrum, liquid chromatography), purity (related substances [liquid chromatography]), water content, uniformity of dosage units (content uniformity testing [liquid chromatography]), dissolution (liquid chromatography), microbial limits, and assay (liquid chromatography).

2.2.4 Stability of drug product

The stability studies of the drug product are shown in Table 1. The photostability study showed that the drug product is photostable.

Table 1. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches (tablets packaged in 30-count bottles)	30°C	75%RH	High-density polyethylene bottle	36 months
	1 pilot-scale batch (tablets packaged in 30-count bottles)				18 months
	3 pilot-scale batches (tablets packaged in 14-count bottles)				12 months
Accelerated	6 pilot-scale batches (tablets packaged in 30-count bottles)	40°C	75%RH		6 months
	3 pilot-scale batches (tablets packaged in 14-count bottles)				6 months

Based on the above, a shelf-life of 36 months has been proposed for the tablets packaged in 30-count high-density polyethylene bottles when stored at room temperature. Although only 12-month long-term stability data were available for the tablets packaged in 14-count bottles, the same container closure system was used for the tablets packaged in 14-count bottles and the tablets packaged in 30-count bottles. The long-term and accelerated stability data demonstrated similar stability. Thus, the applicant explained that as with the tablets packaged in 30-count bottles, a shelf-life of 36 months can be proposed for the tablets packaged in 14-count bottles when stored at room temperature. The long-term testing of the tablets packaged in 14-count bottles and the tablets in packaged 30-count bottles will be continued for up to [redacted] months.

2.R Outline of the review conducted by PMDA

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

3. Non-clinical pharmacology studies and outline of the review conducted by PMDA

In addition to the data that had been submitted and evaluated for marketing applications for "Tenozet Tablets 300 mg," "Complera Combination Tablets," and "Genvoya Combination Tablets," data including results from new primary pharmacodynamic and pharmacodynamic interaction studies were submitted in the present application. The newly submitted study data for the present application are described in this section.

3.1 Primary pharmacodynamics

In vitro antiviral activity (CTD 4.2.1.1-5, 4.2.1.1-6)

The antiviral activity of TAF was evaluated in HepG2 cells transfected with the genomes of wild type HBV clinical isolates and the HBV genome of the laboratory strain (pHY92). The results are shown in Table 2**Table 2**. The CC_{50} values of TAF in HepG2 cells were >44,400 nmol/L.

Table 2. Antiviral activity of TAF against genotypes A-H HBV clinical isolates

HBV genotype	Cloned [a)]	EC_{50} (nmol/L)
Laboratory strain (pHY92) (A)	Full-length	102.3
A	Full-length	112.0
B	Full-length	109.3
C	Full-length	107.5
	Full-length	64.6
D	Full-length	70.5
	Full-length	62.8
E	Full-length	134.4
F	pol/RT	92.5
G	pol/RT	120.4
	pol/RT	43.8
H	pol/RT	34.7

Mean

a) Full-length HBV genomes or polymerase/reverse transcriptase (pol/RT) regions isolated from treatment-naïve patients infected with HBV genotypes A-H were amplified and cloned into an expression vector, followed by transfection into HepG2 cells.

The antiviral activity of TAF was evaluated against a panel of isolates containing mutations associated with resistance to other nucleoside/nucleotide reverse transcriptase inhibitors (ADV, LAM, or ETV) (*Gastroenterology*. 2006; 131: 1743-51, *Gastroenterology.* 2003; 125: 1714-22, etc.) in HepG2 cells. The results are shown in Table 3.

Table 3. Susceptibility of HBV containing ADV-, LAM-, or ETV-resistant mutations to TAF

Type	RT mutations	EC_{50} (nmol/L)				Fold change [a)]			
		TAF	TFV	LAM	ETV	TAF	TFV	LAM	ETV
Wild-type		99.1	14.4	4.1	17.5	1.0	1.0	1.0	1.0
ADV-resistant	rtA181T/sW172*[b)]	166.8	13.1	−	−	1.7	0.9	−	−
	rtA181T/sW172L	107.3	7.8	−	−	1.1	0.6	−	−
	rtA181V	118.8	13.7	−	−	1.2	1.0	−	−
	rtN236T	142.8	8.8	−	−	1.4	0.6	−	−
	rtA181V + rtN236T	364.7	40.5	−	−	3.7	2.8	−	−
LAM-resistant	rtM204I	161.9	25.3	>200	−	1.6	1.8	>48.8	−
	rtL180M + rtM204V	176.4	21.3	>200	−	1.8	1.5	>48.8	−
	rtV173L + rtL180M + rtM204V	85.4	23.7	>200	−	0.9	1.6	>48.8	−
ETV-resistant	rtL180M + rtM204V + rtT184G	164.4	17.7	−	>500	1.7	1.2	−	>28.6
	rtL180M + rtM204V + rtS202G	152.0	13.1	−	>500	1.5	0.9	−	>28.6
	rtL180M + rtM204V + rtM250V	114.7	20.9	−	>500	1.2	1.5	−	>28.6

Mean

a) Mutant EC_{50}/wild-type EC_{50}

b) rtA181T mutation resulted in a W172 stop codon mutation in HBsAg.

3.2 Pharmacodynamic interaction studies

3.2.1 Effect of various protease inhibitors on the anti-HBV activity of TAF (CTD 4.2.1.1-1, 4.2.1.4-1)

The effect of various protease inhibitors on the anti-HBV activity of TAF was evaluated in HepAD38 cells transfected with HBV. The results are shown in Table 4.

Table 4. Effect of various protease inhibitors on the anti-HBV activity of TAF in HepAD38 cells

Test drug (concentration) [a]		Fold change in TAF EC_{50} [b]
HIV protease inhibitor	DRV (8.9 μmol/L)	0.9
HCV protease inhibitor	Telaprevir (5.2 μmol/L)	1.2
	Boceprevir [c] (3.3 μmol/L)	1.3
	Simeprevir (3.3 μmol/L)	0.7
CYP3A inhibitor	COBI (2.2 μmol/L)	0.9
Factor Xa inhibitor	Apixaban (0.17 μmol/L)	0.8
	Rivaroxaban (0.3 μmol/L)	0.9
Thrombin inhibitor	Argatroban (0.4 μmol/L)	1.0
	Dabigatran (0.4 μmol/L)	1.0
Dipeptidyl peptidase-4 inhibitor	Sitagliptin (1.0 μmol/L)	0.7

a) Simeprevir was evaluated at 25% of clinical C_{max} due to cytotoxicity observed at high concentrations. Other test drugs were evaluated at clinical C_{max}.
b) Ratio of TAF EC_{50} in the presence versus the absence of test drug
c) Boceprevir is unapproved in Japan.

The effect of inhibition of cathepsin A and carboxylesterase 1 on the anti-HBV activity of TAF was evaluated in HepAD38 cells. The results are shown in Table 5. The anti-HBV activity of TAF was unaffected in the presence of a cathepsin A inhibitor, telaprevir (5.2 μmol/L), or a carboxylesterase 1 inhibitor, bis-p-nitrophenyl phosphate (50 μmol/L). However, the anti-HBV activity of TAF was reduced in the presence of telaprevir plus bis-p-nitrophenyl phosphate.

Table 5. Effect of inhibition of cathepsin A and carboxylesterase 1 on the anti-HBV activity of TAF in HepAD38 cells

Target protein	Inhibitor	Fold change [a]
Cathepsin A	Telaprevir	0.9
Carboxylesterase 1	Bis-p-nitrophenyl phosphate	1.4
Cathepsin A + carboxylesterase 1	Telaprevir + bis-p-nitrophenyl phosphate	2.1

a) Ratio of EC_{50} in the presence versus the absence of inhibitor

3.2.2 Effect of TAF on the anti-HCV activity of other antivirals (CTD 4.2.1.4-3)

The effect of TAF on the anti-HCV activity and cytotoxicity of various antivirals was evaluated in HCV genotype 1a (Huh-7) replicon cells. The anti-HCV activities (EC_{50} values) of various antivirals (interferon-α, ribavirin, NS3/4A protease inhibitors [telaprevir, boceprevir, simeprevir], an NS5B polymerase inhibitor [sofosbuvir], NS5A inhibitors [ledipasvir, GS-5816]) in the presence of TAF ranged from 0.8- to 1.3-fold those in the absence of TAF. The CC_{50} values of various antivirals were not affected by TAF.

3.R Outline of the review conducted by PMDA

3.R.1 Antiviral activity of TAF against HBV

Based on the submitted data, PMDA considers that the antiviral activity of TAF against HBV is expected.

3.R.2 Resistance to TAF

The applicant's explanation of the resistance to TAF:

TAF and TDF are both prodrugs of TFV and the two prodrugs are metabolized intracellularly to the active metabolite, TFV diphosphate. This suggests that TAF has similar resistance profile to that of TDF. In phase III studies of TAF (Studies 0108 and 0110), no resistance mutations were observed in CHB patients receiving TAF or TDF [see Section 7.R.2.3]. In a >6-year study of TDF, genotypic and phenotypic analyses detected no evidence of TDF resistance (*Hepatology*. 2014;59:434-42). Given that the intracellular concentration of TFV diphosphate was higher following incubation of primary human hepatocytes with TAF versus TDF, TAF resistance mutations are also unlikely to develop during clinical use of TAF.

PMDA's view on resistance to TAF:
Although no TAF or TDF resistance mutations have been observed to date in patients receiving TAF or TDF, the presence or absence of resistance mutations can be important information regarding the efficacy of TAF. Therefore, post-marketing information on resistance should be collected, and new information should be communicated to healthcare professionals if it becomes available.

4. Non-clinical pharmacokinetic studies and outline of the review conducted by PMDA

In addition to the data that had been submitted and evaluated for marketing applications for "Tenozet Tablets 300 mg," "Complera Combination Tablets," and "Genvoya Combination Tablets," the results from new pharmacokinetic interaction studies of TAF or TFV were submitted in the present application. Concentrations of TFV and its active metabolite TFV diphosphate in samples were determined by high performance liquid chromatography/tandem mass spectrometry (Lower limit of quantification [LLOQ], 0.2 or 2.38 nmol/L for TFV; 0.412 pmol/10^6 cells for TFV diphosphate). All concentrations of TAF are expressed as free base.

4.1 Pharmacokinetic interactions

4.1.1 Assessment of TAF/TFV as a substrate for drug transporters (CTD 4.2.2.6-12, 4.2.2.6-14, 4.2.2.6-15, 4.2.2.6-23)

The contribution of OATP1B1 and OATP1B3 to TAF (0.5 μmol/L) uptake into primary human hepatocytes was assessed. The intracellular concentration of TFV diphosphate was reduced by approximately 13% in the presence of an OATP inhibitor, rifampicin (20 μmol/L). On the other hand, the uptake of an OATP substrate, bosentan, was reduced by approximately 38% in the presence of rifampicin. The applicant explained that these results indicate a limited contribution of OATP to TAF uptake into hepatocytes and that TAF uptake is highly attributable to passive diffusion.

The membrane permeability of TFV (9.5-16.8 μmol/L) was evaluated in P-gp-transfected and wild-type MDCKII cells. The efflux ratios in P-gp-transfected and wild-type MDCKII cells were 1.0 and 1.5, respectively. In the presence of a P-gp inhibitor, cyclosporin A (10 μmol/L), the efflux ratio in P-gp-transfected MDCKII cells was 1.5, indicating that TFV is not a substrate for P-gp.

The membrane permeability of TFV (9.5-13.1 μmol/L) was evaluated in BCRP-transfected and wild-type MDCKII cells. The efflux ratios in BCRP-transfected and wild-type MDCKII cells were 2.3 and 1.5, respectively. In the presence of a BCRP inhibitor, Ko134 (10 μmol/L), the efflux ratio in BCRP-transfected MDCKII cells was 3.4, indicating that TFV is not a substrate for BCRP.

The intracellular accumulation of TFV was assessed in OCT2-transfected and wild-type CHO cells. TFV was incubated for 2 or 20 minutes at final concentrations of 1 and 10 μmol/L to determine the ratio of TFV in OCT2-transfected CHO cells versus wild-type CHO cells. The fold accumulation values were 1.24 and 1.37, respectively, for TFV 1 μmol/L and 0.82 and 0.98, respectively, for TFV 10 μmol/L, indicating that TFV is not a substrate for OCT2.

4.1.2 Inhibition of drug transporters (CTD 4.2.2.6-17, 4.2.2.6-18, 4.2.2.6-24)

The inhibition of BCRP, OATP1B1, and OATP1B3 by TFV was assessed in MDCKII cells expressing BCRP and CHO cells transfected with the genes encoding OATP1B1 or OATP1B3. The IC_{50} values were all >100 μmol/L.

The potential for TFV to inhibit OCT1 and BSEP was assessed in OCT1-transfected CHO cells and membrane vesicles expressing bile salt export pump (BSEP). The IC_{50} values were both >100 μmol/L.

4.R Outline of the review by PMDA

PMDA concluded that there is no particular concern about pharmacokinetic interactions based on the newly submitted data from TAF and TFV non-clinical studies.

5. Toxicology studies and outline of the review conducted by PMDA

The data that had been submitted and evaluated for a marketing application for "Genvoya Combination Tablets" were submitted in the present application, and no new data were submitted.

5.R Outline of the review conducted by PMDA

Based on the following findings, PMDA concluded that there is no new toxicological concern about the use of TAF in CHB patients.

- Steady-state plasma exposure parameters of TAF and TFV administered in humans at the clinical dose of Vemlidy (25 mg/day of TAF) were 267 and 392 ng·h/mL, respectively, for AUC_{last} and 284 and 24.8 ng/mL, respectively, for C_{max} [see Section 6.2.2.2]. These values are not markedly higher than the estimated steady-state plasma exposure parameters of TAF and TFV at the clinical dose of Genvoya Combination Tablets (10 mg/day of TAF) (206 and 293 ng·h/mL, respectively, for AUC_{tau}; 162 ng/mL and 15.2 ng/mL, respectively, for C_{max} [Genvoya Combination Tablets Review Report, dated May 19, 2016]).
- Toxicology findings in the repeat-dose toxicity studies of TAF fumarate included degeneration/inflammation in the nasal mucosa and infiltration of mononuclear cells in the eye or other organs, which were not observed with TDF. However, the incidences of adverse events potentially related to these findings were not higher with TAF compared to TDF in clinical studies of TAF fumarate. These findings are unlikely to raise new safety concerns during clinical use.
- Impurities with acceptance criteria exceeding the qualification threshold given in the notification titled "Revision of the Guideline on Impurities in New Drug Substances (PMSB/ELD Notification No.1216001, dated December 16, 2002)" were previously evaluated in the regulatory review of the application for Genvoya Combination Tablets. Other than impurities present in the TAF drug substance, no new impurities (e.g., degradation products derived from TAF) occur in the drug product.

Renal toxicity and effects on bone parameters noted in the repeat-dose toxicity studies of TAF fumarate[2)] were observed also with TDF.[3)] These findings are likely to be associated with plasma TFV exposure. In humans, plasma TFV exposure following administration of TAF 25 mg QD (the clinical dose of Vemlidy) (steady-state AUC_{tau}, 392 ng·h/mL) is lower than that following administration of TDF 300 mg QD (the approved clinical dose of TDF) (AUC, 3224 ng·h/mL) [see Section 6.2.2.2]. Thus, no further toxicological evaluation is necessary. Nephrotoxicity of TAF and the effects on bone parameters in humans are described separately in Section 7.R.3.

6. Biopharmaceutic studies and associated analytical methods, clinical pharmacology studies, and outline of the review conducted by PMDA

6.1 Biopharmaceutic studies and associated analytical methods

The applicant submitted the results from biopharmaceutic studies of TAF, including a food effect study, in the present application. The following 3 different formulations (Formulations 1-3)[4)] were mainly used during the clinical development of TAF. Formulation 3 is the one proposed for marketing.

- Formulation 1: white film-coated tablets, each containing 8, 25, or 40 mg of TAF as the fumarate salt
- Formulation 2: white film-coated tablets, each containing 10 or 25 mg of TAF as the fumarate salt
- Formulation 3: yellow film-coated tablets, each containing 25 mg of TAF as the fumarate salt

The results from a biopharmaceutic study with Formulation 3 proposed for marketing (a food effect study) are described in this section.

Concentrations of TAF and TFV in human plasma were determined by liquid chromatography/tandem mass spectrometry (LLOQ: 1 ng/mL for TAF, 0.3 or 5 ng/mL for TFV). Unless otherwise specified, PK parameters are expressed as the mean, and all doses and concentrations of TAF are expressed as free base.

6.1.1 Food effect study (Reference data, CTD 5.3.3.4-11, Study GS-US-320-1382 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A 2-treatment, 2-period, crossover study was conducted with Formulation 3 (TAF 25 mg) in non-Japanese healthy volunteers (40 subjects included in PK analysis) to determine the effect of food on the pharmacokinetics of TAF. Subjects received a single oral dose of TAF under fasted conditions or within 5 minutes after a high-fat meal (approximately 800 kcal, approximately 50% fat). The results are shown in Table 6. The geometric least-squares mean ratios for the C_{max} and AUC_{inf} of TAF (fed/fasted) [90% confidence interval (CI)] were 0.94 [0.78, 1.13] and 1.68 [1.54, 1.82], respectively. Food tended to prolong the t_{max} of TAF.

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2) The renal toxicity was renal tubular karyomegaly observed in rat 4-week and dog 4-week repeat-dose studies (CTD 4.2.3.2.3 and 4.2.3.2.5). The effects on bone parameters included tibial cancellous bone atrophy and increases in biochemical markers of bone metabolismin a rat 26-week repeat-dose study (CTD 4.2.3.2.4) and decreases in bone mineral density in a dog 39-week repeat-dose study (CTD 4.2.3.2.6) (Genvoya Combination Tablets Review Report, dated May 19, 2016).

3) Viread Tab. 300 mg Review Report (as of February 6, 2004)

4) The following main clinical studies were conducted with Formulations 1-3:
Formulation 1: Study GS-US-320-0101,
Formulation 2: Study GS-US-120-0117,
Formulation 3: Studies GS-US-120-1538, GS-US-120-1554, GS-US-320-1228, GS-US-320-0108, and GS-US-320-0110

Table 6. TAF PK parameters following administration of Formulation 3 under fasted or fed conditions

	N	C_{max} (ng/mL)	t_{max} [a)] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL/F (L/h)	V_d/F (L)
Fasted	39	266.3 (46.9)	0.50 [0.25-2.00]	171.5 (33.6)	0.37 (21.3)	167.8 (45.6)	89.8 (50.2)
Fed	40	252.6 (46.4)	1.00 [0.25-4.00]	288.9 (39.2)	0.54 (51.7)	100.2 (40.5)	76.5 (58.9)

Mean (CV%), a) Median [Range]

6.2 Clinical pharmacology

Clinical pharmacology data submitted in the current application included the data that had been submitted and evaluated for a marketing application for "Genvoya Combination Tablets" and new data (e.g., the results from studies in healthy subjects, CHB patients, or subjects with severe hepatic impairment, the results from pharmacokinetic interaction studies, and the results of PPK analysis). Unless otherwise specified, PK parameters are expressed as the mean.

6.2.1 Studies in healthy subjects

6.2.1.1 Phase I study (CTD 5.3.3.3-1, Study GS-US-320-1228 [[redacted] 20[redacted] to [redacted] 20[redacted]])

The PK profiles of TAF and TFV were investigated in Japanese and non-Japanese healthy subjects (10 subjects each included in PK analysis) following a single oral dose of 25 mg of TAF. The results are shown in Table 7. The applicant explained that the C_{max} and AUC_{inf} of TAF and TFV in Japanese subjects were largely comparable to those in non-Japanese subjects.

Table 7. PK parameters of TAF and TFV following a single oral dose of TAF

	N	C_{max} (ng/mL)	t_{max} [a)] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
TAF PK parameter					
Japanese	10	164.9 (57.0)	1.25 [0.25-2.50]	212.8 (45.9)	0.34 (31.5)
Non-Japanese	10	144.9 (79.4)	1.5 [0.50-5.0]	191.6 (57.8)[b)]	0.45 (43.2)[b)]
TFV PK parameter					
Japanese	10	10.0 (23.4)	2.25 [1.5-3.0]	305.1 (35.9)	43.9 (17.2)
Non-Japanese	10	7.2 (36.6)	2.75 [1.0-6.0]	225.7 (29.6)	40.2 (13.5)

Mean (CV%), a) Median [Range], b) N = 9

6.2.2 Studies in patients

6.2.2.1 Foreign phase I study (CTD 5.3.4.2-1, Study GS-US-320-0101 [December 2011 to April 2013])

In the study, patients with CHB received oral doses of TAF 8 to 120 mg or TDF 300 mg QD for 28 days (51 subjects included in PK analysis). The PK parameters of TAF and TFV on Day 1 and the trough concentrations on Days 2 to 28 were determined. The PK parameters on Day 1 are shown in Table 8. The C_{max} and AUC_{inf} of TAF were dose-proportional over the range of 8 to 120 mg. Following multiple-dose administration of TAF, plasma TFV concentrations reached a steady-state by Day 10. TFV trough concentrations at steady state (Days 10-29) were lower with any dose of TAF relative to TDF 300 mg, except for the trough concentration at 120 mg on Day 29.

Table 8. PK parameters of TAF and TFV following a single oral dose of TAF or TDF

Dose (mg)		N	C_{max} (ng/mL)	t_{max}[a)] (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)
TAF PK parameter						
TAF	8	10	83.2 (46.3)	0.50 [0.25 - 2.0]	60.6 (52.7)	0.41 (36.1)
	25	10	249.5 (45.9)	0.50 [0.25 - 0.50]	154.3 (41.0)	0.49 (29.9)
	40	11	527.4 (50.6)	0.50 [0.25 - 1.2]	329.9 (58.1)	0.64 (27.9)
	120	10	1129 (33.7)	0.50 [0.25 - 1.5]	855.1 (37.8)	0.74 (28.5)
TFV PK parameter						
TAF	8	10	3.0 (34.5)	1.25 [1.0 - 2.0]	69.3 (36.3)	24.0 (21.5)
	25	10	8.3 (41.6)	1.0 [1.0 - 6.0]	176.1 (32.8)	21.9 (47.8)
	40	11	20.3 (43.2)	1.0 [0.5 - 1.9]	426.7 (44.1)	23.8 (18.6)
	120	10	61.0 (33.5)	1.0 [0.5 - 2.0]	1518 (50.4)	29.0 (38.6)
TDF	300	10	306.8 (24.5)	1.0 [0.25 - 1.5]	2268 (26.4)	10.3 (20.5)

Mean (CV%), a) Median [Range]

6.2.2.2 Multi-regional phase III study (CTD 5.3.5.1-2, Study GS-US-320-0110 [ongoing since August 2013])

Following oral administration of TAF 25 mg or TDF 300 mg QD, the steady-state PK of TAF and TFV in plasma and the steady-state PK of TFV diphosphate in peripheral blood mononuclear cells were evaluated in some of CHB patients enrolled in this study (7 subjects in the TAF group and 6 subjects in the TDF group). Following administration of TAF 25 mg, the C_{max}, t_{max}, and AUC_{last} of plasma TAF were 284 ng/mL, 0.5 hours, and 267 ng·h/mL, respectively, those of plasma TFV were 24.8 ng/mL, 1.0 hour, and 392 ng·h/mL, respectively. The (geometric least-squares mean) trough concentration of intracellular TFV diphosphatewas 75.4 pg/10^6 cells. Following administration of TDF 300 mg, the C_{max}, t_{max}, and AUC_{last} of plasma TFV were 389 ng/mL, 1.0 hour, and 3224 ng·h/mL, respectively. The (geometric least-squares mean) trough concentration of intracellular TFV diphosphate was 6.7 pg/10^6 cells.

6.2.2.3 PPK analysis (CTD 5.3.3.5-2)

A PPK analysis (NONMEM version 7.3) was performed on TAF and TFV PK data from clinical studies in healthy adult volunteers or HIV-1-infected patients[5)] and clinical studies in CHB patients (Studies GS-US-320-0101, 0108, and 0110) (TAF, 1268 subjects, 5333 sampling points; TFV, 1462 subjects, 10,938 sampling points). The final model was a 2-compartment model with sequential zero- and first-order absorption for both TAF and TFV. For TAF, food and coadministration of ATV/RTV were selected as covariates on the absorption rate;[6)] food, coadministration of ATV/RTV and LPV/RTV, and sex were selected as covariates on oral relative bioavailability; and disease status (HIV) were selected as a covariate on V_c/F. For TFV, food and coadministration of ATV/RTV and DRV/RTV were selected as covariates on the absorption rate; coadministration of ATV/RTV, LPV/RTV, and DRV/RTV and sex were selected as covariates on oral relative bioavailability; CL_{cr}, race (black), and disease status (healthy vs. HIV or HBV vs. treatment-experienced patients with HBV) as covariates on V_c/F; CL_{cr} were selected as a covariate on V_p/F; and CL_{cr} and disease status (healthy vs. HIV or HBV) were selected as covariates on CL/F.[7)] The mean steady-state C_{max} and AUC of TAF and TFV following oral administration of TAF 25 mg QD in CHB patients were estimated from

[5)] Healthy adult volunteer studies: GS-US-120-0107, GS-US-120-0108, GS-US-120-0109, GS-US-120-0117, GS-US-120-0118, GS-US-292-0101, and GS-US-320-1228
HIV-1-infected patient studies: GS-US-120-0104 and GS-US-311-1089

[6)] It was defined that the duration of zero-order absorption (D_1) is inversely proportional to the absorption rate and that the first-order absorption rate constant (k_a) is proportional to the absorption rate.

[7)] Coadministration of ATV/RTV, LPV/RTV, and DRV/RTV and food were tested as potential covariates on the absorption rate and oral relative bioavailability of TAF and TFV. Body weight, CL_{cr}, age, sex, race, population (healthy vs. HIV or HBV), liver fibrosis score, and cirrhosis score were tested as potential covariates on CL/F, V_c/F, and V_p/F of TAF and TFV.

the model. The mean steady-state C_{max} and AUC were 177.6 ng/mL and 215.5 ng·h/mL, respectively, for TAF, and 17.2 ng/mL and 321.9 ng·h/mL, respectively, for TFV.

6.2.2.4 Exposure-response analyses (CTD 5.3.4.2-4, 5.3.4.2-5)

The C_{max} or AUC_{tau} values of TAF in CHB patients participating in multi-regional phase III studies (Study 0108 or 0110) were estimated from the PPK model [see Section 6.2.2.3], and the resulting values were divided into quartiles to evaluate relationships between the estimated C_{max} or AUC_{tau} of TAF and the virologic response rate.[8)] The results revealed that the C_{max} and AUC_{tau} of TAF were not associated with the virologic response rate in either Study 0108 or 0110.

An analysis was performed to evaluate relationships between the estimated C_{max} or AUC_{tau} of TAF and TFV in CHB patients and commonly observed adverse events (diarrhoea, nausea, vomiting, gastrointestinal/abdominal pain) in the multi-regional phase III studies (Studies 0108 and 0110). The results revealed that diarrhoea, nausea, and gastrointestinal/abdominal pain were not associated with the C_{max} or AUC_{tau} of TAF or TFV. The C_{max} and AUC_{tau} of TAF tended to be higher in subjects with vomiting than in those without vomiting, but there were no differences in the C_{max} or AUC_{tau} of TFV.

Relationships between the estimated C_{max} and AUC_{tau} of TAF and TFV in CHB patients and the changes from baseline to Week 48 in bone, renal, and lipid parameters (percent changes in hip and spine bone mineral density [BMD], the maximum increase in serum creatinine, changes in fasting lipid values) were evaluated. The results showed no relationships between the parameters and the C_{max} or AUC_{tau} of TAF or TFV.

6.2.3 Intrinsic factor pharmacokinetic studies

Phase I study in subjects with severe hepatic impairment (Reference data, CTD 5.3.3.3.4, Study GS-US-320-1615 [December 2014 to April 2015])

The PKs of TAF and TFV were evaluated in subjects with severe hepatic impairment (Child-Pugh-Turcotte class C) and subjects with normal hepatic function (N = 10/group) following a single oral dose of TAF 25 mg. The results are shown in Table 9. The C_{max} and AUC_{inf} of TAF were lower in subjects with severe hepatic impairment than in subjects with normal hepatic function, but the unbound fraction increased. The C_{max} and AUC_{inf} of unbound TAF were similar between subjects with severe hepatic impairment and those with normal hepatic function (the C_{max} values were 29.9 and 36.2 ng/mL, respectively, and the AUC_{inf} values were 42.8 and 46.5 ng·h/mL, respectively). Based on the above findings, the applicant considers that no dosage adjustment of TAF is required in patients with severe hepatic impairment.

8) The proportion of subjects with plasma HBV DNA <29 IU/mL at Week 48 (subjects with missing data were defined as failures).

Table 9. PK parameters of TAF and TFV following a single oral dose of TAF in subjects with severe hepatic impairment and subjects with normal hepatic function

Hepatic impairment	N	C_{max} (ng/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	Unbound fraction (%)	Geometric least-squares mean ratio [90% CI] (severe hepatic impairment/normal hepatic function)	
						C_{max}	AUC_{inf}
TAF							
Normal hepatic function	10	176.0 (45.3)	228.2 (37.4)	0.48 (17.4)	20.4 (10.6)	—	—
Severe hepatic impairment	10	79.6 (49.4)	120.6 [a)] (28.2)	0.70 [a)] (49.0)	37.8 (22.1)	0.45 [0.32, 0.64]	0.54 [0.42, 0.70]
TFV							
Normal hepatic function	10	7.6 (24.0)	304.0 (23.8)	57.4 (28.1)	>95	—	—
Severe hepatic impairment	10	7.5 (52.4)	219.9 (54.0)	50.8 (31.2)	>95	0.90 [0.65, 1.25]	0.63 [0.43, 0.93]

Mean (CV%), a) N = 8

6.2.4 Pharmacokinetic interactions[9)]

Studies were conducted to evaluate the drug-drug interaction potential between TAF and coadministered drugs. The geometric least-squares mean ratios [90% CI] of the PK parameters of TAF and TFV (coadministration/administration alone) are shown in Table 10 and those of the PK parameters of coadministered drugs (coadministration/administration alone) in Table 11.

Table 10. Effect of coadministered drug on PK parameters of TAF and TFV

Coadministered drug	Dosing regimen			N	Geometric least-squares mean ratio [90% CI]		
	Coadministered drug	TAF			C_{max}	AUC [a)]	C_{tau}
ATV/RTV	300/100 mg QD	10 mg single dose [b)]	TAF	10	1.77 [1.28, 2.44]	1.89 [1.55, 2.30]	—
			TFV	10	2.12 [1.86, 2.43]	2.62 [2.14, 3.20]	—
DRV/RTV	800/100 mg QD	10 mg single dose [b)]	TAF	10	1.42 [0.96, 2.09]	1.04 [0.84, 1.29]	—
			TFV	10	2.42 [1.98, 2.95]	2.05 [1.54, 2.72]	—
LPV/RTV	800/200 mg QD	10 mg single dose [b)]	TAF	10	2.19 [1.72, 2.79]	1.45 [1.14, 1.84]	—
			TFV	10	3.75 [3.19, 4.39]	4.16 [3.50, 4.96]	—
DTG	50 mg QD	10 mg single dose [b)]	TAF	10	1.24 [0.88, 1.74]	1.17 [0.93, 1.45]	—
			TFV	10 [c)]	1.10 [0.96, 1.25]	1.25 [1.06, 1.47]	—
RPV	25 mg QD	25 mg QD	TAF	32 [d)]	1.01 [0.84, 1.22]	1.01 [0.94, 1.10]	—
			TFV	32 [d)]	1.12 [1.02, 1.23]	1.11 [1.07, 1.14]	1.17 [1.13, 1.23]
ATV/COBI	300/150 mg QD	10 mg QD [e)]	TAF	20	1.80 [1.48, 2.18]	1.75 [1.55, 1.98] [f)]	—
			TFV	20	3.16 [3.00, 3.33]	3.47 [3.29, 3.67]	3.73 [3.54, 3.93]
Sofosbuvir/GS-5816 [g)]	400/100 mg QD	10 mg QD [h)]	TAF	24 [i)]	0.80 [0.68, 0.94]	0.87 [0.81, 0.94]	—
			TFV	24 [i)]	1.20 [1.16, 1.24]	1.22 [1.18, 1.25]	1.23 [1.19, 1.28]
Ledipasvir/Sofosbuvir	90/400 mg QD	25 mg QD [j)]	TAF	42	1.03 [0.94, 1.14]	1.32 [1.25, 1.40] [f)]	—
			TFV	42	1.62 [1.56, 1.68]	1.75 [1.69, 1.81]	1.85 [1.78, 1.92]
Carbamazepine	300 mg BID [k)]	25 mg single dose [l)]	TAF	26 [m)]	0.43 [0.36, 0.51]	0.46 [0.40, 0.54]	—
			TFV	26 [m)]	0.70 [0.65, 0.74]	0.77 [0.74, 0.81]	—

—: Not determined,
a) AUC_{inf} for single-dose administration, AUC_{tau} for multiple-dose administration
b) Coadministered with FTC 200 mg
c) Coadministration, N = 9
d) Administration of TAF alone, N = 17
e) Administered as the FTC/TAF (200/10 mg) fixed-dose combination (FDC)
f) AUC_{last}
g) Unapproved in Japan
h) Administered as the EVG/COBI/FTC/TAF (150/150/200/10 mg) FDC
i) Administration of the EVG/COBI/FTC/TAF FDC alone, N = 23
j) Administered as the FTC/RPV/TAF (200/25/25 mg) FDC
k) 100 mg BID for 3 days, 200 mg BID for 3 days, and 300 mg BID for 14 days followed by 300 mg BID plus TAF
l) Administered as the FTC/TAF (200/25 mg) FDC
m) Coadministration, N = 22

[9)] CTD 5.3.3.4-2 (reference data), Study GS-US-120-0118 [[redacted]]; CTD 5.3.3.4-3 (reference data), Study GS-US-120-1538 [[redacted]]; CTD 5.3.3.4-4 (reference data), Study GS-US-120-1554 [[redacted]]; CTD 5.3.3.4-9 (reference data), Study GS-US-311-1388 [[redacted]]; CTD 5.3.3.4-10 (reference data), Study GS-US-311-1790 [[redacted]]; CTD 5.3.3.4-12 (reference data), Study GS-US-342-1167 [[redacted]]; CTD 5.3.3.4-13 (reference data), Study GS-US-366-1689 [[redacted]]; CTD 5.3.3.4-15 (reference data), Study GS-US-311-1387 [[redacted]]

Table 11. Effect of TAF on PK parameters of coadministered drug

Drug	Dosing regimen		N	Geometric least-squares mean ratio [90% CI]		
	Coadministered drug	TAF		C_{max}	AUC [a]	C_{tau}
ATV	ATV/RTV 300/100 mg QD	10 mg single dose [b]	10	0.98 [0.89, 1.07]	0.99 [0.96, 1.01]	1.00 [0.96, 1.04]
DRV	DRV/RTV 800/100 mg QD	10 mg single dose [b]	10	0.99 [0.91, 1.08]	1.01 [0.96, 1.06]	1.13 [0.95, 1.34]
LPV	LPV/RTV 800/200 mg QD	10 mg single dose [b]	10	1.00 [0.95, 1.06]	1.00 [0.92, 1.09]	0.98 [0.85, 1.12]
DTG	50 mg QD	10 mg single dose [b]	9 [c]	0.87 [0.79, 0.96]	0.98 [0.93, 1.03]	0.95 [0.88, 1.03]
Midazolam	Midazolam 2.5 mg single oral dose	25 mg QD	18	1.02 [0.92, 1.13]	1.13 [1.04, 1.23]	—
1'-OH midazolam [d]			18	0.91 [0.77, 1.07]	0.98 [0.88, 1.09]	—
Midazolam	Midazolam 1 mg single intravenous dose	25 mg QD	18	0.99 [0.89, 1.11]	1.08 [1.04, 1.13]	—
1'-OH midazolam [d]			18	0.96 [0.86, 1.09]	1.11 [1.02, 1.20]	—
RPV	25 mg QD	25 mg QD	32 [e]	0.93 [0.87, 0.99]	1.01 [0.96, 1.06]	1.13 [1.04, 1.23]
ATV	ATV/COBI 300/150 mg QD	10 mg QD [f]	20	0.98 [0.94, 1.02]	1.06 [1.01, 1.11]	1.18 [1.06, 1.31]
COBI			20	0.96 [0.92, 1.00]	1.05 [1.00, 1.09]	1.35 [1.21, 1.51]
Ethinylestradiol	Ethinylestradiol /Norgestimate 25/180-250 µg [g] QD	25 mg QD [h]	15 [i]	1.22 [1.15, 1.29]	1.11 [1.07, 1.16]	1.02 [0.92, 1.12]
Norelgestromin			15 [i]	1.17 [1.07, 1.26]	1.12 [1.07, 1.17]	1.16 [1.08, 1.24]
Norgestrel			15 [i]	1.10 [1.02, 1.18]	1.01 [1.07, 1.18]	1.11 [1.03, 1.20]
Sofosbuvir	Sofosbuvir/GS-5816 400/100 mg QD	10 mg QD [j]	24 [k]	1.23 [1.07, 1.42]	1.37 [1.24, 1.52]	—
GS-566500 [l]			24 [k]	1.15 [1.07, 1.23]	1.21 [1.15, 1.28]	—
GS-331007 [l]			24 [k]	1.29 [1.25, 1.33]	1.48 [1.43, 1.53]	1.58 [1.52, 1.65]
GS-5816 [m]			24 [k]	1.30 [1.17, 1.45]	1.50 [1.35, 1.66]	1.60 [1.44, 1.78]
Sofosbuvir	Ledipasvir/Sofosbuvir 90/400 mg QD	25 mg QD [n]	42 [o]	0.96 [0.89, 1.04]	1.05 [1.01, 1.09]	—
GS-566500 [l]			42 [o]	0.99 [0.95, 1.03]	1.02 [0.99, 1.05]	—
GS-331007 [l]			42 [o]	1.08 [1.05, 1.11]	1.08 [1.06, 1.10]	1.10 [1.07, 1.12]
Ledipasvir			42 [o]	1.01 [0.97, 1.05]	1.02 [0.97, 1.06]	1.02 [0.98, 1.07]

—: Not determined
a) AUC_{inf} for single-dose administration, AUC_{tau} for multiple-dose administration
b) Coadministered with FTC 200 mg
c) Administration of DTG alone, N = 8
d) A metabolite of midazolam
e) Administration of RPV alone, N = 16
f) Administered as the FTC/TAF (200/10 mg) FDC
g) Administration without TAF: 2 cycles of 7 days each (a total of 28 days) of ethinylestradiol/norgestimate 25/180 µg, 25/215 µg, 25/250 µg, and 0/0 µg QD;
Coadministration with TAF: 7 days each (a total of 14 days) of ethinylestradiol/norgestimate 25/180 µg QD and 25/215 µg QD plus TAF 25 mg QD
h) Aadministered as the FTC/TAF (200/25 mg) FDC
i) Coadministration, N = 14
j) Administered as the EVG/COBI/FTC/TAF (150/150/200/10 mg) FDC
k) Administration without TAF, N = 23
l) Metabolites of sofosbuvir
m) Unapproved in Japan
n) Administered as the FTC/RPV/TAF (200/25/25 mg) FDC
o) Administration without TAF, N = 41

6.R Outline of the review conducted by PMDA

6.R.1 Special dosing recommendations regarding timing of meals

The applicant's explanation of the timing of dosing of TAF relative to meals:

In a food effect study of TAF (Study GS-US-320-1382), there were no clear differences in the C_{max} of TAF between fasted and fed conditions, but the AUC_{inf} was higher under fed conditions than under fasted conditions [see Section 6.1.1]. Although the AUC_{inf} values of TAF under fasted and fed conditions (171.5 and 288.9 ng·h/mL, respectively) were differed in Study GS-US-320-1382, the difference was not considered clinically relevant, in light of the distribution of the AUC_{tau} values of TAF (56.6-2688 ng·h/mL) in phase III studies conducted to evaluate the efficacy and safety of TAF in CHB patients (Studies 0108 and 0110).

Based on the above findings, TAF can be administered without regard to meals, and no special dosing recommendations regarding timing of meals are required.

PMDA considers that the applicant's explanation (TAF can be administered without regard to meals, and no special dosing recommendations regarding timing of meals are required) is acceptable.

6.R.2 PK in subjects with renal impairment

PK parameters were determined following administration of TAF 25 mg in subjects with severe renal impairment (CL_{cr}, ≥15 and ≤29 mL/min) on or not on dialysis. The results are shown in Table 12. The PK parameters of TAF and TFV were higher in subjects with severe renal impairment than in subjects with normal renal function (Genvoya Combination Tablets Review Report, dated May 19, 2016).

Table 12. PK parameters of TAF and TFV following administration of TAF 25 mg in subjects with severe renal impairment and subjects with normal renal function

	Subjects with severe renal impairment (N = 14)	Subjects with normal renal function (N = 13)	Geometric least-squares mean ratio [90% CI]
TAF PK parameter			
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 PK parameter			
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 determined

For submission of the present application, the applicant performed a PPK analysis using the data from phase III studies (Studies 0108 and 0110) to assess the impact of renal function on TAF and TFV exposures and simulated the PK of TFV in patients with end-stage renal disease (ESRD) undergoing hemodialysis. The applicant's explanation of the results is as follows:

The impact of renal function ($eGFR_{CG}$) at baseline on the estimated C_{max} and AUC_{tau} of TAF and TFV and the estimated trough concentration of TFV in CHB patients was assessed using the PPK model [see Section 6.2.2.3]. The results are shown in Table 13. While baseline $eGFR_{CG}$ had no marked impact on the C_{max} and AUC_{tau} of TAF, the C_{max}, AUC_{tau}, and trough concentration of TFV tended to increase with increasing degree of renal impairment.

Table 13. PK parameters of TAF and TFV by renal function following repeated administration of TAF 25 mg in CHB patients (estimates)

	TAF			TFV			
$eGFR_{CG}$ (mL/min)	N	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	N	C_{max} (ng/mL)	AUC_{tau} (ng·h/mL)	Trough concentration (ng/mL)
≥30 and <60	4	260.8 (63.9)	266.4 (58.8)	5	27.5 (21.5)	515.8 (16.3)	18.6 (15.0)
≥60 and <90	162	184.8 (52.6)	234.0 (64.3)	194	20.2 (30.9)	387.1 (28.9)	13.9 (30.1)
≥90	532	174.9 (53.4)	209.5 (67.4)	657	16.2 (34.7)	301.1 (29.2)	10.6 (30.4)

Mean (CV%)

The steady-state C_{max}, AUC_{tau}, and trough concentration of TFV in CHB patients with ESRD on chronic hemodialysis three times a week,[10] estimated using the PPK model [see Section 6.2.2.3], were 110 ng/mL, 2360 ng·h/mL, and 90.0 ng/mL, respectively.

Although the above results suggested a trend toward higher TFV exposure in subjects with renal impairment, the estimated C_{max} and AUC_{tau} of TFV following repeated administration of TAF 25 mg in CHB patients with $eGFR_{CG}$ of ≥30 mL/min and <60 mL/min and CHB patients with ESRD on chronic hemodialysis three times a week were lower than or similar to the C_{max} (335.5 ng/mL) and AUC (2184.5 ng·h/mL) of TFV following administration of TDF 300 mg in subjects with normal renal function.[11] Extensive safety data from CHB patients and patients with HIV infection receiving TDF are also available. For these reasons, and from the pharmacokinetic standpoint, no dosage adjustment is required in patients with renal impairment including those with ESRD requiring dialysis.

PMDA's view:

TAF can be used without dosage adjustment in patients with renal impairment (CL_{cr} ≥15 mL/min), in light of the data and information including (1) the PK parameters following administration of TAF 25 mg in subjects with severe renal impairment (CL_{cr}, ≥15 and ≤29 mL/min), (2) comparison of the PK parameters in CHB patients with renal impairment (those estimated using the PPK model) with the PK parameters of TDF in subjects with normal renal function, and (3) experience with the products containing TDF in clinical practice. However, no clinical studies have been conducted in patients with renal impairment (CL_{cr} <15 mL/min). It is therefore necessary to advise physicians to confirm that patients' CL_{cr} is ≥15 mL/min before initiating TAF and consider discontinuation of TAF if their CL_{cr} is <15 mL/min during TAF therapy. Since the data on the safety and efficacy of TAF in patients with renal impairment are limited, post-marketing information should be collected from this patient population. New information should be appropriately communicated to healthcare professionals if it becomes available.

7. Clinical efficacy and safety and outline of the review by PMDA

The applicant submitted the data on the efficacy and safety of TAF in the present application. The submitted data included the results from 2 international phase III studies in CHB patients (GS-US-320-0108 and GS-US-320-0110). An overview of these studies is presented in Table 14.

Table 14. Overview of the main efficacy and safety studies of TAF

Study Number (Phase)	Study design	Study population	Dosing regimen	Number of subjects
GS-US-320-0108 (III)	Randomized, double-blind, parallel-group study	HBeAg-negative CHB patients	TAF group: TAF 25 mg QD TDF group: TDF 300 mg QD	TAF group: 285 TDF group: 140
GS-US-320-0110 (III)	Randomized, double-blind, parallel-group study	HBeAg-positive CHB patients	TAF group: TAF 25 mg QD TDF group: TDF 300 mg QD	TAF group: 581 TDF group: 292

[10] Based on patient data from studies conducted in CHB patients (Studies GS-US-320-0101, GS-US-320-0108, and GS-US-320-0110), CLcr was adjusted to 5 mL/min.

[11] Healthy subjects with normal renal function (CLcr >80 mL/min) (Viread Tab. 300 mg package insert, 9th edition)

7.1 Multi-regional phase III study (CTD 5.3.5.1-1, Study GS-US-320-0108 [ongoing since September 2013]) (Data cutoff on [redacted], 20[redacted])

A randomized, double-blind, parallel-group study was conducted at 105 sites in 17 countries including the US, Japan, and Canada to evaluate the efficacy and safety of TAF versus TDF in HBeAg-negative, CHB patients[12)] [target sample size, 390 subjects (260 in the TAF group, 130 in the TDF group)].

TAF 25 mg QD (for subjects in the TAF group) or TDF 300 mg QD (for subjects in the TDF group) was administered orally for 96 weeks.[13)]

A total of 425 subjects were randomized and received study drug (285 in the TAF group, 140 in the TDF group). All of the subjects were included in the FAS and in the Safety Analysis Set. The FAS was used for efficacy analyses.

The primary efficacy endpoint was the proportion of subjects with HBV DNA <29 IU/mL at Week 48. The proportions of subjects who achieved this endpoint were 94.0% (268 of 285 subjects) in the TAF group and 92.9% (130 of 140 subjects) in the TDF group. The treatment difference [95% CI] was 1.8 [–3.6, 7.2]%[14)] and the lower bound of the 95% confidence interval was above the pre-defined non-inferiority margin (−10%), therefore demonstrating the non-inferiority of TAF to TDF. In the Japanese subpopulation, the proportions of subjects with HBV DNA <29 IU/mL at Week 48 were 95.2% (20 of 21 subjects) in the TAF group and 100% (6 of 6 subjects) in the TDF group.

Safety data through Week 48 was analyzed. The incidence of adverse events (including abnormal laboratory changes) was 73.7% (210 of 285 subjects) in the TAF group and 70.7% (99 of 140 subjects) in the TDF group, and the incidence of adverse drug reactions was 13.7% (39 of 285 subjects) in the TAF group and 18.6% (26 of 140 subjects) in the TDF group. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either group are shown in Table 15.

Table 15. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either group

Event term	Adverse events		Adverse drug reactions	
	TAF (N = 285)	TDF (N = 140)	TAF (N = 285)	TDF (N = 140)
Any event	210 (73.7)	99 (70.7)	39 (13.7)	26 (18.6)
Headache	40 (14.0)	14 (10.0)	5 (1.8)	3 (2.1)
Upper respiratory tract infection	35 (12.3)	10 (7.1)	2 (0.7)	0
Nasopharyngitis	30 (10.5)	15 (10.7)	0	0
Cough	18 (6.3)	8 (5.7)	0	0
Fatigue	16 (5.6)	9 (6.4)	4 (1.4)	4 (2.9)
Nausea	15 (5.3)	9 (6.4)	4 (1.4)	7 (5.0)
Back pain	14 (4.9)	7 (5.0)	1 (0.5)	0
Arthralgia	11 (3.9)	10 (7.1)	3 (1.1)	3 (2.1)

n (%)

[12)] Eligible patients were HBeAg-negative and HBeAb-positive, CHB patients (with or without compensated cirrhosis) who had HBV DNA ≥2×10^4 IU/mL, serum ALT >60 IU/L (in men) or >38 IU/L (in women), and ≤10 × the upper limit of normal (ULN) at screening. Because patients receiving TDF were included as a control group, patients with $eGFR_{CG}$ ≥50 mL/min were eligible for the study.

[13)] All subjects in the TAF or TDF group who completed 96 weeks of double-blind treatment were eligible to receive open-label TAF 25 mg for up to 240 weeks (the open-label extension period).

[14)] Calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories (<7 $\log_{10}$ IU/mL; ≥7 $\log_{10}$ IU/mL and <8 $\log_{10}$ IU/mL; ≥8 $\log_{10}$ IU/mL) and previous nucleoside/nucleotide analog treatment status strata.

One death occurred in the TDF group (hepatocellular carcinoma) 9 days after the last dose of study drug, and its relationship to study drug was ruled out.

Serious adverse events occurred in 14 subjects in the TAF group. The serious adverse events were ureteric calculus (2 subjects); haematuria, cervical radiculopathy, hypertension, hypoglycaemia, hypoaesthesia, adenocarcinoma of colon, lobar pneumonia, *Escherichia* bacteraemia/*Escherichia* urinary tract infection, hand fracture, pancreatitis, meniscus injury, hepatocellular carcinoma, and breast cancer in situ (1 subject each) (some subjects had more than one event). Serious adverse events occurred in 9 subjects in the TDF group. The serious adverse events are hepatocellular carcinoma (3 subjects); cellulitis (2 subjects); inguinal hernia, urinary tract infection, hepatic fibrosis, cerebrospinal fluid leakage, pulmonary embolism, anaemia, leukocytosis, hyperkalaemia, unstable angina, urinary calculus, and pyelonephritis (1 subject each) (some subjects had more than one event). A relationship to study drug was ruled out for all the events. The outcome was reported as "resolved" for all the events, except for ureteric calculus, adenocarcinoma of colon, and hand fracture (1 subject each) occurring in the TAF group and hepatocellular carcinoma (3 subjects) and hepatic fibrosis, pulmonary embolism, anaemia, leukocytosis, hyperkalaemia, and pyelonephritis (1 subject each) occurring in the TDF group.

Adverse events led to discontinuation in 3 subjects in the TAF group. The adverse events leading to discontinuation were hepatocellular carcinoma, pruritus, maculo-papular rash, and amylase increased (1 subject each) (1 subject had more than one event). Adverse events led to discontinuation in 2 subjects in the TDF group. The adverse events leading to discontinuation were hepatocellular carcinoma (2 subjects); anaemia, leukocytosis, and pulmonary embolism (1 subject each) (1 subject had more than one event). A relationship to study drug could not be ruled out for the events reported by 2 subjects in the TAF group (amylase increased, pruritus, and maculo-papular rash [1 subject each]; 1 subject had more than one event). The outcome was reported as "resolved" for all those events, except for hepatocellular carcinoma (2 subjects) and anaemia, leukocytosis, and pulmonary embolism (1 subject each) occurring in the TDF group.

7.2 Multi-regional phase III study (CTD 5.3.5.1-2, Study GS-US-320-0110 [ongoing since August 2013]) (Data cutoff date of [redacted], 20[redacted])

A randomized, double-blind, parallel-group study was conducted at 161 sites in 19 countries including the US, Japan, and Canada to evaluate the efficacy and safety of TAF versus TDF in HBeAg-positive, chronic hepatitis B patients[15)] [target sample size, 864 subjects (576 in the TAF group, 288 in the TDF group)].

TAF 25 mg QD (for subjects in the TAF group) or TDF 300 mg QD (for subjects in the TDF group) was administered orally for 96 weeks.

A total of 873 subjects were randomized and received study drug (581 in the TAF group, 292 in the TDF group).

[15)] Eligible patients were HBeAg-positive, CHB patients (with or without compensated cirrhosis) who had HBV DNA $\geq 2\times10^4$ IU/mL, serum ALT >60 IU/L (in men) or >38 IU/L (in women), and $\leq 10\times$ the ULN at screening. Because patients receiving TDF were included as a control group, patients with $eGFR_{CG}$ ≥50 mL/min were eligible for the study.

All of the subjects were included in the FAS and in the Safety Analysis Set. The FAS was used for efficacy analyses.

The primary efficacy endpoint was the proportion of subjects with HBV DNA <29 IU/mL at Week 48. The proportions of subjects who achieved this endpoint were 63.9% (371 of 581 subjects) in the TAF group and 66.8% (195 of 292 subjects) in the TDF group. The treatment difference [95% CI] was –3.6 [–9.8, 2.6]%[16] and the lower bound of the 95% confidence interval was above the pre-defined non-inferiority margin (–10%), therefore demonstrating the non-inferiority of TAF to TDF. In the Japanese subpopulation, the proportions of subjects with HBV DNA <29 IU/mL at Week 48 were 62.9% (22 of 35 subjects) in the TAF group and 81.8% (9 of 11 subjects) in the TDF group.

Safety data through Week 48 was analyzed. The incidence of adverse events (including abnormal laboratory changes) was 68.5% (398 of 581 subjects) in the TAF group and 65.8% (192 of 292 subjects) in the TDF group, and the incidence of adverse drug reactions was 14.5% (84 of 581 subjects) in the TAF group and 14.4% (42 of 292 subjects) in the TDF group. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either group are shown in Table 16.

Table 16. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either group

Event term	Adverse events		Adverse drug reactions	
	TAF (N = 581)	TDF (N = 292)	TAF (N = 581)	TDF (N = 292)
Any event	398 (68.5)	192 (65.8)	84 (14.5)	42 (14.4)
Nasopharyngitis	56 (9.6)	16 (5.5)	1 (0.2)	0
Upper respiratory tract infection	51 (8.8)	22 (7.5)	1 (0.2)	0
Headache	42 (7.2)	22 (7.5)	7 (1.2)	5 (1.7)
Cough	37 (6.4)	19 (6.5)	0	0
Fatigue	33 (5.7)	14 (4.8)	8 (1.4)	5 (1.7)
Diarrhoea	27 (4.6)	15 (5.1)	4 (0.7)	4 (1.4)
Upper abdominal pain	19 (3.3)	15 (5.1)	3 (0.5)	2 (0.7)

n (%)

One death occurred in the TAF group 3 days after the last dose of study drug (CHB, pneumonitis, sepsis, acute renal failure, hepatic encephalopathy, aspiration pneumonitis, respiratory failure, cardio-respiratory arrest due to an influenza complication), and its relationship to study drug was ruled out.

Serious adverse events occurred in 22 subjects in the TAF group. The serious adverse events were dizziness (2 subjects); retinal detachment, nasal septum deviation, appendicitis, periodontitis, limb crushing injury, gastrointestinal submucosal tumour, back pain, intervertebral disc degeneration, scrub typhus, pyrexia, nephrolithiasis, anaemia, infectious diarrhoea, anal abscess, chronic bronchitis, pneumonia, syncope, basilar artery occlusion, vertigo, angina pectoris, hand fracture, spinal compression fracture, and ligament rupture (1 subject each) (some subjects had more than 1 event). Serious adverse events occurred in 12 subjects in the TDF group. The serious adverse events were hepatocellular carcinoma (2 subjects); upper abdominal pain, ovarian cyst, thymoma, dengue fever, transitional cell carcinoma, optic neuritis, cellulitis, lower limb

[16] Calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories (<8 $\log_{10}$ IU/mL; ≥8 $\log_{10}$ IU/mL) and previous nucleoside/nucleotide analog treatment status strata.

fracture, epilepsy, and spondylolisthesis (1 subject each) (some subjects had more than 1 event). A relationship to study drug was ruled out for all those events. The outcome was reported as "resolved" for all those events, except for retinal detachment, anaemia, basilar artery occlusion, spinal compression fracture, and ligament rupture (1 subject each) occurring in the TAF group and hepatocellular carcinoma, epilepsy, and spondylolisthesis (1 subject each) occurring in the TDF group.

Adverse events led to discontinuation in 6 subjects in the TAF group. The adverse events leading to discontinuation were nausea (2 subjects); dyspepsia, diarrhoea, vomiting, musculoskeletal chest pain, basilar artery occlusion, dizziness, postural dizziness, depressed mood, ALT increased, and lipase increased (1 subject each) (some subjects had more than 1 event). Adverse events led to discontinuation in 3 subjects in the TDF group. The adverse events leading to discontinuation were dyspepsia, abdominal discomfort, upper abdominal pain, fatigue, anxiety, and ALT increased (1 subject each) (some subjects had more than 1 event). A relationship to study drug could not be ruled out for the events reported by 3 subjects in the TAF group (dyspepsia, diarrhoea, dizziness, ALT increased, and lipase increased [some subjects had more than 1 event]) and the events reported by 1 subject in the TDF group (dyspepsia, fatigue, and abdominal discomfort [the subject had more than 1 event]). The outcome was reported as "resolved" for all those events, except for musculoskeletal chest pain, basilar artery occlusion, and ALT increased (1 subject each) occurring in the TAF group and upper abdominal pain, anxiety, and ALT increased (1 subject each) occurring in the TDF group.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical data package

The clinical data package submitted in the present application consists of clinical study data containing those from 2 multi-regional phase III studies that evaluated the efficacy and safety of TAF in both HBeAg-negative and HBeAg-positive CHB patients.

PMDA asked the applicant to explain the influences of differences in the medical environment, treatment algorithm, and other factors for CHB between Japan and foreign coutnries and of pharmacokinetic differences between Japanese and non-Japanese patients on the efficacy and safety of TAF.

The applicant's explanation:
The medical environment, treatment algorithm, and other factors for CHB in and outside Japan are presented in Table 17.

Table 17. Medical environment, treatment algorithm, and other factors for chronic hepatitis B in and outside Japan

		Japan [a]	Overseas [b]
Definition of chronic hepatitis B		HBeAg-positive, chronic hepatitis B patients: HBeAg-positive, high HBV DNA, and high ALT HBeAg-negative, chronic hepatitis B paitents: HBeAg-negative, low to high HBV DNA, and high ALT	Persistence of HBsAg for ≥6 months after acute infection with HBV [c]
Patient eligibility criteria for nucleoside/ nucleotide analog therapy	Noncirrhotics	Patients with HBV DNA ≥4 $\log_{10}$ copies/mL (≥2000 IU/mL) and ALT ≥31 U/L	US ・HBeAg-positive: Patients with immune-active hepatitis with ALT >2 times the ULN and HBV DNA >20,000 IU/mL, or immune-active hepatitis with histological evidence and HBV DNA >20,000 IU/mL ・HBeAg-negative: Patients with immune-active hepatitis with ALT >2 times the ULN and HBV DNA >2000 IU/mL, or immune-active hepatitis with histological evidence and HBV DNA >2000 IU/mL Europe ・Patients with HBV DNA >20,000 IU/mL and ALT >2 times the ULN Asia ・HBeAg-positive: Patients with histological evidence or HBV DNA >20,000 IU/mL and ALT >2 times the ULN of the laboratory range ・HBeAg-negative: Patients with histological evidence or HBV DNA >2000 IU/mL and ALT > 2 times the ULN of the laboratory range
	Compensated cirrhotics	Patients with HBV DNA ≥2.1 $\log_{10}$ copies/mL	US: Patients with HBV DNA >2000 IU/mL Europe: Patients with detectable HBV DNA levels Asia: Patients with HBV DNA >2000 IU/mL
Predominant genotype		Genotype C	US and Europe: Genotypes A and D [d),e),f)] Asia: Genotypes B and C [d),e)]
Incidences of LAM, ADV, and ETV resistance		LAM [g)]: 70% (at 6 years) ADV [g)]: 21% (at 5 years) in HBeAg-positive patients 29% (at 5 years) in HBeAg-negative patients ETV [h)]: 3.3% (at 3 years) in treatment-naïve patients 26% (at 3 years) in LAM-resistant patients (No TDF resistance mutations have been reported.)	US LAM [d)]: 60% to 70% (at 5 years) ADV [d)]: 29% (at 5 years) ETV [d)]: 1.2% (through up to 5 years of therapy) 51% (through up to 5 years of therapy) in LAM-resistant patients Europe LAM [i)]: 70% (at 5 years) ADV [i)]: 29% (at 5 years) ETV [j)]: 1.2% (at 3-5 years) in treatment-naïve patients 35.3% in patients previously exposed to nucleoside/nucleotide analogs including LAM (No TDF resistance mutations have been reported.)

a) 2016 Guidelines for Treatment of Chronic Hepatitis B/Cirrhosis [2015 Japan Agency for Medical Research and Development, Practical Research Project for Infections (Research Program on Hepatitis), Research Group for developing viral hepatitis management guidelines based on scientific evidence], 2016
b) US: *Hepatology.* 2016; 63: 261-83
Europe: *J Hepatol*. 2012; 57: 167-85
Asia: *Hepatol Int*. 2016; 10: 1-98
c) Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection. World Health Organization. 2015
d) *Hepatology*. 2009; 50: 1-36
e) PLoS ONE 2015; 10: e0136074
f) *J Hepatol.* 2016; 64 (1 Suppl): S4-S16
g) Guidelines for the Management of Hepatitis B Virus Infection, 2.2nd edition. Drafting Committee for Hepatitis Management Guidelines, the Japan Society of Hepatology ed. May 2016
h) *J Gastroenterol Hepatol.* 2009; 24: 429-35
i) *J Hepatology*. 2012; 57: 167-85
j) *J Infect Dis*. 2016; 213: 39-48

There appear to be no major differences in the definition of CHB and the incidences of LAM, ADV, and ETV resistance between Japanese and non-Japanese patients. Despite some differences in the criteria for individual tests, the eligibility of patients for nucleoside/nucleotide analog therapy is determined based on their HBV

DNA and ALT levels, etc., in both Japan and foreign countries. There should be no major differences in the status of patient populations between Japan and foreign countries. HBV genotype distribution is different between Japanese and non-Japanese patients. The clinical picture and course of liver disease differ among genotypes, and HBV genotype is known to have an impact on response to interferon therapy (Guidelines for the Management of Hepatitis B Virus Infection, 2.2nd edition). However, clinical studies of TDF showed no differences in its efficacy according to genotype (Tenozet Tablets Review Report, dated February 19, 2014 [in Japanese only]). Therefore, differences in genotype distribution between Japanese and non-Japanese patients are unlikely to affect the efficacy of TAF.

Evaluation of the PK parameters in Japanese and non-Japanese healthy subjects receiving a single dose of TAF 25 mg showed that the C_{max} and AUC_{inf} of TAF and TFV were similar between Japanese and non-Japanese subjects [see Section 6.2.1].

Based on the above, differences in the medical environment, treatment algorithm, and other factors for CHB between Japan and foreign countries and pharmacokinetic differences between Japanese and non-Japanese patients are considered to have only a small impact on the efficacy and safety of TAF.

The applicant added the following explanation of the phase III studies using TDF as a comparator conducted in HBeAg-negative CHB patients (Studies 0108) and HBeAg-positive CHB patients (Studies 0110):
The results from a clinical study of TDF showed differences in efficacy between HBeAg-negative and HBeAg-positive populations (Guidelines for the Management of Hepatitis B Virus Infection, 2.2nd edition).[17)] TAF, as with TDF, is a prodrug of TFV. Considering that efficacy would differ also in clinical studies of TAF, the applicant conducted clinical studies of TAF separately for HBeAg-negative and HBeAg-positive CHB populations.

TDF was chosen as a comparator for the phase III studies because (1) the Japanese hepatitis management guidelines (Guidelines for the Management of Hepatitis B Virus Infection, 2.2nd edition) recommend TDF as a first-line nucleoside/nucleotide analog for both treatment-naïve and treatment-experienced patients with CHB, (2) major foreign hepatitis management guidelines (*Hepatology*. 2016; 63: 261-83, *J Hepatol.* 2012; 57: 167-85, etc.) also recommend TDF as first-line therapy for CHB patients, and (3) TAF and TDF are prodrugs of TFV.

PMDA's view:
Although there are differences in the patient eligibility criteria for nucleoside/nucleotide analog therapy for CHB and HBV genotype distribution in clinical practice between Japan and foreign countries, the efficacy and safety of TAF can be evaluated based on the multi-regional phase III studies (including Japan) concudted separately in HBeAg-negative CHB patients (Studies 0108) and HBeAg-positive CHB patients (Studies 0110), for the following reasons:

[17)] In a comparative study of TDF vs. ADV in treatment-naïve patients, the proportions of subjects with HBV DNA <29 IU/mL at Week 48 were 76% in the TDF group and 13% in the ADV group for HBeAg-positive patients and 93% in the TDF group and 63% in the ADV group for HBeAg-negative patients.

- Despite some differences in the criteria for individual tests, the eligibility of patients for nucleoside/nucleotide analog therapy is determined based on their HBV DNA and ALT levels, etc., in both Japanese and non-Japanese patients, and there should be no major differences in the status of patient populations between Japan and foreign countries.
- The results of clinical studies of TDF indicates that differences in HBV genotype are unlikely to affect the efficacy of TAF.
- There were no major differences in the PK parameters of TAF and TFV between Japanese and non-Japanese subjects.

7.R.2 Efficacy

Based on the review presented in subsections below, PMDA concluded that the efficacy of TAF is expected in the treatment of CHB patients. However, post-marketing information should be collected on the efficacy of TAF (including the long-term efficacy of TAF) in Japanese patients and resistance mutations. New information should be communicated appropriately to healthcare professionals if it becomes available.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.2.1 Efficacy in both HBeAg-negative and HBeAg-positive CHB patients

The applicant's explanation of the efficacy of TAF in both HBeAg-negative and HBeAg-positive CHB patients:

The primary endpoint of the phase III studies conducted in HBeAg-negative CHB patients (Studies 0108) and HBeAg-positive CHB patients (Studies 0110) was the proportion of subjects with plasma HBV DNA <29 IU/mL at Week 48. The results are shown in Table 18. In both Studies 0108 and 0110, the lower bound of the 95% confidence interval for the difference in the proportion between the TAF and TDF groups was above the pre-defined non-inferiority margin (–10%), therefore demonstrating the non-inferiority of TAF to TDF in both HBeAg-negative and HBeAg-positive CHB patients.

Subgroup analyses of the proportion of subjects with HBV DNA <29 IU/mL at Week 48 in the TAF group were performed. There were no major differences in response rates among HBeAg-negative subjects, regardless of previous nucleoside/nucleotide analog treatment status, race (Japanese subjects vs. non-Japanese subjects), and the FibroTest score. Among HBeAg-positive subjects, the response rate was lower in nucleoside/nucleotide analog-experienced subjects (treatment-experienced subjects) than in nucleoside/nucleotide analog-naïve subjects (treatment-naïve subjects), while the response rate was similar between the TAF and TDF groups in both treatment-naïve and treatment-experienced subjects. A subgroup analysis by race showed similar response rates between Japanese and non-Japanese subjects in the TAF group, but there was a trend toward a higher response rate in Japanese subjects than that in non-Japanese subjects in the TDF group. However, the observed difference in response rates between Japanese and non-Japanese subjects in the TDF group are not considered clinically meaningful because (1) the proportion of non-Japanese subjects achieving HBV DNA <29 IU/mL in the TDF group (66.2%) was similar to that of subjects achieving HBV DNA <29 IU/mL in a foreign clinical study of TDF (68.8%) (Tenozet Tablets 300 mg package insert,

4th edition) and (2) the number of Japanese patients enrolled in Study 0110 was limited. There were no major differences in response rates by the FibroTest score.

Table 18. Proportion of CHB patients with HBV DNA <29 IU/mL at Week 48 (FAS)

		HBeAg-negative (Study 0108)		HBeAg-positive (Study 0110)	
		TAF	TDF	TAF	TDF
Overall population		94.0 (268/285)	92.9 (130/140)	63.9 (371/581)	66.8 (195/292)
	Treatment difference [95% CI] [a)]	1.8 [–3.6, 7.2]		–3.6 [–9.8, 2.6]	
Previous nucleoside/ nucleotide analog treatment status [b)]	No (treatment-naïve)	94.3 (216/229)	93.6 (102/109)	68.1 (301/442)	71.0 (157/221)
	Yes (treatment-experienced)	95.2 (40/42)	95.8 (23/24)	52.1 (49/94)	58.1 (25/43)
Japanese		95.2 (20/21)	100 (6/6)	62.9 (22/35)	81.8 (9/11)
Non-Japanese		93.9 (248/264)	92.5 (124/134)	63.9 (349/546)	66.2 (186/281)
FibroTest score [c)]	<0.75 (noncirrhotics)	95.2 (237/249)	92.4 (110/119)	63.7 (332/521)	66.2 (172/260)
	≥0.75 (compensated cirrhotics)	87.1 (27/31)	95.0 (19/20)	68.9 (31/45)	77.3 (17/22)

% (n/N)

a) Calculated based on the Mantel-Haenszel proportions adjusted by baseline HBV DNA categories and previous nucleoside/nucleotide analog treatment status strata.

b) ≥12 weeks of previous treatment with any nucleoside or nucleotide analog (subjects previously exposed to TDF or TAF were excluded from the analysis)

c) FibroTest score was used as a surrogate marker of liver disease progression. Cirrhosis was defined as having FibroTest score ≥0.75 (equivalent to Metavir score F4) (*Comp Hepatol*. 2004; 3:8, *Am J Gastroenterol*. 2014; 109: 796-809).

According to a pooled analysis of the phase III studies (Studies 0108 and 0110), the proportions of subjects with HBV DNA <29 IU/mL at Week 48 by genotype in the TAF and TDF groups were 83.3% (45 of 54 subjects) and 74.2% (23 of 31 subjects), respectively, for genotype A; 73.8% (118 of 160 subjects) and 79.5% (70 of 88 subjects), respectively, for genotype B; 78.5% (328 of 418 subjects) and 78.4% (156 of 199 subjects), respectively, for genotype C; and 62.5% (140 of 224 subjects) and 65.7% (69 of 105 subjects), respectively, for genotype D. Although the proportion of subjects with HBV DNA <29 IU/mL at Week 48 tended to be lower for genotype D relative to other genotypes, TAF was considered to have comparable efficacy to TDF against all genotypes.

The secondary endpoints were as follows:

(a) ALT normalization

The proportions of subjects with ALT normalization[18)] at Week 48 were 83.1% (196 of 236 subjects) in the TAF group and 75.2% (91 of 121 subjects) in the TDF group in the phase III study enrolling HBeAg-negative patients (Study 0108) and 71.5% (384 of 537 subjects) in the TAF group and 66.8% (179 of 268 subjects) in the TDF group in the phase III study enrolling HBeAg-positive patients (Study 0110).

(b) HBeAg loss and HBsAg loss

In the phase III study enrolling HBeAg-positive patients (Study 0110), the proportions of subjects with HBeAg loss at Week 48 were 13.8% (78 of 565 subjects) in the TAF group and 11.9% (34 of 285 subjects) in the TDF group and the proportions of subjects with HBeAg seroconversion were 10.3% (58 of 565 subjects) in the TAF group and 8.1% (23 of 285 subjects) in the TDF group. Furthermore, the proportions of subjects with HBsAg loss at Week 48 were 0.7% (4 of 565 subjects) in the TAF group and 0.4% (1 of 285 subjects) in the TDF group, of whom 3 subjects in the TAF group experienced HBsAg seroconversion. In the phase III study enrolling HBeAg-negative patients (Study 0108), HBsAg loss or seroconversion at Week 48 was not observed in either treatment group.

[18)] Based on the ULN of the central laboratory range.

(c) Improvement in liver fibrosis

In the phase III studies (Studies 0108 and 0110), the mean changes from baseline to Week 48 in the FibroTest score were –0.05 and –0.07, respectively, in the TAF group and –0.03 and –0.04, respectively, in the TDF group. Although reductions in the FibroTest score were observed in both treatment groups, the clinical significance of short-term improvement in liver histology in patients with a decrease in the FibroTest score is unknown at present.

The above-mentioned proportions of subjects with HBV DNA <29 IU/mL at Week 48 and the results of other endpoints demonstrated the efficacy of TAF comparable to TDF and similar efficacy between Japanese and non-Japanese subjects. Thus, the efficacy of TAF is expected in both Japanese patients with HBeAg-negative CHB and those with HBeAg-positive CHB.

PMDA's view:

The multi-regional phase III studies conducted in HBeAg-negative and HBeAg-positive CHB patients (Studies 0108 and 0110, respectively) demonstrated the efficacy of TAF comparable to that of TDF. There were no major differences in efficacy between Japanese and non-Japanese subjects. Although the proportion for HBV DNA <29 IU/mL at Week 48 was lower in treatment-experienced patients than in treatment-naïve patients, TAF can be expected to have some efficacy also in treatment-experienced patients because (1) the proportion for HBV DNA <29 IU/mL in the TAF group was comparable to that in the TDF group and (2) TDF is listed as a therapeutic option also for patients who have relapsed after initial therapy in the Japanese hepatitis management guidelines (Guidelines for the Management of Hepatitis B Virus Infection, 2.2nd edition). Despite the small number of CHB patients with compensated cirrhosis evaluated for efficacy in these studies, TAF can be expected to have some efficacy in this patient population in light of the fact that TAF is another prodrug of TFV, and based on the outcomes in CHB patients with compensated cirrhosis receiving TDF (Tenozet Review Report, dated February 19, 2014 [in Japanese only]).

However, since the number of Japanese patients evaluated in Studies 0108 and 0110 was limited, post-marketing information should be collected on the efficacy of TAF. New findings should be communicated to healthcare professionals immediately if they become available.

Although the FibroTest score was used as a marker of liver fibrosis progression in the two studies, the relationship between the FibroTest score and liver fibrosis has not been established at present. The long-term efficacy of TAF was not evaluated in the two studies. Therefore, post-marketing information should be collected on the long-term efficacy of TAF, such as slowing of the progression of liver fibrosis. New findings should be communicated to healthcare professionals immediately if they become available.

7.R.2.2 Long-term efficacy of TAF

Since no long-term data were obtained from the phase III studies (Studies 0108 and 0110), PMDA asked the applicant to explain the long-term efficacy of TAF.

The applicant's explanation:

The goal of antiviral therapy in patients with persistent HBV infection is to suppress the activity of hepatitis and progression of liver fibrosis for prevention of chronic liver failure and hepatocellular carcinoma, thereby improving the patient's life expectancy and QOL" (Guidelines for the Management of Hepatitis B Virus Infection, 2.2nd edition). According to the guidelines, HBsAg elimination is a useful surrogate marker for attaining this treatment goal, and the three short-term goals of antiviral treatment prior to elimination of HBsAg are (1) persistent normalization of ALT, (2) HBeAg-negative and anti-Hbe-positive status (HBeAg seroconversion in HBeAg-positive patients and persistence of anti-HBe antibody in HBeAg-negative patients), and (3) suppression of HBV DNA replication. For the phase III studies (Studies 0108 and 0110), suppression of HBV DNA replication was chosen as the primary endpoint and HBsAg loss, improvement in ALT levels, etc. were also chosen as secondary endpoints. On the basis of the results of these endpoints, the applicant concluded that TAF was demonstrated to have efficacy comparable to that of TDF.

In foreign clinical studies of TDF in both HBeAg-negative and HBeAg-positive CHB patients, the primary endpoint was defined as the proportion of patients with HBV DNA <29 IU/mL at Week 48. The primary endpoint was achieved by 93% (233 of 250) of HBeAg-negative patients receiving TDF and 76% (134 of 176) of HBeAg-positive patients receiving TDF (*N Engl J Med*. 2008; 359: 2442-55). Also after 5 years of treatment with TDF,[19] high viral suppression was maintained (HBV DNA <29 IU/mL was achieved by 99% [292 of 295] of HBeAg-negative patients and 97% [170 of 175] of HBeAg-positive patients), and most of patients with liver biopsy results had the reversal of liver fibrosis and HBV-related cirrhosis (*Lancet*. 2013; 381: 468-75). Furthermore, an analysis was performed using the data from these studies, which showed that the risk of hepatocellular carcinoma in CHB patients without baseline cirrhosis who were treated with TDF for 8 years was statistically significantly lower than the predicted risk if untreated for up to 8 years (*Cancer.* 2015; 121: 3631-8). This finding is consistent with the results of clinical studies of ETV; long-term antiviral therapy resulted in persistent viral suppression, histological improvement in liver fibrosis, and the reversal of HBV-related cirrhosis (*Hepatology*. 2010; 52: 886-93), suggesting the possibility that antiviral therapy reduced the incidence of hepatocellular carcinoma (*Hepatol Int.* 2016 Mar;10: 320-7).

These reports suggest that suppression of HBV DNA replication leads to improvement in liver fibrosis and prevention of hepatocellular carcinoma (i.e., the goal of antiviral therapy). Although no long-term data for TAF are available, TAF is also expected to show long-term efficacy similar to that of TDF because (1) the phase III studies of TAF demonstrated that the efficacy of TAF at Week 48 was comparable to that of TDF, and (2) TAF, as with TDF, is a TFV prodrug. Long-term data for TAF will continue to be collected in the post-marketing setting.

PMDA's view:

On the basis of the reports on the long-term efficacy of TDF and the results from the phase III studies of TAF, TAF can also be expected to show long-term efficacy similar to that of TDF, though no long-term data are available for TAF. However, long-term data for TAF should continue to be collected in the post-marketing

[19] The foreign clinical studies of TDF were randomized, double-blind studies comparing TDF with ADV. After 48 weeks, patients in the TDF group remained on TDF and patients in the ADV group were switched to TDF in an open-label, long-term treatment study.

setting. New information should be appropriately communicated to healthcare professionals if it becomes available.

7.R.2.3 Viral resistance mutations

The applicant's explanation of the emergence of resistant virus and the impact of baseline drug resistance mutations on the efficacy of TAF in phase III studies (Studies 0108 and 0110):
In Studies 0108 and 0110, genotypic resistance analysis was performed by population sequencing of the polymerase/reverse transcriptase region for subjects who either experienced virologic breakthrough[20] through Week 48 or had viremia (HBV DNA ≥69 IU/mL) at early discontinuation at or after Week 24[21] (24 subjects in the TAF group, 14 subjects in the TDF group). Polymorphic site substitutions were observed in 5 subjects in the TAF group and polymorphic site and conserved site substitutions were observed in 2 subjects each in the TDF group. No specific amino acid substitutions associated with resistance to TAF, TDF, or TFV were detected in either treatment group.

In the two studies, primary mutations associated with resistance to nucleoside/nucleotide analogs[22] were detected at baseline in 4.7% (41 of 866) of subjects in the TAF group (LAM-resistance mutations, 23 subjects; ADV-resistance mutations, 10 subjects; ETV-resistance mutations, 5 subjects; LAM-resistance + ADV-resistance mutations, 3 subjects) and 6.7% (29 of 432) of subjects in the TDF group (LAM-resistance mutations, 9 subjects; ADV-resistance mutations, 9 subjects; ETV-resistance mutations, 8 subjects; LAM-resistance + ADV-resistance mutations, 3 subjects). The proportions of subjects with HBV DNA <29 IU/mL at Week 48 were 46.3% (19 of 41 subjects) in the TAF group and 62.1% (18 of 29 subjects) in the TDF group. The proportions were lower than those among subjects without drug resistance mutations (75.7% [587 of 775 subjects] in the TAF group, 76.5% [293 of 383 subjects] in the TDF group). The reason why the proportion for HBV DNA <29 IU/mL was particularly lower in subjects with primary mutations associated with resistance to nucleoside/nucleotide analogs at baseline in the TAF group relative to other subject groups is unclear. No amino acid substitutions exhibiting reduced susceptibility to TAF were detected even in subjects who did not achieve HBV DNA <29 IU/mL. At present, therefore, there is no risk that drug resistance mutations affect the efficacy of TAF.

As described above, the proportion for HBV DNA <29 IU/mL was lower in subjects with baseline primary drug resistance mutations than in subjects without drug resistance mutations in Studies 0108 and 0110. However, drug resistance mutations are unlikely to affect the efficacy of TAF at present, because no amino acid substitutions associated with resistance to TAF, TDF, or TFV were observed through Week 48.

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[20] Defined as two consecutive visits with either HBV DNA ≥69 IU/mL after having been <69 IU/mL or ≥1.0 $\log_{10}$ copies/mL increase in HBV DNA from nadir.
[21] Subjects with persistent viremia who never achieved HBV DNA <69 IU/mL were to be evaluated at Week 96 to allow sufficient time to achieve virologic suppression.
[22] LAM-resistance mutation: rtM204V/I/S (EPIVIR-HBV tablets, US labeling, GlaxoSmithKline)
ADV-resistance mutation: rtA181T/V, rtN236T (Hepsera tablets, US labeling, Gilead Sciences Inc., 2012)
ETV-resistance mutation: rtM204V/I, rtT184X, rtS202X, rtM250X (Baraclude 0.5 mg and 1.0 mg film-coated tablets SPC, Bristol-Myers Squibb Pharmaceutical Limited, 2014)
No TDF resistance mutations have been reported.

PMDA's view:

No HBV variants with TAF, TDF, or TFV resistance mutations were detected in Studies 0108 and 0110. However, the proportion for HBV DNA<29 IU/mL tended to be lower in subjects with baseline primary drug resistance mutations and the currently available information on resistance mutations is limited. For these reasons, post-marketing information should be collected on the emergence of resistance mutations, and new information should be communicated to healthcare professionals when it becomes available. The applicant should collect information on the impact of drug resistance mutations before the initiation of therapy on the efficacy of TAF, including the published literature. New findings should be communicated to healthcare professionals if they become available.

7.R.3 Safety

On the basis of the safety review presented in the subsections below, PMDA concluded that the safety profile of TAF in CHB patients is tolerable, although attention needs be paid to the occurrence of bone-related events, renal function-related events, and hepatic dysfunction including the exacerbation of hepatitis.

However, there is limited clinical experience with TAF in Japanese patients with CHB and no long-term safety data are available. Therefore, post-marketing information should be collected on the safety of TAF, including long-term safety. New information should be appropriately communicated to healthcare professionals if it becomes available.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.3.1 Safety profile

The applicant's explanation of the safety profile of TAF:

Safety summary of multi-regional phase III studies (a pooled analysis of Studies 0108 and 0110) and common adverse events in the studies are presented in Table 19. The incidences of overall adverse events, serious adverse events, Grade 3 or 4 adverse events, and adverse events leading to discontinuation were similar between the TAF and TDF groups. There were 1 death in the TAF group and 1 death in the TDF group, but a relationship to study drug was ruled out for both fatal cases. The incidences and nature of adverse events reported by ≥5% of subjects in either treatment groupwere similar between the TAF and TDF groups. The safety profile of TAF was considered largely comparable to that of TDF.

Table 19. Safety summary of multi-regional phase III studies (pooled data from Studies 0108 and 0110) (Week 48 analysis)

	TAF (N = 866)	TDF (N = 432)
Any adverse event	608 (70.2)	291 (67.4)
Adverse events for which a relationship to study drug could not be ruled out (adverse drug reactions)	123 (14.2)	68 (15.7)
Deaths	1 (0.1)	1 (0.2)
Serious adverse events	36 (4.2)	21 (4.9)
Grade 3 or 4 adverse events [a)]	39 (4.5)	17 (3.9)
Adverse events leading to discontinuation	9 (1.0)	5 (1.2)
Adverse events reported by ≥5% of subjects in either treatment group		
Upper respiratory tract infection	86 (9.9)	32 (7.4)
Nasopharyngitis	86 (9.9)	31 (7.2)
Headache	82 (9.5)	36 (8.3)
Cough	55 (6.4)	27 (6.3)
Fatigue	49 (5.7)	23 (5.3)
Nausea	43 (5.0)	22 (5.1)

n (%)

a) The severity of adverse events was assessed using the Grading Scale for Severity of Adverse Events and Laboratory Abnormalities established by Gilead Sciences, Inc. (adapted from the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. National Institutes of Health. August, 2009).

A safety analysis was performed in the Japanese subpopulation. The incidence of adverse events through Week 48 was 94.6% (53 of 56 subjects) in the TAF group and 88.2% (15 of 17 subjects) in the TDF group and the incidence of adverse drug reactions was 16.1% (9 of 56 subjects) in the TAF group and 23.5% (4 of 17 subjects) in the TDF group. No deaths were reported in either treatment group. Serious adverse events and adverse events leading to discontinuation occurred in the TAF group only. Three subjects experienced serious adverse events (meniscus injury, hepatocellular carcinoma, ureteric calculus) and 1 subject experienced an adverse event leading to discontinuation (hepatocellular carcinoma). A relationship to study drug was ruled out for all those events. Except for Grade 3 ureteric calculus reported by 1 subject in the TAF group, all those events were of Grade 1 or 2. Commonly reported adverse events in the Japanese subpopulation were as follows: nasopharyngitis (44.6%, 25 of 56 subjects), headache (8.9%, 5 of 56 subjects), diarrhoea (7.1%, 4 of 56 subjects), nausea (7.1%, 4 of 56 subjects), and upper respiratory tract infection (7.1%, 4 of 56 subjects) in the TAF group and nasopharyngitis (29.4%, 5 of 17 subjects), anaemia (11.8%, 2 of 17 subjects), abdominal pain upper (11.8%, 2 of 17 subjects), enteritis infectious (11.8%, 2 of 17 subjects), periodontitis (11.8%, 2 of 17 subjects), and pruritus (11.8%, 2 of 17 subjects) in the TDF group.

Although the nature of some of the commonly reported adverse events was different between the Japanese subpopulation and the overall study population, most events were of Grade 1 or 2. Therefore, the safety profile of TAF in CHB patients, including Japanese patients with CHB, should be tolerable.

PMDA's view:

The analysis of data from Studies 0108 and 0110 showed no particular differences in the safety profiles between TAF and TDF. Although there is limited clinical experience with TAF in Japanese patients with CHB, the available safety data raised no particular concerns. The long-term safety of TAF and the occurrence of bone-related events, renal function-related events, and the exacerbation of hepatitis are described in the following subsections.

7.R.3.2 Bone-related events

In clinical studies of TDF, decreases in BMD at Treatment Week 96 were reported (Tenozet Tablets 300 mg package insert, 4th edition). The applicant provided the following explanation of the occurrence of bone-related adverse events in the phase III studies of TAF (Studies 0108 and 0110):

An analysis of bone-related adverse events reported in Studies 0108 and 0110 revealed fracture occurring in 6 subjects (0.7%) in the TAF group and 1 subject (0.2%) in the TDF group, and a relationship to study drug was ruled out for all those events. Osteopenia occurred in 6 subjects (0.7%) in the TAF group and 4 subjects (0.9%) in the TDF group, osteoporosis in 5 subjects (0.6%) in the TAF group and 4 subjects (0.9%) in the TDF group, and bone density decreased in 1 subject (0.1%) in the TAF group and 1 subject (0.2%) in the TDF group.

The percentage changes in hip BMD from baseline to Week 72 (mean ± SD) were –0.284 ± 2.37% with TAF and –2.43 ± 2.93% with TDF and the percentage changes in spine BMD from baseline to Week 72 were –0.608 ± 3.22% with TAF and –2.52 ± 3.54% with TDF. Percentage changes in BMD were smaller in the TAF group than in the TDF group.

Based on the above, the bone effect of TAF is considered smaller than that of TDF.

PMDA's view:

The occurrence of bone-related adverse events and the percentage changes in BMD in the phase III studies (Studies 0108 and 0110) raised no new concerns about the use of TAF relative to TDF. Meanwhile, reductions in BMD were observed also in the TAF group, although the percentage change from baseline in BMD was smaller in the TAF group than in the TDF group in the phase III studies. Decreases in BMD and increases in biochemical markers of bone turnover were observed in non-clinical studies of TAF, suggesting increased bone turnover (Genvoya Combination Tablets Review Report, dated May 19, 2016). Thus, the possibility that TAF affects BMD cannot be ruled out. In light of the above finidings, precautionary advice about bone-related events should be included in the package insert as in the case of the products containing TDF. Post-marketing information should also be collected on the bone effect of long-term treatment with TAF (e.g., bone-related events, reductions in BMD). New information should be appropriately communicated to healthcare professionals if it becomes available.

7.R.3.3 Renal function-related adverse events

The applicant's explanation of renal function-related adverse events associated with the use of TAF:

Data from the phase III studies (pooled data from Studies 0108 and 0110) were analysed. The incidence of renal function-related adverse events[23)] was 0.2% (2 of 866 subjects; acute kidney injury [1 subject] and renal impairment [1 subject]) in the TAF group and 0.2% (1 of 432 subjects, calculus urinary) in the TDF group. Serious adverse events occurred in 1 subject (acute kidney injury) in the TAF group and 1 subject (calculus urinary) in the TDF group. The subject with acute kidney injury in the TAF group also experienced other adverse events including lower respiratory tract infection, coma, pneumonia aspiration, and sepsis, leading to

[23)] Adverse events identified by the MedDRA/J SOC "renal and urinary disorders," and serious adverse events and adverse events leading to discontinuation identified by the SOC "investigations" and HLT "renal function analyses"

TAF interruption. The subject died 3 days after the last dose of TAF. The other subject in the TAF group experienced diabetes in addition to renal impairment and the dosage of TAF was adjusted (reduction in dose frequency from once-daily dosing to once-every-other-day dosing). Both events occurring in the TAF group were considered unrelated to study drug.

The changes from baseline in serum creatinine and $eGFR_{CG}$ to Weeks 48 and 72 are shown in Table 20 and Table 21, respectively. The changes were smaller in the TAF group than in the TDF group.

Table 20. Changes from baseline in serum creatinine to Weeks 48 and 72

	TAF		TDF	
Serum creatinine at baseline	N = 866	0.814 ± 0.172	N = 432	0.827 ± 0.161
Change from baseline to Week 48	N = 828	0.010 ± 0.114	N = 418	0.024 ± 0.097
Change from baseline to Week 72	N = 818	0.009 ± 0.093	N = 399	0.016 ± 0.091

Mean ± SD (mg/dL)

Table 21. Changes from baseline in $eGFR_{CG}$ to Weeks 48 and 72

	TAF		TDF	
$eGFR_{CG}$ at baseline	N = 866	106.2 (91.0, 125.4)	N = 432	104.5 (89.9, 123.5)
Change from baseline to Week 48	N = 827	–1.2 (–8.4, 7.5)	N = 417	–5.4 (–12.0, 3.0)
Change from baseline to Week 72	N = 818	–0.6 (–9.0, 7.8)	N = 399	–4.2 (–12.0, 4.1)

Median (Q1, Q3) (mL/min)

The changes from baseline in renal function parameters are shown in Table 22. Except for the change in the ratio of renal tubular maximum reabsorption rate of phosphate to the glomerular filtration rate, those changes were smaller in the TAF group than in the TDF group.

Table 22. Change in renal function parameters (Week 48 analysis)

	TAF (N = 866)	TDF (N = 432)
Urine protein/creatinine ratio (mg/g)	6.0 (–31.0, 57.6)	16.5 (–21.6, 72.4)
Urine albumin/creatinine ratio (mg/g)	6.9 (–25.8, 46.7)	12.2 (–21.0, 63.5)
Urine retinol binding protein/creatinine ratio (μg/g)	–0.3 (–23.2, 33.3)	25.1 (–7.9, 73.2)
Urine β2-microglobulin/creatinine ratio (μg/g)	–3.5 (–34.3, 32.0)	37.9 (–4.6, 152.4)

Median change from baseline (Q1, Q3)

Although renal adverse events were reported in the TAF group, their causal relationship to TAF was ruled out. The changes in serum creatinine, $eGFR_{CG}$, and renal function parameters suggest that the renal effect of TAF is considered smaller than that of TDF.

PMDA's view:

The occurrence of renal function-related adverse events and the changes in renal function parameters in Studies 0108 and 0110 raised no new concerns about the use of TAF compared to TDF. However, renal function-related adverse events occurred in the TAF group in these studies, and there was a trend toward increases in serum creatinine and decreases in $eGFR_{CG}$ even in the TAF group, albeit smaller changes with TAF relative to TDF. Therefore, as in the case of the products containingTDF, precautionary advice about renal impairment associated with the use of TAF should be included in the package insert, and the package insert should advise that renal function tests should be performed before and during TAF therapy and that appropriate actions such as treatment discontinuation should be taken if abnormal renal function or other abnormalities are detected. Post-marketing information should also be collected on new onset or worsening of renal impairment associated

with TAF. New information should be appropriately communicated to healthcare professionals if it becomes available.

7.R.3.4 Exacerbation of hepatitis

The applicant's explanation of the exacerbation of hepatitis following treatment with TAF:

In phase III studies (Studies 0108 and 0110), the incidence of the exacerbation of hepatitis (defined as 2 consecutive visits with serum ALT >2 times the baseline value and >10 times the ULN following the start of study drug administration) was 0.6% (5 of 866 subjects) in the TAF group and 0.9% (4 of 432 subjects) in the TDF group. Of these subjects, 1 in the TAF group experienced the exacerbation of hepatitis 66 days after discontinuation of study drug. Many of the events occurred within 8 weeks after the start of treatment. The events were asymptomatic and resolved with continued study treatment.

As described above, the exacerbation of hepatitis occurred infrequently in patients on treatment and after treatment discontinuation. Thus, hepatic function should be monitored periodically during TAF therapy and appropriate measures should be taken also after treatment discontinuation.

PMDA's view:

The exacerbation of hepatitis occurred during TAF therapy and after treatment discontinuation. It is often difficult to differentiate the exacerbation of hepatitis from liver disorders caused by other factors. For this reason, patients should be monitored closely not only during TAF therapy but also after the end of treatment, and appropriate actions should be taken according to the clinical course of the disease. Post-marketing information should be collected on hepatic dysfunction including the exacerbation of hepatitis. New information should be appropriatelycommunicated to healthcare professionals if it becomes available.

7.R.3.5 Long-term safety of TAF

The applicant's explanation of the long-term safety of TAF:

Although no long-term safety data are currently available, the phase III studies demonstrated the favorable safety profile of TAF. The effects of TAF on renal and bone parameters were smaller than those of TDF at Week 48. Similar results were obtained at Week 72 [see Section 7.R.3]. Because treatment with TAF resulted in lower plasma TFV exposurethan that with TDF 300 mg [see Section 6.2.2.1], the long-term safety of TAF is considered superior to that of TDF. Information on the long-term safety of TAF will continue to be collected through the ongoing phase III studies (Studies 0108 and 0110) and a post-marketing surveillance study.

PMDA's view:

Since no long-term safety data are available, post-marketing information should be collected. New information should be appropriately communicated to healthcare professionals if it becomes available.

7.R.4 Clinical positioning

The applicant's explanation of the clinical positioning of TAF:

In Japan, interferon products, peginterferon products, and nucleoside/nucleotide analogs (LAM, ADV, ETV, TDF) have been approved for the treatment of CHB. The Japanese hepatitis management guidelines (Guidelines for the Management of Hepatitis B Virus Infection, 2.2nd edition) advise that peginterferon products or nucleotide/nucleoside analogs should be selected for treatment-naïve patients with CHB, according to individual patients' condition and disease state, and recommend ETV or TDF as the first-line nucleotide/nucleoside analog. The guidelines recommend nucleotide/nucleoside analogs (ETV or TDF as monotherapy or as part of a combination regimen with other nucleotide/nucleoside analogs) for treatment-experienced patients with CHB and cirrhotic patients with CHB.

TAF, as with TDF, is a prodrug of TFV, and the multi-regional phase III studies of TAF in patients with CHB (Studies 0108 and 0110) assessed the non-inferiority of TAF to TDF. The studies demonstrated the efficacy of TAF comparable to that of TDF across subgroups (with or without prior treatment experience and cirrhosis) and similar efficacy of TAF between Japanese and non-Japanese patients [see Section 7.R.2]. Safety analysis revealed similarity in the incidence of adverse events between TAF and TDF. Safety data demonstrated the benefitial effects of TAF versus TDF on bone and renal function [see Section 7.R.3].

Based on the above findings and the fact that CHB patients require chronic therapy, TAF is considered to have greater benefits than TDF and can be a therapeutic option that replaces TDF.

PMDA's view:

TAF is expected to have efficacy and safety profiles comparable to those of TDF in CHB patients, and it can therefore provide a new therapeutic option, as with similar drugs including TDF. However, despite the applicant's explanation of the benefitial effects of TAF versus TDF on bone and renal function, precautionary advise about the bone and renal effects of TAF is required as in the case of the currently available products containing TDF. This is because (1) its clinical significance (taking also account of long-term prognosis) is unclear and (2) TAF also affected bone and renal function parameters [see Section 7.R.3].

In addition, the study data showed a trend toward lower efficacy of TAF in subjects with LAM, ETV, or ADV resistance mutations at baseline. This information should be communicated appropriately.

7.R.5 Indication

On the basis of the considerations presented below and the reviews described in Sections 7.R.2, 7.R.3, and 7.R.4, as well as the indications for similar drugs, PMDA concluded that the following indication statement is acceptable.

"Suppression of hepatitis B virus replication in chronic hepatitis B patients with evidence of viral replication and abnormal liver function"

As discussed below, there is no clinical experience with TAF in chronic hepatitis B patients with decompensated cirrhosis. For this reason, precautionary advice about the use of TAF in CHB patients with

decompensated cirrhosis should be included in the package insert, and post-marketing information should be collected. New information should be appropriately communicated to healthcare professionals if it becomes available.

The above conclusion by PMDA will be discussed at the Expert Discussion.

Chronic hepatitis B patients with decompensated cirrhosis

PMDA asked the applicant to explain the efficacy and safety of TAF in CHB patients with decompensated cirrhosis.

The applicant's explanation:

The efficacy and safety of TAF in CHB patients with decompensated cirrhosis have not been studied. The pharmacokinetics of TAF and TFV were evaluated in subjects with severe hepatic impairment following a single dose of TAF 25 mg. The results showed no clinically relevant differences in the plasma pharmacokinetics of TAF and TFV between subjects with severe hepatic impairment and those with normal hepatic function [see Section 6.2.3].

Although no data on the efficacy and safety of TAF in CHB patients with decompensated cirrhosis are available, phase III studies demonstrated the efficacy of TAF comparable to that of TDF in CHB patients excluding those with decompensated cirrhosis. The safety profile of TAF was also similar to that of TDF. The applicant, therefore, considered that the efficacy and safety of TAF could be evaluated based on the results from a clinical study of TDF in CHB patients with decompensated cirrhosis.

Safety summary through Week 48 in a clinical study of TDF in CHB patients with decompensated cirrhosis[24)] (*Hepatology*. 2011; 53: 62-72) are shown in Table 23. Although there were deaths and adverse events including serious ones, a relationship to study drug was ruled out for many of the events. The safety profile of TDF was considered tolerable.

Table 23. Safety summary through Week 48 (CHB patients with decompensated cirrhosis)

	TDF [a)] (N = 45)	Emtricitabine/TDF [a)] (N = 45)	ETV [a)] (N = 22)
Any adverse event	37 (82.2)	42 (93.3)	17 (77.3)
Adverse events for which a relationship to study drug could not be ruled out (adverse drug reactions)	8 (17.8)	7 (15.6)	2 (9.1)
Deaths	2 (4.4)	2 (4.4)	2 (9.1)
Serious adverse events	11 (24.4)	19 (42.2)	5 (22.7)
Grade 3 or 4 adverse events [b)]	14 (31.1)	9 (20.0)	5 (22.7)
Adverse events leading to discontinuation	3 (6.7)	2 (4.4)	2 (9.1)

n (%)

a) TDF 300 mg QD, emtricitabine 200 mg/TDF 300 mg QD, and ETV 0.5 or 1.0 mg QD were administered to subjects in respective treatment groups.

b) The severity of adverse events was assessed using the Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (adapted from the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events. National Institutes of Health. August, 2009) established by Gilead Sciences, Inc.

[24)] Patients with HBV DNA $\geq 10^3$ copies/mL, CL_{cr} $\geq$50 mL/min, and Child-Pugh-Turcotte score of 7 to 12.

The proportions of subjects with HBV DNA <69 IU/mL at Week 48 were 70.5% (31 of 44 subjects) in the TDF group, 87.8% (36 of 41 subjects) in the emtricitabine/TDF group, and 72.7% (16 of 22 subjects) in the ETV group. The proportions of subjects with normalized ALT were 46.2% (12 of 26 subjects) in the TDF group, 64.0% (16 of 25 subjects) in the emtricitabine/TDF group, and 41.2% (7 of 17 subjects) in the ETV group.

The above results suggested a largely favorable tolerability profile and a certain level of efficacy of TDF in CHB patients with decompensated cirrhosis.

The plasma pharmacokinetics of TFV following a single dose of TDF 300 mg in subjects with moderate to severe hepatic impairment were similar to those in subjects with normal hepatic function (*Clin Pharmacokinet.* 2006; 45: 1115-24).

In summary, a certain level of efficacy and favorable tolerability of TAF are expected also in CHB patients with decompensated cirrhosis, based on the following findings: (a) there were no clinically meaningful differences in the plasma pharmacokinetics of TAF and TFV following administration of TAF 25 mg between subjects with severe hepatic impairment and those with normal hepatic function, (b) the phase III studies suggested the efficacy and favorable safety of TAF comparable to those of TDF in CHB patients excluding those with decompensated cirrhosis [see Sections 7.R.2 and 7.R.3], and (c) the published literature has reported that a certain level of efficacy and favorable tolerability of TDF are expected in CHB patients with decompensated cirrhosis.

PMDA's view:
Although the safety and efficacy of TAF in CHB patients with decompensated cirrhosis have not been studied, a certain level of efficacy and tolerability of TAF may be expected also in CHB patients with decompensated cirrhosis. This conclusion is supported by the data including (1) the pharmacokinetics of TAF in subjects with severe hepatic impairment, (2) the results from phase III studies of TAF in CHB patients excluding those with decompensated cirrhosis, and (3) the results from a clinical study of TDF in CHB patients with decompensated cirrhosis, and the fact that the Japanese hepatitis management guidelines (Guidelines for the Management of Hepatitis B Virus Infection, 2.2nd edition) list ETV or TDF as a therapeutic option for CHB patients with decompensated cirrhosis. Based on the above discussion, TAF may be indicated in CHB patients with decompensated cirrhosis as well. However, because of no clinical experience with TAF in CHB patients with decompensated cirrhosis, such patients on TAF should be monitored closely. Post-marketing information should be collected on the efficacy and safety of TAF in CHB patients with decompensated cirrhosis. New information should be appropriately communicated to healthcare professionals if it becomes available.

7.R.6 Dosage and administration

The applicant's explanation of the rationale for the dosing regimen of TAF:
Based on the following findings, a 25 mg dose of TAF was selected for the phase III studies (Studies 0108 and 0110).

- In a foreign phase I study, the median changes from baseline to Week 4 in serum HBV DNA were –2.18, –2.05, –1.69, and –2.15 $\log_{10}$ IU/mL with TAF 8, 25, 40, and 120 mg, respectively, and –2.31 $\log_{10}$ IU/mL

with TDF 300 mg. No relationship was observed between HBV DNA change and the dose of TAF over the range of 8 to 120 mg throughout the 4-week treatment period. HBV DNA changes with any dose level of TAF were comparable to HBV DNA change with the 300 mg dose of TDF (approved dose).

- Although the above study demonstrated the efficacy of TAF 8 mg, the 8 mg dose was not selected as a means to maintain the exposure required for efficacy because drugs that reduce the TAF exposure may be coadministered in clinical practice.
- A phase II study in patients with HIV infection indicated an acceptable safety profile of TAF 25 mg.

As discussed above, TAF 25 mg QD was selected for the phase III studies enrolling CHB patients (Studies 0108 and 0110), and the studies demonstrated the non-inferiority of TAF 25 mg QD to TDF 300 mg QD [see Sections 7.R.2 and 7.R.3]. Therefore, the proposed dosage regimen is TAF 25 mg QD.

PMDA's view:
Based on the reviews presented in Sections 7.R.2 and 7.R.3 and the above explanation by the applicant, the dosage and administration statement as shown below is acceptable.

"The usual adult dosage is 25 mg of Tenofovir Alafenamide administered orally once daily."

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.7 Post-marketing investigations

The applicant is planning the following post-marketing surveillance study of the product.

Specified use-results survey

- Objective: To evaluate the safety and efficacy of the product in routine clinical practice.
- Planned sample size: 500 patients (approximately 375 treatment-naïve patients, approximately 125 treatment-experienced patients)

  Basis for sample size determination

  Considering the feasibility of the survey and dropouts (assuming a dropout rate of 15%), a target sample size of 500 should allow for evaluation of the safety of the product with certain precision.
- Observation period: 144 weeks from the initiation of therapy
- Survey period: 5 years (the enrollment period is 2 years)

In the post-marketing period, the ongoing phase III studies (Studies 0108 and 0110) will be continued as post-marketing clinical studies (for up to 384 weeks) to evaluate the long-term safety and efficacy of the product.

PMDA considers that the following post-marketing information should also be collected.

- Safety and efficacy in CHB patients with compensated or decompensated cirrhosis
- Safety and efficacy in patients with renal impairment
- Occurrence of bone-related events (including changes in BMD parameters), renal function-related events, and hepatic dysfunction (including the exacerbation of hepatitis)

- Inhibition of the progression of liver fibrosis by long-term treatment with the product
- Emergence of resistance mutations and their impact on the efficacy of the product

Information on the emergence of TAF resistance mutations and their impact on the efficacy of the product (including the published literature) should continue to be collected in the post-marketing setting. New information should be communicated to healthcare professionals if it becomes available.

The above conclusion by PMDA will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

8.1 PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted 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 (PMD Act) for the data submitted in the new drug application. PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection was conducted in accordance with the provisions of the PMD Act for the data submitted in the new drug application (CTD 5.3.5.1.1, CTD 5.3.5.1.2). PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

9. Overall Evaluation at the Time of Preparation of Review Report (1)

PMDA has concluded that the data submitted demonstrate the efficacy of TAF in CHB patients and acceptable safety in view of the observed benefits. TAF provides a new therapeutic option for CHB patients, which is of clinical significance.

PMDA has concluded that TAF may be approved if TAF is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

October 14, 2016

Product Submitted for Approval

Brand Name	Vemlidy Tablets 25 mg
Non-proprietary Name	Tenofovir Alafenamide Fumarate
Applicant	Gilead Sciences K.K.
Date of Application	March 31, 2016

1. Content of the Review

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

PMDA's conclusions on the issues described in the Review Report (1) ("7.R.2 Efficacy," "7.R.3 Safety," "7.R.5 Indication," "7.R.6 Dosage and administration") were supported by the expert advisors at the Expert Discussion.

PMDA conducted an additional review of the following issues and took necessary actions.

1.1 Draft risk management plan

Based on the review presented in "7.R.7 Post-marketing investigations" of the Review Report (1) and the comments from the expert advisors at the Expert Discussion, PMDA considers that the following additional issues should be investigated in the post-marketing setting.

- Safety and efficacy in CHB patients with compensated or decompensated cirrhosis
- Safety and efficacy in patients with renal impairment
- Occurrence of bone-related events (including changes in BMD parameters), renal function-related events, and hepatic dysfunction (including the exacerbation of hepatitis)
- Inhibition of the progression of liver fibrosis by long-term treatment with Vemlidy Tablets 25 mg
- Emergence of resistance mutations and their impact on the efficacy of Vemlidy Tablets 25 mg

PMDA instructed the applicant to investigate the above issues in the post-marketing setting.

The applicant accepted the above instruction.

In view of the discussion above, PMDA has concluded that the safety and efficacy specifications listed in Table 24 should be included in the current draft risk management plan for Vemlidy Tablets 25 mg and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities listed in Table 25. An outline of the draft drug use-results survey plan and the post-marketing clinical study plan submitted are presented in Table 26 and Table 27, respectively.

Table 24. Safety and efficacy specifications of the draft risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
· Acute exacerbation of hepatitis after discontinuation of treatment · Renal toxicity · Bone-related events/reductions in BMD · Lactic acidosis and severe hepatomegaly with steatosis · Lipodystrophies	· Pancreatitis	· Safety of long-term treatment
Efficacy specification		
· Efficacy in routine clinical settings · Development of drug resistance in long-term use		

Table 25. Summary of additional pharmacovigilance activities and risk minimization activities in the draft risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
· Early Post-marketing Phase Vigilance (EPPV) · Drug use-results survey · Post-marketing clinical studies [a)]	· EPPV

a) The ongoing phase III studies (Studies GS-US-320-0108 and GS-US-320-0110) will be continued as post-marketing clinical studies after the approval of Vemlidy Tablets 25 mg.

Table 26. Outline of the draft drug use-results survey plan

Objective	To collect safety and efficacy data in routine clinical settings.
Survey method	Central registry system
Patients population	Chronic hepatitis B patients
Observation period	144 weeks from the initiation of therapy
Planned sample size	500 patients
Main survey items	patient characteristics, safety and efficacy in CHB patients with compensated or decompensated cirrhosis, safety and efficacy in patients with renal impairment, the occurrence of bone-related events (including changes in BMD parameters), renal function-related events, and hepatic dysfunction (including exacerbation of hepatitis)

Table 27. Post-marketing clinical studies (Studies GS-US-320-0108 and GS-US-320-0110)

Objective	To evaluate the efficacy and safety of long-term treatment with Vemlidy Tablets 25 mg.
Study population	Subjects who have completed 144 weeks of double-blind treatment with Vemlidy Tablets 25 mg or tenofovir disoproxil fumarate in phase III studies (Studies GS-US-320-0108 and GS-US-320-0110) will all receive open-label Vemlidy Tablets 25 mg for up to 240 weeks. Subjects who have already been assigned to receive open-label Vemlidy Tablets 25 mg at Week 96 will continue to receive open-label Vemlidy Tablets 25 mg until Week 384 or discontinuation.
Observation period	384 weeks from the initiation of double-bind treatment
Target sample size	Study GS-US-320-0108: 390 patients Study GS-US-320-0110: 864 patients
Main survey items	Long-term efficacy and safety

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following condition. Vemlidy Tablets 25 mg contains the same active ingredient as “Genvoya Combination Tablets” but is used for a different indication. “Genvoya Combination Tablets” is designated as an orphan drug for the specific indication only. Therefore, in accordance with the notification of “the Enforcement of the Law for Partial Revision of the Pharmaceutical Affairs Act and the Act on the Fund for Adverse Drug Reaction Relief and R&D Promotion” (PAB/NDD Notification No.

92, dated October 1, 1993), the re-examination period for Vemlidy Tablets 25 mg is 5 years and 10 months. The product is not classified as a biological product or a specified biological product. The drug product is classified as a powerful drug.

Indication

Suppression of hepatitis B virus replication in chronic hepatitis B patients with evidence of viral replication and abnormal liver function

Dosage and Administration

The usual adult dosage is 25 mg of Tenofovir Alafenamide administered orally once daily.

Condition for Approval

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