Report on the Deliberation Results

March 4, 2014

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau

Ministry of Health, Labour and Welfare

[Brand name]	Tivicay Tablets 50 mg
[Non-proprietary name]	Dolutegravir Sodium (JAN*)
[Name of applicant]	ViiV Healthcare K.K.
[Date of application]	December 5, 2013

[Results of deliberation]

In the meeting held on February 28, 2014, 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.

Since the product is an orphan drug, the re-examination period is 10 years, and the drug substance and the drug product are both classified as powerful drugs. The product is not classified as a biological product or a specified biological product.

[Conditions for approval]

The applicant is required to:

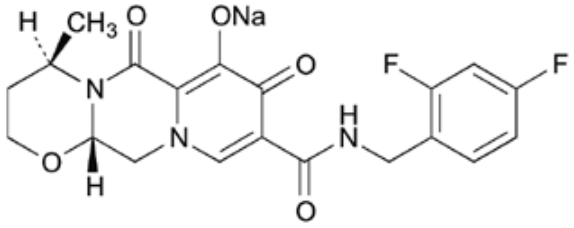
1. Request physicians to fully explain to their patients that further efficacy and safety data are still being collected etc. and obtain their informed consent prior to the use of the product.
2. Submit the study data and analysis results from ongoing or planned foreign clinical studies promptly after the study completion.
3. Conduct a post-marketing surveillance study, covering all patients treated with the product in Japan as a rule, until the completion of the re-examination period, in order to collect and periodically report the drug utilization information (patient characteristics, efficacy and safety [including the efficacy and safety of the product in combination with other drugs], drug interaction data, etc.), and submit the survey results as application data for re-examination.

**Japanese Accepted Name (modified INN)*

Review Report

February 19, 2014
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]	Tivicay Tablets 50 mg
[Non-proprietary name]	Dolutegravir Sodium
[Applicant]	ViiV Healthcare K.K.
[Date of application]	December 5, 2013
[Dosage form/Strength]	Tablets: Each tablet contains 52.6 mg of Dolutegravir Sodium (50 mg as Dolutegravir).
[Application classification]	Prescription drug (1) Drug with a new active ingredient
[Chemical structure]	 Molecular formula: $C_{20}H_{18}F_2N_3NaO_5$ Molecular weight: 441.36 Chemical name: Monosodium (4*R*,12a*S*)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}-4-methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5] pyrazino[2,1-*b*] [1,3]oxazin-7-olate
[Items warranting special mention]	● The product is eligible for prior assessment based on the PMSB/ELD Notification No.1015 dated November 12, 1998. ● Orphan drug (Designation No. [25 Drug] No.314, PFSB/ELD Notification No.0913-9 dated September 13, 2013)
[Reviewing office]	Office of New Drug IV

Review Results

February 19, 2014

[Brand name] Tivicay Tablets 50 mg
[Non-proprietary name] Dolutegravir Sodium
[Name of applicant] ViiV Healthcare K.K.
[Date of application] December 5, 2013
[Results of review]
Based on the submitted data, the efficacy of the product in the treatment of HIV infection has been demonstrated and its safety is acceptable in view of its observed benefits. Since the efficacy and safety of the product in Japanese patients with HIV infection have not been confirmed, it is necessary to carefully collect post-marketing information. As soon as any information become available, it should be appropriately evaluated and provided.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency concluded that the product may be approved for the "indication and dosage and administration as shown below, with the following conditions.

[Indication]
HIV infectious disease

[Dosage and administration]
Usually in adults, dolutegravir is orally given as described below. The drug may be given without regard to meals. It should be given with other anti-HIV drugs.

1. Treatment-naïve patients and patients who experienced treatment with other anti-HIV drugs than integrase inhibitors
   Dolutegravir is orally given at a dose of 50 mg once daily.
2. Patients with integrase inhibitor resistance
   Dolutegravir is orally given at a dose of 50 mg twice daily.

In treatment-naïve patients who are aged 12 years or older weighing 40 kg or more, and pediatric patients who experienced treatment with other anti-HIV drugs than integrase inhibitors, dolutegravir may be orally given at a dose of 50 mg once daily.

[Conditions for approval]
The applicant is required to:

1. Request physicians to fully explain to their patients that further efficacy and safety data are still being collected etc. and obtain their informed consent prior to the use of the product.
2. Submit the study data and analysis results from ongoing or planned foreign clinical studies promptly after

the study completion.

3. Conduct a post-marketing surveillance study, covering all patients treated with the product in Japan as a rule, until the completion of the re-examination period, in order to collect and periodically report the drug utilization information (patient characteristics, efficacy and safety [including the efficacy and safety of the product in combination with other drugs], drug interaction data, etc.), and submit the survey results as application data for re-examination.

Prior Assessment Report (1)

December 2, 2013

I. Product for which prior assessment was requested

[Expected brand name] Tivicay Tablets 50 mg

[Prior assessment requestor] ViiV Healthcare K.K.

[Non-proprietary name] Dolutegravir Sodium

[Dosage form/Strength] Tablets: Each tablet contains 52.6 mg of Dolutegravir Sodium (50 mg as Dolutegravir).

[Expected indication] HIV infectious disease

[Expected dosage and administration]

Usually in adults, dolutegravir is orally given at a dose of 50 mg once daily. The drug may be given without regard to meals. It should be given with other anti-HIV drugs.

[Date of preparatory meeting for prior assessment] June 27, 2013

[Items warranting special mention]

Orphan drug (Designation No. [25 Drug] 314, PFSB/ELD Notification No.0913-9 dated September 13, 2013)

The product is eligible for prior assessment based on the PMSB/ELD Notification No.1015 dated November 12, 1998.

Date of approval in the US: August 12, 2013

This prior assessment is based on the US application dossier.

II. Comments from the Pharmaceuticals and Medical Devices Agency (PMDA) Given to the Prior Assessment Requestor at the Preparatory Meeting for Prior Assessment and Its Evaluation Results

1. Origin or history of discovery and usage conditions in foreign countries etc.

Dolutegravir sodium is a novel human immunodeficiency virus (HIV) integrase strand transfer inhibitor (INSTI) developed by a joint venture between Shionogi & Co., Ltd. and GlaxoSmithKline K.K. (later ViiV Healthcare K.K.). It inhibits the catalytic activity of HIV integrase (IN), which is responsible for insertion of the viral genome into the DNA of the host cell.

In Japan, as for INSTIs, raltegravir (RAL) was approved in June 2008 and a combination tablet containing elvitegravir (EVG) was approved in March 2013. Resistance to these INSTIs found in clinical studies have been reported[1)] and there is also a report that cross-resistance is likely to occur[2)].

Under the above situation, Tivicay Tablets demonstrated non-inferiority to comparators at Week 48 and was

[1)] Cooper DA, et al. *N Engl J Med*. 2008;359:355-365, Molina J, et al. *Lancet Infect Dis*. 2012;12:27-35, Lennox JL, et al. *J Acquir Immuno Defic Syndr*. 2010;55(1):39-48, Sax PE, et al. *Lancet*. 2012;379(9835):2439-2448, DeJesus E, et al. *Lancet*. 2012;379(9835):2429-2438.

[2)] Molina J, et al. *Lancet Infect Dis*. 2012;12:27-35.

well tolerated in foreign phase III studies (ING113086, ING114467, ING111762) and a foreign phase III study in HIV infected, INSTI-experienced patients (ING112574) also showed a certain level of efficacy of dolutegravir. Therefore, it was considered that dolutegravir can become a therapeutic option for patients with HIV infection. Based on the above clinical study data, a new drug application for dolutegravir was submitted in December 2012 and approved as of August 12, 2013 in the US. Regulatory applications were filed in December 2012 in the EU and Canada and in January 2013 in 12 foreign countries including Switzerland and Australia; the applications are currently under review.

In Japan, ViiV Healthcare K.K. requested prior assessment of dolutegravir.

2. Physicochemical properties and specifications

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is a white to light yellow powder and its polymorphism, melting point, crystal habit, particle size, hygroscopicity, solubility, dissociation constant (pKa), pH, partition coefficient, and optical rotation have been investigated. [redacted]

The chemical structure of the drug substance has been elucidated by elemental analysis, mass spectrometry, nuclear magnetic resonance spectrometry (^{1}H-NMR and ^{13}C-NMR), infrared spectrophotometry, and single-crystal x-ray crystallography. Theoretically, 1 enantiomer and 2 diastereomers exist for the drug substance.

2.A.(1).2) Manufacturing process

[redacted]

3) [redacted]
4) [redacted]
5) [redacted]
6) [redacted]

2.A.(1).3) Control of drug substance

[redacted]

2.A.(1).4) Stability of drug substance

Stability studies on the drug substance are shown in Table 1. Photostability data showed that the drug substance is photolabile.

Table 1. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 production batches	30°C	65%RH	Double low-density polyethylene bags	24 months
Accelerated	3 production batches	40°C	75%RH		6 months

Based on the above, a re-test period of [redacted] months has been proposed for the drug substance when stored in low-density polyethylene bags at room temperature and protected from light. The long-term stability study will be continued up to [redacted] months.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug substance is formulated as a tablet. Each tablet contains 52.6 mg of dolutegravir sodium (50 mg as dolutegravir). [redacted]

2.A.(2).2) Manufacturing process

[redacted]

2.A.(2).3) Control of drug product

The proposed specification for the drug product includes strength, description, identification (ultraviolet-visible spectrophotometry), uniformity of dosage units (HPLC), dissolution, microbial limits, and assay (HPLC).

2.A.(2).4) Stability of drug product

Stability studies on the drug product are shown in Table 2. [redacted] Photostability data showed that the drug product is photostable.

Table 2. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 pilot-scale batches	25°C	60%RH	High-density polyethylene bottles	24 months
	3 pilot-scale batches	30°C	75%RH		24 months
Accelerated	3 pilot-scale batches	40°C	75%RH		6 months

Based on the above, a shelf life of 24 months has been proposed for the drug product when stored in high-density polyethylene bottles at room temperature. The long-term stability study will be continued up to [redacted] months.

2.B Outline of prior assessment by PMDA

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

2.B.(1) Storage conditions and shelf life for drug product

[redacted]

The prior assessment requestor explained as follows:

[redacted]

PMDA accepted the above explanation.

3. Non-clinical data

3.(i) Pharmacology

3.(i).A Summary of the submitted data

For this application, the results from primary pharmacodynamic studies (inhibition of HIV type 1 IN [HIV-1 IN], binding and dissociation kinetics with HIV-1 IN, *in vitro* antiviral activity against various laboratory strains and clinical isolates, the effect of serum protein on antiviral activity, pathways for acquiring resistance, etc.) were submitted. The results from secondary pharmacodynamic studies (effects on a panel of enzymes, receptors,

[7] Measured for reference.

and ion channels and isolated tissues) were submitted. The results from safety pharmacology studies (effects on the cardiovascular, central nervous, and respiratory systems) were submitted. All doses and concentrations of dolutegravir sodium and dolutegravir in this section are expressed in terms of dolutegravir.

3.(i).A.(1) Primary pharmacodynamics (5.3.5.4)

3.(i).A.(1).1) Mechanism of action

The antiviral mechanism of dolutegravir on HIV replication was investigated using quantitative PCR. While a non-nucleoside reverse transcriptase inhibitor (NNRTI), efavirenz (EFV) decreased the amount of reverse transcription products, HIV-1 DNA (50% effective concentration [EC_{50}], 4.8 nM), neither dolutegravir nor RAL, an INSTI, affected it at up to the highest concentration tested (20 nM). Dolutegravir and RAL inhibited the integration of HIV-1 DNA into host cells in a dose-dependent manner and the EC_{50} values were 0.72 nM for dolutegravir and 2.4 nM for RAL.

Dolutegravir's antiviral activity against various drug-resistant strains of HIV (2 NNRTI-resistant, 3 nucleoside reverse transcriptase inhibitor [NRTI]-resistant, and 2 protease inhibitor [PI]-resistant strains) was equivalent to that against the wild-type strain. In addition, passage studies with dolutegravir selected mutations within the IN enzyme and direct dolutegravir binding to IN protein was demonstrated.

3.(i).A.(1).2) Antiviral activity

3.(i).A.(1).2).(a) Activity against laboratory strains

The antiviral activity of dolutegravir was examined using peripheral blood mononuclear cells (PBMC) infected with HIV-1 (strain NL432 or Ba-L), MT-4 cells infected with HIV-1 (strain IIIB), and CIP4 cells[8)] infected with HIV-1 (pseudotype[9)]). The 50% inhibitory concentrations (IC_{50}) against HIV-1 (strain NL432), HIV-1 (strain Ba-L), HIV-1 (strain IIIB), and HIV-1 (pseudotype) were 0.53, 0.51, 0.71, and 2.2 nM, respectively. The 50% cytotoxic concentrations (CC_{50}) in MT-4 and CIP4 cells were >0.25 and >5.0 μM, respectively. Dolutegravir showed antiviral activities against HIV-1 (strain IIIB) with a selectivity index (SI) of >350 and against HIV-1 (pseudotype) with a SI of >2200. The CC_{50} values in human leukemic and lymphomic cell lines (IM-9, U-937, MT-4, Molt-4) and phytohemagglutinin (PHA) stimulated and unstimulated PBMCs were 4.8, 7.0, 14, 15, 52, and 189 μM, respectively.

The effect of serum protein on the antiviral activity of dolutegravir was evaluated *in vitro* using MT-4 cells infected with HIV-1 (strain IIIB). In the presence of human serum albumin (40 mg/mL), α1-acid glycoprotein (2 mg/mL), and human serum (100%), the IC_{50} of dolutegravir increased 12-, 2-, and 75-fold, respectively.

The antiviral activities of dolutegravir and other anti-HIV agents were tested against various drug-resistant strains of HIV (2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI-resistant strains). The results are shown in Table

[8)] A derivative of the 293T cell line, which expresses macrophage scavenger receptor SRA-I to improve adhesion.
[9)] Its envelope protein is replaced with an envelope protein of vesicular stomatitis virus (VSV-g).

3 and Table 4.

Table 3. Antiviral activity against RTI-resistant viruses

Virus [a)]	EC_{50} (nM)			
	Dolutegravir	AZT	3TC	EFV
Wild type (NL432)	1.4	54	210	1.9
K103N	1.7	67	210	74
M184V	1.3	42	> 10000	1.4
Y188L	2.1	72	250	560
D67N/K70R/T215Y	1.5	930	1000	0.95
V75I/F77L/F116Y/Q151M	1.3	> 10000	1500	2.2

AZT: Zidovudine, 3TC: Lamivudine

a) Amino acid mutations are abbreviated to the single letter amino acid code of the wild-type residue, followed by its amino acid number and the single letter amino acid code of the mutant residue.

Table 4. Antiviral activity against PI-resistant viruses

Virus	EC_{50} (nM)		
	Dolutegravir	APV	Ritonavir
Wild type (NL432)	0.88	36	43
M46I/I47V/I50V	0.36	220	59
L24I/M46I/L63P/A71V/G73S/V82T	0.37	24	620

APV: Amprenavir

3.(i).A.(1).2).(b) Antiviral activity in combination with other anti-HIV agents

Dolutegravir was tested for antiviral activity in combination with other anti-HIV agents[10)] using MT-4 cells infected with HIV-1 (strain IIIB) and in combination with maraviroc (MVC) using MAGI-CCR5 cells infected with HIV-1 (strain Ba-L). The results are shown in Table 5 and Table 6. The antiviral activity of dolutegravir was not antagonistic when combined with these agents.

Table 5. Antiviral activity of dolutegravir in combination with other anti-HIV agents

Compound	Deviation from additivity [a)]
dolutegravir	0.031 ± 0.151
d4T	-0.473 ± 0.083
ABC	-0.605 ± 0.150
EFV	-0.356 ± 0.102
NVP	-0.246 ± 0.087
LPV	-0.310 ± 0.082
APV	-0.332 ± 0.085
Enfuvirtide	-0.245 ± 0.110
RAL	-0.05 ± 0.16

Average ± Standard Error (SE)

a) Parameter calculated based on Selleseth DW et al.'s report (*Antimicrob Agents Chemother*. 2003;47:1468-1471).

Table 6. Antiviral activity of dolutegravir in combination with MVC

Combination of drugs	Volume [a)] (nM^2%)	
	Synergy	Antagonism
dolutegravir + MVC	36.3	-0.21

a) Mean volume calculated using MacSynergy II™ software, based on Prichard MN et al.'s report (*Antiviral Res*. 1990;14:181-205).

3.(i).A.(1).2).(c) Activity against clinical isolates

The antiviral activity of dolutegravir was tested using 293 cells infected with 13 clinically diverse HIV-1 clade B isolates[11)]. The IC_{50} of dolutegravir was 0.41 to 0.60 nM.

[10)] Dolutegravir was combined with the NRTIs sanilvudine (d4T) or abacavir (ABC); the NNRTIs EFV or nevirapine (NVP); the PIs lopinavir (LPV) or amprenavir (APV); the fusion inhibitor enfuvirtide; or the INSTI RAL.

[11)] Petropoulos CJ, et al. *Antimicrob Agents Chemother*. 2000;44(4):920-928.

The IC_{50} values of dolutegravir (mean) against a panel of HIV-1 isolates (clades A [3 isolates], B [5 isolates], C [4 isolates], D [3 isolates], E [3 isolates], F [4 isolates], and G [3 isolates] and group O [3 isolates]) and 4 HIV type 2 (HIV-2) isolates in PBMCs and 4 HIV-1 clade B isolates in macrophages were 0.26, 0.62, 0.23, 0.23, 0.22, 0.25, 0.36, 0.87, 0.29, and 1.07 nM, respectively.

3.(i).A.(1).2).(d) Activity against non-HIV viruses

Dolutegravir was evaluated for antiviral activity against a panel of 19 non-HIV viruses. The results are shown in Table 7.

Table 7. Antiviral activity against non-HIV viruses

Virus	IC_{50} (μM)	CC_{50} (μM)	SI
Adenovirus	> 100	> 100	NA
Bovine Viral Diarrhea Virus	66.0	> 100	> 1.52
Dengue Virus	69.5	> 100	> 1.44
Yellow Fever Virus	> 100	> 100	NA
Herpes Simplex Virus type 1 (HSV-1)	> 100	> 100	NA
HSV-2	> 100	> 100	NA
Influenza A	> 100	64.9	NA
Influenza B	> 100	75.7	NA
Human Parainfluenza	> 100	> 100	NA
Measles Virus (Morilli Virus)	30.3	> 100	> 3.30
Respiratory Syncytial Virus	> 100	> 100	NA
Coxsackie A Virus	> 100	97.6	NA
Coxsackie B Virus	> 100	> 100	NA
Enterovirus	> 100	> 100	NA
Polio Virus	> 100	> 100	NA
Rhinovirus	> 100	> 100	NA
Hepatitis C Virus	11.2	96.7	8.64
Human Cytomegalovirus	> 100	> 100	NA
Varicella Zoster Virus	88.1	> 100	> 1.13

NA: not applicable

3.(i).A.(1).2).(e) Resistant viruses

Virus cultures were derived by co-culturing MT-2 cells with Molt-4 cells persistently infected with HIV-1 (strain IIIB) and serial passage in the presence of dolutegravir was used to study resistance evolution. Amino acid substitutions observed during passage and susceptibility[12)] are shown in Table 8.

[12)] Fold Change from wild-type strain or mutant strain before passage in antiviral activity (IC_{50}) of compound.

Table 8. Amino acid substitutions observed during passage with HIV-1 (strain IIIB) and susceptibility

Days of culture	Amino acid substitution	Dolutegravir fold change
14	T124A	1.2-2.5
28	T124A	0.57-1.0
	T124A/S153F	1.9
42	T124A	0.48-1.7
	T124A/S153F	1.7
56	T124A	0.95-2.9
	T124A/S153F	2.7
70	T124A	1.1-3.1
	T124A/S153Y	2.9
	L101I/T124A/S153F	2.4
84	T124A	0.82-3.1
	S153Y	3.7
	T124A/S153Y	3.3
	L101I/T124A/S153F	2.4
98	T124A	1.3-3.1
	T124A/S153Y	4.1
	L101I/T124A/S153F	3.0
112	T124A	1.2-4.1
	S153Y	2.1
	T124A/S153Y	1.8-2.6
	L101I/T124A/S153F	2.0

Wild-type HIV-1 (strain NL432) and molecular clones with RAL resistance substitutions (E92Q, Q148H, Q148K, Q148R, N155H) were passaged sequentially in the presence of dolutegravir and passaged virus populations were analyzed for genotypic and phenotypic changes. Amino acid substitutions observed during passage and susceptibility are shown in Table 9.

Table 9. Amino acid substitutions observed during passage of HIV-1 (strain NL432) and RAL-resistant mutants with dolutegravir and susceptibility

Initial virus	Dolutegravir initial concentration/ Final concentration (nM)	Days of culture	Amino acid substitution	Dolutegravir fold change
Wild type	6.4/6.4	56	E92Q	3.1
			G193E	3.2
Q148K	6.4/32	14	E138K/Q148K	—
		28	E138K/Q148K	—
		42	E138K/Q148K	—
		56	E138K/Q148K	47-190
Q148R	6.4/6.4 or 32	14	Q148R	—
		28	G140S/Q148R	—
		42	G140S/Q148R	—
		56	G140S/Q148R	16 [a)]
			G140S/Q148R/V201I	39 [b)]
Q148R	6.4/6.4	14	E138K/Q148R	—
		28	E138K/Q148R	—
		42	E138K/Q148R	—
		56	E138K/G140S/Q148R	13
Q148H	6.4/6.4 or 32	14	G140S/Q148H	—
		28	G140S/Q148H	—
		42	G140S/Q148H	—
		56	G140S/Q148H	4.8-8.0 [a)]
			T97A/G140S/Q148H	44 [b)]
			V75I/E138K/G140S/Q148H/M154I	46 [b)]
N155H	6.4/32	14	N155H	—
		28	N155H	—
		42	N155H	—
		56	N155H	2.0-3.9
E92Q	6.4/6.4	14	E92Q	—
		28	E92Q	—
		42	E92Q	—
		56	E92Q	2.9-4.1

a) Dolutegravir final concentration was 6.4 μM.
b) Dolutegravir final concentration was 32 μM.

Passage of site-directed mutant viruses with polymorphic substitutions L101I and L101I/T124A and RAL resistance substitutions Y143C and Y143R in the presence of dolutegravir did not lead to additional substitutions.

Serial passage experiments were performed with dolutegravir using HIV-1 clades B, A/G, and C[13]. R263K emerged as a mutation affecting the antiviral activity of dolutegravir. The IC_{50} against a site-directed mutant virus harboring R263K was 36.7 nM and the dolutegravir fold change was 11.2.

3.(i).A.(1).2).(f) Activity against INSTI-resistant viruses

Susceptibility to dolutegravir, RAL, and EVG was determined for 60 INSTI-resistant site-directed HIV-1 (strain NL432) mutants. The results are shown in Table 10.

Table 10. Antiviral activity of compounds against INSTI-resistant HIV-1 mutants

Virus	Fold change		
	Dolutegravir	RAL	EVG
Wild type [a]	1.0 (IC_{50} 1.9-2.1 nM)	1.0 (IC_{50} 6.1-8.6 nM)	1.0 (IC_{50} 1.2-1.4 nM)
T66A	0.26	0.61	—
T66I	0.26	0.51	8
T66K	2.3	9.6	84
E92I	1.5	2.1	—
E92Q	1.6	3.5	19
E92V	1.3	1.4	—
G118R	10	7.2	—
G118S	1.1	1.2	—
F121Y	0.81	6.1	36
T124A	0.95	0.82	1.2
E138K	0.97	1.0	0.93
G140S	0.86	1.1	2.7
Y143C	0.95	3.2	1.5
Y143R	1.4	16	1.8
Y143H	0.89	1.8	1.5
P145S	0.49	0.87	> 345
Q146R	1.6	1.2	2.8
Q148H	0.97	13	7.3
Q148K	1.1	83	> 1726
Q148R	1.2	47	244
I151L	3.6	8.4	—
S153F	1.6	1.3	2.8
S153Y	2.5	1.3	2.3
M154I	0.93	0.82	1.1
N155H	0.99	8.4	25
N155S	1.4	6.2	68
N155T	1.9	5.2	—
G193E	1.3	1.3	1.3
T66I/I74M	0.35	2.0	—
T66I/E92Q	1.2	18	185
T66K/L74M	3.5	40	117
V72I/F121Y/T125K	1.3	13	—
V72I/F121Y/T125K/I151V	1.2	7.0	—
L74M/N155H	0.91	28	42
V75I/E138K/G140S/Q148H/M154I	21	> 660	2600
E92Q/N155H	2.5	> 130	320
T97A/N155H	1.1	26	37
T97A/G140S/Q148H	13	> 660	3900
L101I/S153F	2.0	1.3	2.6
L101I/T124A/S153F	1.9	1.4	2.0

[13] Quashie P, et al. *J Virol*. 2012;86(5):2696-2705.

Virus	Fold change		
	Dolutegravir	RAL	EVG
F121Y/T125K	0.98	11	—
E138K/Q148H	0.89	17	6.7
E138K/Q148K	19	330	—
E138K/Q148R	4.0	110	461
E138A/Q148R	2.6	110	260
E138K/G140S/Q148H	4.5	500	1600
E138K/G140S/Q148R	8.3	> 660	190
E138K/G140S/Q148H/M154I	8.4	> 660	2400
E138A/S147G/Q148R	1.9	27	130
G140C/Q148R	4.9	200	—
G140S/Q148H	2.6	> 130	> 890
G140S/Q148K	1.5	3.7	94
G140S/Q148R	8.4	200	—
G140S/Q148H/M154I	7.0	> 660	3000
G140S/Q148R/V201I	10	> 660	420
Y143H/N155H	1.7	38	16
Q148R/N155H	10	> 140	390
N155H/G163R	1.1	17	35
N155H/G163K	1.4	23	35
N155H/D232N	1.4	20	36

a) Four studies were performed. Fold change compared to wild-type virus, which was used to determine antiviral activity against mutant viruses, was calculated.

The results for site-directed HIV-2 (strain ROD) mutants are shown in Table 11.

Table 11. Antiviral activity of compounds against INSTI-resistant HIV-2 mutants

Virus	Fold change			
	Dolutegravir	RAL	EVG	AZT
Wild type	1.0 (IC_{50} 1.4 nM)	1.0 (IC_{50} 4.8 nM)	1.0 (IC_{50} 0.84 nM)	1.0 (IC_{50} 13 nM)
S163D	0.87	0.86	1.1	1.2
E92Q/N155H	8.5	110	340	2.8
G140A/Q148R	0.6	6.4	110	0.21
G140S/Q148R	17	420	640	0.43
A153G/N155H/S163G	3.8	16	22	4.5
E92Q/T97A/N155H/S163D	3.9	57	200	0.43

Susceptibility to dolutegravir and RAL was determined for RAL-resistant clinical isolates. The results are shown in Table 12.

Table 12. Antiviral activity against RAL-resistant clinical isolates

Virus	N	Fold change	
		Dolutegravir	RAL
N155H	5	1.37 (1.22-1.45)	19.0 (14.0-36.0)
G140S/Q148H	7	3.75 (2.05-15.0)	> 87 (58.0-> 87)
G140S/Q148R	2	13.3 (7.57-19.0)	> 87 (> 87-> 87)
T97A/Y143R	2	1.05 (1.04-1.06)	> 81 (> 81-> 81)

Median (Range)

Clinical isolates (705 isolates) from RAL-containing anti-retroviral therapy (ART)-experienced patients were analyzed for susceptibility to dolutegravir. The proportion of clinical isolates for INSTI resistance mutation categories[14] is shown in Table 13. Overall, 93.9% of the 705 isolates (662 of 705 isolates) had a dolutegravir fold-change of ≤10 and 1.8% (13 of 705 isolates) had a dolutegravir fold-change of >25. Of the 43 isolates with

[14] INSTI resistance mutations list: Y143C, Y143H, Y143R, Q148H, Q148K, Q148R, and N155H were defined as primary resistance mutations and H51Y, L74I, L74M, E92Q, E92V, T97A, G118R, E138A, E138K, E138T, G140A, G140C, G140S, S147G, V151I, S153F, S153Y, G163K, G163R, G193E, and R263K were classified as other resistance mutations.

a dolutegravir fold-change of >10, 41 isolates were within the Q148 + ≥2 secondary mutation category or within the Q148 + 1 secondary mutation category (25 isolates and 16 isolates, respectively).

Table 13. Proportion of clinical isolates for INSTI resistance mutation categories

Mutation category	N (%)
Q148 + ≥2 secondary mutations	92 (13.0)
Q148 + 1 secondary mutation	184 (26.1)
Y143	98 (13.9)
N155	204 (28.9)
≥2 Primary mutations	42 (6.0)
Primary not detected	85 (12.1)

The binding of dolutegravir, RAL, and EVG was determined for wild-type and INSTI-resistant IN proteins. Dissociation rate constants (K_{off}) and half-lives ($t_{1/2}$) of dissociation of [^{3}H]-thymidine-labeled dolutegravir, RAL, and EVG from IN-DNA complexes are shown in Table 14.

Table 14. Dissociation rate constant and dissociative half-life for IN-DNA complexes

IN protein	K_{off} (S^{-1}) (10^{-6})			$t_{1/2}$ (h)		
	Dolutegravir	RAL	EVG	Dolutegravir	RAL	EVG
Wild type	2.7 ± 0.4	22 ± 2	71 ± 4	71	8.8	2.7
E92Q	11.4 ± 0.3	59 ± 9	430 ± 20	17	3.3	0.4
E138K	2.3 ± 0.2	17 ± 0.3	52 ± 1	84	11	3.7
G140S	9.6 ± 0.8	44 ± 3	180 ± 20	20	4.4	1.1
Y143C	3.2 ± 0.1	96 ± 4	91 ± 2	60	2.0	2.1
Y143H	4.4 ± 0.2	78 ± 2	120 ± 6	44	2.5	1.6
Y143R	4.6 ± 0.3	176 ± 4	116 ± 5	42	1.1	1.7
Q148H	37 ± 3	1160 ± 120	1130 ± 140	5.2	0.2	0.2
Q148K	18 ± 5	730 ± 130	ND	11	0.3	ND
Q148R	21 ± 2	480 ± 80	ND	9.2	0.4	ND
N155H	20 ± 2	300 ± 80	500 ± 140	9.6	0.6	0.4
E92Q/N155H	49 ± 3	770 ± 70	ND	3.9	0.3	ND
E138K/Q148H	53 ± 10	900 ± 340	ND	3.6	0.2	ND
G140S/Q148H	58 ± 8	1130 ± 210	ND	3.3	0.2	ND

ND: not determined
Mean or Mean ± Standard Deviation (SD)

The $t_{1/2}$ values for IN mutants observed in a foreign phase II study (ING112961) are shown in Table 15.

Table 15. Dissociative half-life for IN-DNA complexes containing IN substitutions observed in Study ING11296

IN protein	$t_{1/2}$ (h)		
	Dolutegravir	RAL	EVG
Wild type	71	8.8	2.7
T97A/Y143R/N155H	2.3	0.1	ND
L74M/T97A/Y143R	9.6	0.3	0.7
L74M/T97A/Y143R/N155H	2.4	ND	ND
L74M/T97A/E138A/Y143R/N155H	2.2	0.1	0.1
L74M/G140S/Q148H	3.3	0.1	ND
L74M/E138A/G140S/Q148H	2.4	0.1	ND
L74M/T97A/G140S/Q148H	1.1	0.1	ND
G140S/Y143H/Q148H	3.9	ND	ND
E92Q/G140S/Q148H	0.6	ND	ND
E92Q/E138T/G140S/Q148H	0.4	ND	ND
E138K/G140S/Q148H	3.0	0.2	ND
G140S/Q148H/N155H	0.5	ND	ND
E138K/G140S/Q148H/N155H	0.3	ND	ND

ND: not determined

For V75I/E138K/G140S/Q148H/M154I identified during *in vitro* passage, the G118R substitution causing a fold-change of 10, and R263K identified during passage of HIV-1 clades B, A/G, and C in the presence of

dolutegravir, the $t_{1/2}$ values were 1.0, 10.7, and 15.5 to 22.4 hours, respectively[15].

3.(i).A.(2) Secondary pharmacodynamics (4.2.1.2)

Dolutegravir was evaluated *in vitro* for possible interactions with 65 receptors and ion channels and 16 enzymes. Dolutegravir at 10 μM (0.1% DMSO) caused a 64% inhibition of binding at the melanocortin MC_4 receptor and the effect of dolutegravir was <50% inhibition in other assays. Dolutegravir (up to 100 μM [0.1% DMSO]) was tested *in vitro* to assess potential activity against a panel of 12 isolated tissues[16] and no significant responses (≥50% inhibition) were observed.

3.(i).A.(3) Safety pharmacology (4.2.1.3)

Safety pharmacology studies were performed to assess potential effects on the cardiovascular, central nervous, and respiratory systems. The results are shown in Table 16.

Table 16. Summary of safety pharmacology studies

Organ systems evaluated	Animal species/strains	Method of administration	Gender and No. per Group	Doses (concentrations) of dolutegravir	Study findings
CNS	Rat/SD	Oral/Single dose	6M	50, 150, 500 mg/kg	No effects. C_{max} and $AUC_{0\text{-}24h}$ at 500 mg/kg were 87.1 μg/mL and 1360 μg·h/mL [a], respectively.
Respiratory	Rat/SD	Oral/Single dose	8M	50, 150, 500 mg/kg	No effects.
Cardiovascular	HEK293 cells expressing hERG	*In vitro*	-	1, 10, 20 μM (0.42, 4.19, 8.38 μg/mL)	1.1%, 11.5%, and 16.1% inhibition of hERG potassium current occurred at 1, 10, and 20 μM, respectively.
Cardiovascular	Cynomolgus monkey	Oral/Single dose	4M	100, 300, 1000 mg/kg	No effects. C_{max} and $AUC_{0\text{-}24h}$ at 1000 mg/kg were 20.1 μg/mL and 259 μg·h/mL, respectively.

C_{max}, maximum plasma concentration; $AUC_{0\text{-}24h}$, area under the plasma concentration-time curve from time 0 to 24 hours
a) Day 1 data from a rat 14-day toxicity study.

The rat-to-human safety margins[17] of dolutegravir for effects on the central nervous and respiratory systems were 23.5-fold (compared with the 50 mg once daily [QD] human clinical exposure) and 20.7-fold (compared with the 50 mg twice daily [BID] human clinical exposure). The cynomolgus monkey to human safety margins of dolutegravir for cardiovascular effects were 5.4-fold (compared with the 50 mg QD human clinical exposure) and 4.8-fold (compared with the 50 mg BID human clinical exposure).

3.(i).B Outline of prior assessment by PMDA

3.(i).B.(1) Antiviral activity of dolutegravir

PMDA's view on the antiviral activity of dolutegravir is as follows:

In a study to determine mechanism of action, dolutegravir inhibited the integration of HIV-1 DNA into host

[15] For wild-type IN, the $t_{1/2}$ values for dolutegravir were 71 hours (testing for V75I/E138K/G140S/Q148H/M154I and G118R) and 25.7 to 38.5 hours (testing for R263K).

[16] rabbit platelets (aggregability), rat aorta (potassium-depolarization), guinea pig left atrium (cardiac contractility), guinea pig right atrium (heart rate), rat bladder (contractility), rat diaphragm (contractility), guinea pig ileum (potassium-depolarization), guinea pig trachea, rat seminiferous tubule, rat portal vein (potassium-depolarization), guinea pig ileum (electrical stimulation), rat esophagus (serotonin-induced contraction)

[17] A geometric mean C_{max} of 3.7 μg/mL in humans receiving dolutegravir at 50 mg/day in foreign phase II (ING112276) and phase III (ING113086) studies was used as the plasma concentration following 50 mg QD dosing. A geometric mean C_{max} of 4.2 μg/mL in humans receiving dolutegravir at 100 mg/day (50 mg BID) in foreign phase II (ING112961) and phase III (ING111762) studies was used as the plasma concentration following 50 mg BID dosing.

cells in a dose-dependent manner, as did RAL, an INSTI. When various laboratory strains and clinical isolates were analyzed for susceptibility to dolutegravir, dolutegravir inhibited HIV-1 and HIV-2 replication. Dolutegravir exhibited little activity against non-HIV viruses. Therefore, as a selective INSTI of HIV, dolutegravir is expected to have antiviral activity.

3.(i).B.(2) Dolutegravir activity against INSTI-resistant viruses

The prior assessment requestor explained the activity of dolutegravir against INSTI-resistant viruses as follows: Based on the results of studies described in "3.(i).A.(1).2).(f) Activity against INSTI-resistant viruses", dolutegravir retained activity against INSTI-resistant viruses and the efficacy of dolutegravir can be expected also in patients with resistance to existing INSTIs by checking IN resistance mutation profile prior to the use of dolutegravir.

- Comparative susceptibility to dolutegravir and RAL was obtained from 60 RAL-resistant HIV-1 mutants and 6 HIV-2 mutants. Dolutegravir retained activity against a vast majority of these mutants.
- Susceptibility to dolutegravir was determined for RAL-resistant clinical isolates (705 isolates), with dolutegravir retaining activity (<10 fold change) against >90% of HIV-1 isolates.
- The binding of dolutegravir, RAL, and EVG was determined for wild-type and mutant IN proteins complexed with DNA. The dissociation rate constant of dolutegravir was smaller than those of RAL and EVG for wild-type IN-DNA complexes. Dolutegravir also demonstrated slower dissociation for all of IN-DNA complexes with single, double, and up to four residue IN substitutions, compared with RAL and EVG, and dolutegravirretained significant binding to the IN-DNA complexes.

PMDA considers as follows:

In vitro studies showed that the fold changes of dolutegravir against RAL-resistant HIV mutants were not increased compared to those of RAL, which is considered due to a tighter binding of dolutegravir to IN-DNA complexes compared to RAL and EVG. This is understood, but the appropriateness of the use of dolutegravir in patients infected with INSTI-resistant viruses will be discussed in "4.(iii).B.(1).(5) Dosage and administration".

3.(ii) Pharmacokinetics

3.(ii).A Summary of the submitted data

For this application, pharmacokinetics after administration of dolutegravir sodium, ^{14}C-dolutegravir, or unlabeled dolutegravir were studied in the mouse, rat, rabbit, dog, and monkey. In studies with dolutegravir sodium or dolutegravir, radioactivity concentrations in tissues were determined by quantitative whole body autoradiography (QWBA) or liquid scintillation counting (LSC). For dolutegravir concentrations in biological samples, liquid chromatography-tandem mass spectrometry (LC/MS/MS; Lower limit of quantification, 5.00-500 ng/mL) was used.

All doses and concentrations of dolutegravir sodium and dolutegravir in this section are expressed in terms of

dolutegravir. Unless otherwise specified, the results in this section are expressed as the mean.

3.(ii).A.(1) Absorption (4.2.2.2, 4.2.3.1, 4.2.3.2, 4.2.3.4.1, 4.2.3.5.2, 4.2.3.5.4)

Following administration of a single intravenous dose of 1 mg/kg of dolutegravir sodium to rats (3 males), dogs (2 males), and monkeys (1-2 males), the total body plasma clearance was 0.23, 2.2, and 2.1 mL/min/kg, respectively, and the steady state volume of distribution was 0.10, 0.35, and 0.28 L/kg, respectively. Following fasted administration of a single oral dose of 5 mg/kg of dolutegravir sodium, the bioavailability was 75.6%, 39.1%, and 87.0%, respectively. When dolutegravir sodium was administered as single oral doses to rats (2 males), a dog (1 female), and monkeys (4 females) (50-1000 mg/kg to rats; 30-500 mg/kg to a dog; and 50-500 mg/kg and 1-50 mg/kg to monkeys), the increases in systemic exposure (C_{max} and AUC_{0-t}) were less than dose-proportional.

After repeat oral dosing in mice, rats (including juvenile rats), rabbits, and monkeys[18)], neither accumulation nor marked sex differences were observed.

3.(ii).A.(2) Distribution (4.2.2.3, 4.2.2.5)

Following administration of a single 50-mg/kg oral dose of ^{14}C-dolutegravir to rats (N = 7 males/time point), high concentrations of radioactivity were observed in the liver and lung, apart from the alimentary canal. Most tissues had lower radioactivity concentrations than plasma. Concentrations of radioactivity in the brain were about 2% of the blood concentration. By 28 days post-dose, only bone and pigmented skin contained quantifiable levels of radioactivity.

Following administration of a single 50-mg/kg oral dose of ^{14}C-dolutegravir to rats on gestation day 18 (N = 1 female/time point), the tissue to blood concentration ratio was similar for the dam and fetus and placental transfer of radioactivity was observed. The fetal bone marrow concentration was higher than the fetal blood concentration.

Following administration of a single 50-mg/kg oral dose of ^{14}C-dolutegravir to lactating rats at 10 days postpartum (N = 3 females/time point), the highest concentration of radioactivity in milk (47300 ng eq./g) was observed at 8 hours post-dose and the milk to blood concentration ratio was 2.3. Lacteal excretion of radioactivity was also observed.

The *in vitro* protein binding of ^{14}C-dolutegravir (10 μM) in rat, dog, monkey, and human sera was 99.9%, 95.4%, 99.1%, and 99.3%, respectively.

[18)] Mice were given 10 to 1500 mg/kg/day for 2 weeks (N = 36, males and females), 10 to 1500 mg/kg/day for 13 weeks (N = 108, males and females), and 7.5 to 500 mg/kg/day for 104 weeks (N = 90, males and females); rats were given 50 to 500 mg/kg/day for 2 weeks (N = 8, males and females), 2 to 1000 mg/kg/day for 4 weeks (N = 8, males and females), 5 to 500 mg/kg/day for 26 weeks (N = 12, males and females), and 2 to 50 mg/kg/day for 104 weeks (N = 24); pregnant rats were given 100 to 1000 mg/kg/day for 12 days (gestation days 6-17; 5 females); juvenile rats were given 5 to 1000 mg/kg/day for 18 days (Days 4-21 postpartum; N = 8, males and females), 2 to 300 mg/kg/day for 28 days (Days 4-31 postpartum; N = 24, males and females), and 0.5 to 75 mg/kg/day for 63 days (Days 4-66 postpartum; N = 60, males and females); rabbits were given 30 to 1000 mg/kg/day for 2 weeks (3 females); pregnant rabbits were given 40 to 1000 mg/kg/day for 13 days (gestation days 6-18, 5 females); and monkeys were given 100 to 1000 mg/kg/day for 2 weeks (N = 6, males and females), 25 to 100 mg/kg/day for 4 weeks (N = 6, males and females), and 3 to 50 mg/kg/day for 38 weeks (4-6 males and 4-6 females).

Following a single oral administration of ^{14}C-dolutegravir to mice (N = 10/sex/time point), rats (N = 3/sex/time point), and monkeys (N = 3/sex) (100 mg/kg to mice, 50 mg/kg to rats, and 10 mg/kg to monkeys), the blood to plasma ratios of radioactivity were 0.49 to 0.54, 0.51 to 0.53, and 0.64 to 0.73, respectively. The liver to blood concentration ratios were 0.34 to 0.46 in mice and 0.26 to 0.47 in rats, and there were no changes over time.

The transport of ^{14}C-dolutegravir (3 μM) by P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) was investigated. The efflux ratios[19)] were 3.8 and 3.1, respectively, indicating that dolutegravir is a substrate for P-gp and BCRP.

Dolutegravir was tested *in vitro* for the potential to inhibit P-gp, BCRP, multi-drug resistance protein (MRP) 2, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic cation transporter (OCT) 1, and OCT2. The results are shown in Table 17; dolutegravir inhibited OCT2.

Table 17. *In vitro* inhibition of transporters by dolutegravir

Test system		Probe substrate (Concentration μM)	IC_{50} (μM)
Cells	Expressed protein		
MDCK II-hMDR1	P-gp	^{3}H-digoxin (0.03)	>100
MDCK II-BCRP	BCRP	^{14}C-cimetidine (0.1)	IS [a)]
Membrane vesicles	MRP2	^{3}H-17β-estradiol glucuronide (50)	—
Membrane vesicles	MRP2[b)]	^{3}H-17β-estradiol glucuronide (50)	—
CHO	OATP1B1	^{3}H-17β-estradiol glucuronide (0.02)	—
HEK MSR II	OATP1B3	^{3}H-17β-estradiol glucuronide (0.02)	—
HEK293	OCT1	^{14}C-metformin (10)	>10
MDCK II	OCT2	^{14}C-metformin (10)	1.93

a) Inhibition at the highest dolutegravir concentration tested was insufficient to calculate an IC_{50}; 50% inhibition of transport of cimetidine at 100 μM was observed.
b) A major metabolite of dolutegravir, M3 (dolutegravir glucuronide), was the test material in this study.

3.(ii).A.(3) Metabolism (4.2.2.4)

Based on the results of *in vivo* metabolism studies, possible metabolic pathways of dolutegravir are shown in Figure 1. The primary metabolism of dolutegravir is by conjugation to form a glucuronide, M3 (dolutegravir glucuronide). No sex differences were observed in the metabolic profile.

19) Efflux ratio = basolateral to apical (B→A) transport/apical to basolateral (A→B) transport

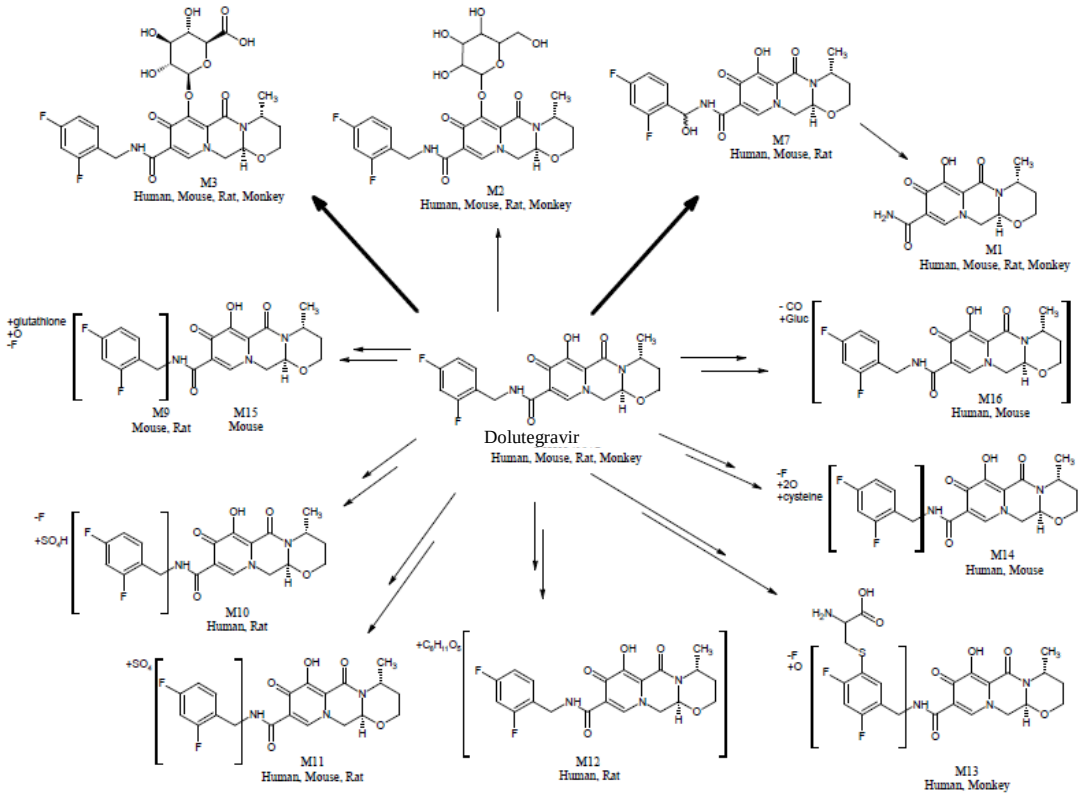


Figure 1. Possible metabolic pathways of dolutegravir

Using human liver microsomes, the metabolism of dolutegravir was investigated in the presence of cytochrome P450 (CYP450) drug-metabolizing isozymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4). In the presence of CYP3A4, dolutegravir was metabolized to M7 (oxidation) and M1 (N-dealkylation), and this metabolism process was inhibited by azamulin, a selective CYP3A4 inhibitor. Since incubations with other CYP450 isozymes showed no metabolism, CYP3A4 is considered to be the primary CYP450 enzyme involved in the metabolism of dolutegravir.

HepG2 cells were transfected with human or rat pregnane X receptor (PXR) and treated with dolutegravir sodium. Comparison of PXR activation by dolutegravir versus PXR activators[20)] indicated that dolutegravir may induce the PXR target gene in humans. However, when the inductive effects of dolutegravir on CYP1A2, CYP2B6, and CYP3A4 mRNA were examined using human hepatocytes, following 48-hour incubations of dolutegravir sodium, no marked effect on the mRNA levels of CYP1A2, CYP2B6, or CYP3A4 in human hepatocytes was observed.

Using human liver microsomes, the metabolism of dolutegravir was investigated in the presence of UGT enzymes (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT2B4, UGT2B7, UGT2B15). In total, 31% of dolutegravir was metabolized to M3 in the presence of UGT1A1. Atazanavir, a UGT1A1 inhibitor, inhibited glucuronidation of dolutegravir. UGT1A3 and UGT1A9 were also involved in glucuronidation of dolutegravir;

[20)] Pregnenolone 16α-carbonitrile as the rat PXR activator and rifampicin as the human PXR activator were used.

2.7% and 5.5% of dolutegravir were metabolized to M3 by UGT1A3 and UGT1A9, respectively. Glucuronidation was not observed in incubations with other UGT enzymes.

Using human liver microsomes, the potential of dolutegravir to inhibit CYP450 enzymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4) and UGT1A1 and UGT2B7 was assessed. Dolutegravir inhibited CYP3A4 (IC_{50} >54 μM). Inhibition of CYP2B6, CYP2C9, CYP2C19, CYP2D6, and UGT1A1 was observed, but IC_{50} could not be calculated (IC_{50} >100 μM). Dolutegravir did not inhibit other enzymes.

3.(ii).A.(4) Excretion (4.2.2.5)

Following oral administration of ^{14}C-dolutegravir to mice (N = 4/sex), rats (N = 3/sex), and monkeys (N = 3/sex) (100 mg/kg to mice, 50 mg/kg to rats, and 10 mg/kg to monkeys), the urinary excretion of radioactivity was 1.2% to 2.0%, 2.5% to 3.9%, and 4.4% to 7.2% of the administered dose, respectively, and the fecal excretion of radioactivity was 86.3% to 94.1%, 86.2% to 92.6%, and 66.9% to 77.5% of the administered dose, respectively. Fecal excretion was the primary route for elimination of radioactivity.

3.(ii).B Outline of prior assessment by PMDA

PMDA concluded that there were no particular problems with the submitted non-clinical pharmacokinetic data.

3.(iii) Toxicology

3.(iii).A Summary of the submitted data

Toxicity studies of dolutegravir conducted include repeat-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity (including juvenile toxicity studies), local tolerance, and other toxicity studies (an immunotoxicity study and genotoxicity studies on impurities). All doses and concentrations of dolutegravir sodium and dolutegravir in this section are expressed in terms of dolutegravir.

3.(iii).A.(1) Repeat-dose toxicity (4.2.3.2)

As the acute toxicity of dolutegravir was assessed in the rat and monkey based on data from 14-day repeat-dose studies, no single-dose toxicity studies were performed. The maximum tolerated doses were determined to be 500 mg/kg/day in rats and 300 mg/kg/day in monkeys[21)].

Gastrointestinal toxicity associated with dolutegravir was considered related to local gastrointestinal irritation, not caused by the systemic exposure. Drug-related body weight loss and moribund condition/death were considered secondary to profound dehydration due to gastrointestinal intolerance.

Hepatic and renal effects observed in long-term repeat-dose studies were also considered secondary to the

[21)] In a preliminary study where single doses of dolutegravir sodium were administered to beagle dogs (4.2.3.1 RD2009/00963), the maximum tolerated dose was 100 mg/kg. Thus, the dog was not considered an appropriate non-rodent species.

moribund condition related to gastrointestinal toxicity.

The no-observed-adverse-effect levels (NOAELs) of dolutegravir sodium in rats and monkeys were 50 and 15 mg/kg/day, respectively. When systemic exposure at the NOAEL[22] was compared with the expected human exposure for a 50 mg QD or BID dose[23], the rat to human exposure ratio was 14.3 or 10.2, respectively, and the monkey to human exposure ratio was 0.72 or 0.52, respectively. However, given that the NOAEL of dolutegravir was defined based on toxicity considered related to local gastrointestinal irritation, safety margins should be calculated using the human mg/kg equivalent dose and the NOAEL in rats was 50 or 25 times the human mg/kg equivalent dose[24] for a 50 mg QD or BID dose, respectively, and the NOAEL in monkeys was 15 or 7.5 times the human mg/kg equivalent dose for a 50 mg QD or BID dose, respectively.

3.(iii).A.(1).1) Mouse 13-week oral toxicity study (RD2009/00028)

Dolutegravir sodium was administered orally to CD-1 mice (N = 10/sex/group) at 0 (vehicle), 10, 50, 500, and 1500 mg/kg/day for 13 weeks. There were no treatment-related deaths. There was a slight or mild increase of mucous neck cells in the glandular mucosa of the stomach with submucosal eosinophilic and lymphocytic infiltrates in animals given 1500 mg/kg/day. Slight increases in blood alkaline phosphatase and total bilirubin in males and mild increases in aspartate aminotransferase (AST) and blood potassium in females were observed. As none of the above findings was considered to be adverse, the NOAEL was determined to be 1500 mg/kg/day.

3.(iii).A.(1).2) Rat 14-day oral toxicity study (RD2007/01140)

Dolutegravir sodium was administered orally to SD rats (N = 10/sex/group) at 0 (vehicle), 50, 150, and 500 mg/kg/day for 14 days. There were no deaths. There were increases in urine specific gravity in males given 500 mg/kg/day and in females given 50 and 500 mg/kg/day. As no histopathological changes were observed in the kidneys, the change was not considered toxicologically significant. Mildly increased mucous neck cells, eosinophil infiltration to submucosa, and focal edema in the glandular stomach occurred in males and females given 500 mg/kg/day. These gastric mucosal lesions were mild findings without clinical signs and macroscopic findings. Since the lesions did not adversely affect the general condition of the animal, they were not considered toxicologically significant. Based on the above, the NOAEL was determined to be 500 mg/kg/day.

3.(iii).A.(1).3) Rat 4-week oral toxicity study (RD2008/01628)

Dolutegravir sodium was administered orally to SD rats (N = 10/sex/group) at 0 (vehicle), 2, 10, 100, and 1000 mg/kg/day for 4 weeks. There were no deaths. Increased mucous neck cells in the glandular mucosa of the stomach with globule leukocytes infiltration, edema, and eosinophilic infiltration in submucosa, as well as edema and mixed cellular infiltration in the limiting ridge were noted at ≥100 mg/kg/day. Hemorrhage was observed in the lamina propria of the mucosa at 1000 mg/kg/day. The hemorrhage was considered to be adverse.

---

[22] The $AUC_{0\text{-}24h}$ values were 607 μg·hr/mL in male rats and 922 μg·hr/mL in female rats (a mean of 764.5 μg·hr/mL) and 36.7 μg·hr/mL in male monkeys and 40.9 μg·hr/mL in female monkeys (a mean of 38.8 μg·hr/mL).

[23] Based on pooled analysis of Study ING112276 and Study ING113086 (50 mg QD), the $AUC_{0\text{-}24h}$ was calculated to be 53.6 μg·hr/mL. Based on pooled analysis of Study ING111762 and Study ING112961 (50 mg BID), the $AUC_{0\text{-}24h}$ was calculated to be 75.1 μg·hr/mL.

[24] Calculations are based on 50 kg human.

All the other gastrointestinal findings were considered nonadverse and due to irritant effects of dolutegravir. All findings were reversible. Based on the above, the NOAEL was determined to be 100 mg/kg/day.

3.(iii).A.(1).4) Rat 26-week oral toxicity study (RD2009/00410)

Dolutegravir sodium was administered orally to SD rats (N = 22 or 28/sex/group) at 0 (vehicle), 5, 50, and 500 mg/kg/day for 26 weeks (for 17 weeks in some animals). There were no deaths. Hemorrhage in the glandular stomach mucosa was observed in 2 of 22 males in the 500 mg/kg/day group, but was not observed after a 4-week recovery period. Macroscopic lesions in the stomach were observed in some animals in the 500 mg/kg/day group. Animals given ≥5 mg/kg/day had slight thickening of the forestomach limiting ridge mucosa, eosinophil infiltration in the glandular stomach submucosa, or increased globule leukocytes and mucous neck cells in the glandular stomach mucosa. These findings were slight and reversible and not considered toxicologically significant. Based on the above, the NOAEL was determined to be 50 mg/kg/day.

3.(iii).A.(1).5) Monkey 14-day oral toxicity study (RD2007/01142)

Dolutegravir sodium was administered orally to cynomolgus monkeys (N = 3/sex/group) at 0, 100, 300, and 1000 mg/kg/day for 14 days. One female in the 1000 mg/kg/day group died on Day 13. Emesis began on Day 2 and diarrhea and decreased activity on Day 5. Subnormal body surface temperature, increases in fibrinogen, alanine aminotransferase (ALT), and urea nitrogen, and decreases in blood Na and Cl were detected immediately prior to death. Treatment-related effects on the digestive tract including emesis, diarrhea, and ulcer in colon were believed to contribute to death. Animals given ≥300 mg/kg/day exhibited persistent decreases in body weight or body weight gain, decreased food consumption, emesis, diarrhea, and decreased activity (at 1000 mg/kg/day). Hematological evaluations showed decreases in the reticulocyte count at ≥300 mg/kg/day and decreases in the platelet count and increases in fibrinogen, a decrease in the reticulocyte ratio (males), prolongation of activated partial thromboplastin time (APTT) (males), and a decrease in the red blood cell count (females) at 1000 mg/kg/day. Clinical chemistry evaluations showed increases in ALT in males at ≥300 mg/kg/day and in females at 1000 mg/kg/day and increases in AST, γ-glutamyl transferase (γ-GTP) (males), total bilirubin, triglycerides (males), urea nitrogen, and creatinine and decreases in Na, Cl, the albumin/globulin ratio, and total cholesterol (females) at 1000 mg/kg/day. Urinalysis revealed decreases in the urinary volume and Na, K (females), and Cl excretion levels at 1000 mg/kg/day. Gross pathology revealed reddish spots in the stomach or colon, small thymus and decreases in the weight of the thymus, brownish discoloration of the mesenteric lymph nodes, and enlargement of the lymph nodes in the abdominal cavity at ≥300 mg/kg/day. Gross pathology also revealed whitish protrusion in the esophagus, reddish spots in the ileum, and increases in the weights of the liver and adrenals at 1000 mg/kg/day. Histopathology revealed atrophy of the mucosal epithelium and cell debris from the crypts of the cecum, colon, and rectum, hemorrhage in the mucosa of the colon, atrophy of acinar cells in the pancreas and parotid glands, a decrease in lipid droplets in zona fasciculata cells in the adrenals, atrophy of the cortex of the thymus, and a decrease in the paracortical lymphocytes of the mesenteric lymph nodes at ≥300 mg/kg/day. Males and females given 1000 mg/kg/day showed a decrease in lymphocytes of the submandibular lymph nodes, renal tubule dilatation, gelatinous bone marrow, and atrophy of the white

pulp in the spleen. Males given 1000 mg/kg/day showed hypertrophy, single cell necrosis, and lobular hepatocyte vacuolation in the liver, hypertrophy of the zona fasciculata of the adrenals, and atrophy of the mucosal epithelium and hemorrhage in the mucosa of the stomach. In the bone marrow examinations, a decrease in the nucleated cell count was noted in 1 of 3 males in the 1000 mg/kg/day group. Based on the above, the NOAEL was determined to be 100 mg/kg/day.

3.(iii).A.(1).6) Monkey 4-week oral toxicity study (RD2008/00107)

Dolutegravir sodium was administered orally to cynomolgus monkeys (N = 3 or 5/sex/group) at 0, 25, 50, and 100 mg/kg/day for 4 weeks. There were no deaths. Clinical signs of vomiting and diarrhea were observed from initiation of dosing. Persistent decreases in body weight or body weight gain and a crouching position were noted in the 100 mg/kg/day group. Decreases in the reticulocyte count, red blood cell count, and platelet count were observed in females given 100 mg/kg/day. A decrease in the reticulocyte count and increases in neutrophil count and its ratio and fibrinogen were observed in males given 100 mg/kg/day. Clinical chemistry evaluations showed increases in urea nitrogen, triglycerides, Ca, K, total protein, and total bilirubin (females) and decreases in Na and Cl (males) in the 100 mg/kg/day group. Urinalysis revealed decreases in Cl excretion level in the 100 mg/kg/day group. Histopathological findings in the 100 mg/kg/day group included slight inflammatory cell infiltration in the lamina propria of the cecum, colon, and rectum, cell debris from the crypts (males), thymic atrophy, acinar cell atrophy in the pancreas, and atrophy of the mucosal epithelium of the cecum and colon (females). These atrophic lesions were accompanied by decreased body weights and considered to be associated with malnutrition. Based on the above, the NOAEL was determined to be 50 mg/kg/day.

3.(iii).A.(1).7) Monkey 38-week oral toxicity study (RD2009/00036)

Dolutegravir sodium was administered orally to cynomolgus monkeys (N = 7 or 9 /sex/group) at 0, 3, 10, 15, and 50[25)] mg/kg/day for 38 weeks (for 17 weeks in some animals). Two of 9 males in the 50 mg/kg/day group were euthanized on Day 55 or died on Day 59 with diarrhea and soft stool, decreased food consumption, body weight loss, hypothermia, bradypnea, enlargement of the adrenals and increased adrenal weight, and small thymus etc. Histopathological findings included mononuclear cell infiltration and hemorrhage in the lamina propria of the cecum and colon and inflammatory cell infiltration in the epithelium in the esophagius and tongue etc. In surviving animals given 50 mg/kg/day (before Day 69), increases in monocyte count and neutrophil count (males) and prolonged APTT (females) were noted. Clinical chemistry changes included decreases in glucose and Cl, increased inorganic phosphorus (males), and an increase in triglycerides (females). Also after the dose was reduced to 30 mg/kg/day, transient diarrhea and soft stool were observed and salivation was observed immediately after dosing, but no decreased food consumption or body weight was noted. At necropsy, red focus and recessed focus in the mucosa of the stomach body, multifocal mononuclear cell infiltration and mild hemorrhage in the lamina propria, and slight multifocal erosions and multifocal epithelial regeneration in the stomach were observed in 1 of 9 females in the 50/30 mg/kg/day group. At the end of the 4-week recovery period, multifocal mononuclear cell infiltration and slight hemorrhage in the lamina propria and multifocal

[25)] The dose level was reduced to 30 mg/kg/day on Day 70 due to two deaths in the 50 mg/kg/day group.

epithelial regeneration in the stomach were observed in 1 of 9 females at 50/30 mg/kg/day. However, the changes in this animal were less severe and there were no active erosions, suggesting regression of changes upon cessation of treatment. In the 15 mg/kg/day group, diarrhea and soft stool were observed in 1 of 7 males and transiently decreased food consumption was also noted. However, these changes resolved during the second half of the dosing period and no body weight change was noted. Thus, the NOAEL was determined to be 15 mg/kg/day.

3.(iii).A.(2) Genotoxicity (4.2.3.3)

Dolutegravir sodium was evaluated for genotoxic potential in the bacterial reverse mutation assay (Ames test), the mouse lymphoma TK assay, and the *in vivo* rat bone marrow micronucleus test (WD2007/00514, WD2007/00515, WD2007/00513). All of these tests produced negative results.

3.(iii).A.(3) Carcinogenicity (4.2.3.4.1)

3.(iii).A.(3).1) Mouse 2-year oral carcinogenicity study (2012N152419)

CD-1 mice (N = 65/sex/group) were orally administered dolutegravirsodium at 0 (water, vehicle), 7.5, 25, or 500 mg/kg/day for 24 months. Dolutegravir had no effect on survival. There were no treatment-related clinical signs or effects on body weight, food consumption, and hematology. There were also no differences in the incidence of neoplastic or non-neoplastic lesions between the dolutegravir and control groups. Thus, dolutegravir was determined not to be carcinogenic in mice.

3.(iii).A.(3).2) Rat 2-year oral carcinogenicity study (2012N152418)

Although SD rats (N = 65/sex/group) were planned to be orally administered dolutegravir sodium at 0 (water, vehicle), 2, 10, or 50 mg/kg/day for 24 months, the control (water) survival reached 20 of 65 females and all females were terminated during Week 95. Dolutegravir had no effect on survival. No effects on body weight, food consumption, ophthalmology, hematology, clinical chemistry, and urinalysis were noted. There were no differences in the incidence of neoplastic or non-neoplastic lesions between the dolutegravir and control groups. Thus, dolutegravir was determined not to be carcinogenic in rats.

3.(iii).A.(4) Reproductive and developmental toxicity (4.2.3.5.1 to 4.2.3.5.4)

A fertility study in male and female rats, embryo-fetal development studies in rats and rabbits, a pre- and postnatal development study in rats, and juvenile toxicity studies in rats were conducted.

3.(iii).A.(4).1) Study of fertility and early embryonic development to implantation (4.2.3.5.1 XD2009/00368)

SD rats (N = 20/sex/group) were orally administered dolutegravir sodium at 0 (vehicle), 100, 300, or 1000 mg/kg/day. Males were treated for 63 to 66 days from 4 weeks prior to mating. Females were treated from 2 weeks prior to mating until Day 7 of gestation. There were no treatment-related effects on fertility or early embryonic development. Thus, the NOAEL was determined to be 1000 mg/kg/day.

3.(iii).A.(4).2) Embryo-fetal development studies

3.(iii).A.(4).2).(a) Rat embryo-fetal development studies (4.2.3.5.2 RD2008/01761 and XD2009/00367)

Dolutegravir sodium was administered orally to pregnant SD rats (N = 20/group) at 0 (vehicle), 100, 300, and 1000 mg/kg/day from gestation day 6 to 17. There were no treatment-related clinical signs or effects on body weight, food consumption, maintenance of pregnancy, and gross findings in dams. Also in fetuses, no treatment-related effects on sex ratio, body weight, or teratogenicity (including visceral and skeletal abnormalities) were observed. Based on the above, the NOAEL for maternal and embryo-fetal toxicity was determined to be 1000 mg/kg/day and systemic exposure at the NOAEL was 37.9 or 27.1 times the expected human exposure for a 50 mg QD or BID dose[23)], respectively.

3.(iii).A.(4).2).(b) Rabbit embryo-fetal development studies (4.2.3.5.2 RD2009/00186 and XD2009/0366)

Dolutegravir sodium was administered orally to pregnant Japanese white rabbits (N = 18-20/group) at 0 (vehicle), 40, 200, and 1000 mg/kg/day from gestation day 6 to 18. In dams in the 1000 mg/kg/day group, suppressed body weight gain and scant or no feces/urine associated with decreased food consumption were observed, but there were no gross lesions noted. In fetuses, no treatment-related effects were noted for viability or teratogenicity (including external, visceral, and skeletal abnormalities) at any dose level. Based on the above, the NOAEL for maternal general toxicity was determined to be 200 mg/kg/day and systemic exposure at 200 mg/kg/day in dams was 0.27 or 0.19 times the expected human exposure for a 50 mg QD or BID dose[23)], respectively. The NOAEL was determined to be 1000 mg/kg/day for maternal reproductive function and fetal toxicity and systemic exposure at 1000 mg/kg/day in dams was 0.56 or 0.40 times the expected human exposure for a 50 mg QD or BID dose[23)], respectively.

3.(iii).A.(4).3) Study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3 2011N121663)

Dolutegravir sodium was administered orally to pregnant SD rats (N = 22/group) at 0 (vehicle), 5, 50, and 1000 mg/kg/day from Day 6 of gestation to Day 20 of lactation. Suppressed body weight gain and decreased food consumption were noted in dams in the 1000 mg/kg/day group during the early stages of the lactation period. Decreased body weights were noted in the F1 generation in the 1000 mg/kg/day group from pre-weaning until adolescence, but there were no treatment-related effects at lower dose levels. Based on the above, the NOAELs were determined to be 50 mg/kg/day for maternal general toxicity and for development of the F1 generation and 1000 mg/kg/day for maternal reproductive functions such as maintenance of pregnancy, delivery, and

nursing.

3.(iii).A.(4).4) Juvenile toxicity study (4.2.3.5.4 CD2010/00023)

Juvenile SD rats (N = 10/sex/group) were orally administered dolutegravir sodium at 0 (vehicle), 0.5, 2, or 75 mg/kg/day from postnatal day 4 through 66. Two of 10 males in the 75 mg/kg/day group were found dead. Although there were no clinical signs or no evidence of gavage trauma, both rats demonstrated a lack of sufficient body weight gain. The deaths were considered test article-related. At 75 mg/kg/day, test article-related decreased body weight gain was noted during the preweaning period and this effect persisted in females also during the postweaning period. However, decreased body weights in females were not associated with delayed bone growth and food consumption was not affected. The decreased body weight was therefore considered attributable to general toxicity of the compound, not due to an effect on developmental growth. Histopathological findings included degeneration/regeneration of the olfactory and/or respiratory epithelium of the nasal cavity of male rats at ≥0.5 mg/kg/day and female rats at 75 mg/kg/day. This was not considered a direct test article effect. In all dose groups, there were no test article-related effects on physical signs, sexual maturation, hematology, urinalysis, clinical chemistry parameters, macroscopic findings, organ weights, or spermatogenesis. There were no test article-related effects on the T cell dependent antibody response to Keyhole Limpet Hemocyanin (KLH) and no effects on lymphocyte subsets (CD4+ and CD8+ T cells, and B cells) and CD4+ or CD8+ T cell receptor Vβ usage in peripheral blood. Based on the above, the NOAEL in juvenile rats was determined to be 2 mg/kg/day.

3.(iii).A.(5) Local tolerance (4.2.3.6)

Skin and ocular irritancy and skin sensitization studies were performed with dolutegravir sodium. Dolutegravir absorbs light in the UV/visible wavelength of 290 to 700 nm, but no skin/ocular findings of concern were observed in clinical or non-clinical studies, suggesting very low risk of phototoxicity. Therefore no phototoxicity studies were performed.

3.(iii).A.(5).1) Irritancy study using reconstituted human epidermal model (ED2010/00004)

Tissue samples were treated with dolutegravir (25 mg/site) for 4 or 24 hours to assess the skin irritation potential of dolutegravir. As a result, dolutegravir was considered to be a non-irritant.

3.(iii).A.(5).2) Skin irritancy study in rabbits (Reference data RD2010/00201)

A skin irritancy study was performed with dolutegravir sodium (0.5 g/site) in male Japanese white rabbits, using the Draize method. Slight erythema was noted at 24 hours after the start of application. Thus, dolutegravir was considered to be a mild skin irritant.

3.(iii).A.(5).3) Irritancy study using reconstituted human corneal model (ED2010/00005)

Tissue samples were treated with dolutegravir (30 mg/site) for 10 or 60 minutes to assess the corneal irritation potential of dolutegravir. Dolutegravir was considered not to be a significant ocular irritant.

3.(iii).A.(5).4) Ocular irritancy study in rabbits (Reference data RD2010/00202)

An ocular irritancy study was performed with dolutegravir sodium (0.1g/eye) in male Japanese white rabbits, using the Draize method. Slight redness was noted at 24 hours after application. Thus, dolutegravir was classified as slightly irritating.

3.(iii).A.(5).5) Mouse local lymph node assays (ED2009/00019 and 2010N109153)

The skin sensitization potential of dolutegravir was determined in female CBA/Ca mice. Following topical application of solutegravir sodium or dolutegravir (0% and 25%) to the ear, no redness was observed and there was no lymphocyte proliferation in the auricular lymph nodes. Thus, dolutegravir was considered to be a non-sensitizer.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) T-cell dependent antibody response study in rats treated orally with dolutegravir sodium for 1 month (4.2.3.7.2 RD2009/00751)

SD rats (N = 10/sex/group) were treated orally with dolutegravir sodium at 0 (vehicle), 10, 100, or 1000 mg/kg/day for 1 month. The rats were given an intravenous injection of KLH on Day 25. Serum immunoglobulin G (IgG) anti-KLH antibody titers on Day 31 were determined to assess the effects of dolutegravir on T-cell dependent antibody response. Increased spleen weight/swelling of the spleen were noted in males at 1000 mg/kg/day. However, these changes in the spleen were not considered toxicologically significant due to a lack of significant histopathological changes in the spleen. No treatment-related effects on IgG anti-KLH antibody titers were noted in any group. Thus, dolutegravir was considered to have no effects on T-cell dependent antibody response.

3.(iii).A.(6).2) Toxicity studies on impurities (3.2.S.4.5, 4.2.3.7.6 2012N153013, WD2010/00483, 2012N105217, 2012N150346)

Synthetic intermediates and potential impurities, gsk001[26)], gsk002, gsk003, gsk004, and gsk005, were positive in the bacterial reverse mutation assay (Ames test) and are of genotoxic concern. These impurities are therefore controlled by specifications so that they do not exceed the threshold of toxicological concern (TTC) of 1.5 μg/day (a maximum daily exposure concentration of 15 ppm).

3.(iii).B Outline of prior assessment by PMDA

3.(iii).B.(1) Gastrointestinal toxicity

Gastrointestinal toxicity was observed in rat and monkey repeat-dose toxicity studies. PMDA asked the prior assessment requestor to explain the reason for the observed differences in the site affected between the animal species and to explain the possibility of characteristic gastrointestinal adverse events occurring in humans taking dolutegravir chronically.

[26)] Positive also in the mouse lymphoma TK assay.

The prior assessment requestor explained as follows:
Gastrointestinal toxicity associated with dolutegravir occurred in both rats and monkeys. Since severe diarrhea occurred in monkeys, lower doses than the doses tolerated by rats were selected for monkeys. Toxicological findings were observed commonly in the stomach of rats, which was considered attributed to the administration of a higher concentration of dolutegravir sodium to rats: The concentration of dolutegravir sodium administered by oral gavage was up to 100 mg/mL in rat 4- and 26-week toxicity studies, in contrast to up to 10 mg/mL in monkey 4- and 38-week toxicity studies. The incidence of lower gastrointestinal symptoms was higher in monkeys than in rats. There was no literature comparing the incidence of diarrhea between rats and monkeys. According to the data from the control group in 28-day repeat-dose toxicity studies performed in the past 3 years at a toxicity testing laboratory, loose stool and staining due to watery stool or moist stool occurred at an incidence of about 15% in primates while these findings were not observed in rats. Furthermore, it is considered that diarrhea tends to occur at a higher incidence in monkeys than in rats, in the absence of drug effects. Thus, the higher incidence of lower gastrointestinal symptoms in monkeys than in rats was considered due to a higher sensitivity of the lower gastrointestinal tract of monkeys compared to rats to adverse effects. The incidences of gastrointestinal adverse events in humans were as follows: In foreign clinical studies, the incidences of upper and lower gastrointestinal adverse events[27] were similar in ART-naïve patients[28] (166 of 980 subjects [17%] and 148 of 980 subjects [15%], respectively). The incidence of lower gastrointestinal adverse events (110 of 564 subjects [20%]) was higher than the incidence of upper gastrointestinal adverse events (50 of 564 subjects [9%]) in ART-experienced patients[29], but the incidence of gastrointestinal adverse events associated with dolutegravir-containing combination regimen was similar to that associated with EFV- or RAL-containing combination regimen (The incidences of upper and lower gastrointestinal adverse events in ART-naïve patients were 14% to 15% and 13% to 20%, respectively, and the incidences of upper and lower gastrointestinal adverse events in ART-experienced patients were 8% and 18%, respectively). Therefore there should be no particular concerns about gastrointestinal safety in clinical use of dolutegravir [see "4.(iii).B.(2).1).(a) Gastrointestinal symptoms"].

PMDA accepted the above explanation.

3.(iii).B.(2) Phototoxicity

PMDA asked the prior assessment requestor to explain the phototoxicity of dolutegravir.

The prior assessment requestor explained as follows:
Of 1571 subjects included in the safety population from foreign clinical studies[30] (median exposure duration [range], 340 days [1-943 days]), 2 subjects had photosensitivity reactions, with a causal relationship to

[27] Nausea and diarrhoea were assumed to be typical upper and lower gastrointestinal adverse events, respectively.
[28] ING112276, ING113086, ING114467
[29] ING112961, ING112574, ING111762
[30] ING112276, ING113086, ING114467, ING111762, ING112961, ING112574

dolutegravir being denied in one of them. Both subjects continued dolutegravir therapy. The times to onset were long, 688 days in one subject and 107 days in the other. Based on these findings, dolutegravir is considered to have very low phototoxic potential. In foreign clinical studies[30], 8 of the 1571 subjects had ocular adverse events for which a causal relationship to dolutegravir could not be denied, which included vision blurred and dry eye. There were no events suggestive of phototoxic damage to the uvea. The above findings indicate that dolutegravir is not phototoxic.

PMDA accepted the prior assessment requestor's explanation.

4. Clinical data

All doses of dolutegravir in this section are expressed in terms of dolutegravir. Human biomaterial studies are described in "3.(ii).A". Unless otherwise specified, pharmacokinetic parameters are expressed as the mean or the geometric mean.

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

As biopharmaceutic data, the results from 3 relative bioavailability (BA) studies in foreign subjects, 2 relative BA and food effect studies in foreign subjects, and 1 food effect study in foreign subjects were submitted. The main relative BA and food effect studies are described in this section.

High performance liquid chromatography/tandem mass spectrometry (HPLC-MS/MS)[31] was used for determination of dolutegravir concentrations in humans.

4.(i).A.(1) Relative BA and food effect

4.(i).A.(1).1) Study with oral suspension and tablet formulation (5.3.3.1, Study ING111322 [February 2008 to June 2008])

A three-period, crossover study[32] was conducted in foreign healthy adult men and women (12 subjects included in pharmacokinetic assessment) to assess the relative BA of a single 20 mg oral dose of dolutegravir administered as an oral suspension compared to a tablet formulation (10 mg/tablet) under fasted conditions[33] and the relative BA of a single 20 mg oral dose of the dolutegravir tablet formulation when given with or without a standard meal (30% fat/669 kcal).

Following administration of the oral suspension and the tablet formulation under fasted conditions, the plasma dolutegravir AUCs from time zero extrapolated to infinite time ($AUC_{0-\infty}$) were 33.5 and 23.5 μg·h/mL,

[31] The lower limit of quantification was 1 ng/mL in Studies ING113097, ING113125, and ING116070, 5 ng/mL in Studies ING111207, ING111322, ING111405, ING111521, ING111602, ING111603, ING111604, ING111853, ING111854, ING111856, ING112276, ING112934, ING112941, and ING112961, and 20 ng/mL in Studies ING111762, ING111855, ING112574, ING113068, ING113086, ING113096, ING113097, ING113099, ING113125, ING113674, ING114005, ING114556, ING114581, ING114819, ING115381, ING115696, ING115697, ING115698, ING116070, and LAI116181.

[32] There was a washout of at least 5 days between treatments.

[33] Subjects were to be fasted from 10 hours before receiving study drug.

respectively, the C_{max} values were 2.24 and 1.30 μg/mL, respectively. The least-squares mean ratios of $AUC_{0-\infty}$ and C_{max} for the tablet formulation vs. the oral suspension (90% confidence interval [CI]) were 0.70 (0.64, 0.76) and 0.58 (0.53, 0.64), respectively. Following administration of the tablet formulation under fasted conditions and after a standard meal, the plasma dolutegravir $AUC_{0-\infty}$ values were 23.5 and 26.0 μg·h/mL, respectively, and the C_{max} values were 1.30 and 1.44 μg/mL, respectively. The least-squares mean ratios of $AUC_{0-\infty}$ and C_{max} for the tablet formulation administered after a standard meal vs. under fasted conditions (90% CI) were 1.11 (1.02, 1.21) and 1.11 (1.01, 1.22), respectively.

4.(i).A.(1).2) Study with tablet formulations used in phase II or III clinical studies (5.3.1.2, Study ING113674 [April 2010 to July 2010])

A three-period, crossover study[32)] was conducted in 22 foreign healthy adult men and women (Part A, 22 subjects included in pharmacokinetic assessment; Part B [34)], 18 subjects included in pharmacokinetic assessment) to assess the relative BA of three different tablet formulations of dolutegravir (AW, AX, AP; all 25-mg tablets) (the relative BA of AW or AX vs. AP used in phase II clinical studies) in Part A and the effect of food on the BA of formulation AW in Part B.

In Part A, three tablet formulations were administered as single 50 mg oral doses of dolutegravir under fasted conditions. The plasma dolutegravir $AUC_{0-\infty}$ values after administration of formulations AP, AW, and AX were 53.2, 50.6, and 53.7 μg·h/mL, respectively, the C_{max} values were 2.67, 2.64, and 2.77 μg/mL, respectively. The least-squares mean ratios of $AUC_{0-\infty}$ and C_{max} for AP vs. AW (90% CI) were 0.96 (0.87, 1.05) and 1.00 (0.91, 1.10), respectively. The least-squares mean ratios of $AUC_{0-\infty}$ and C_{max} for AP vs. AX (90% CI) were 1.02 (0.92, 1.12) and 1.05 (0.95, 1.15), respectively. In Part B, subjects received a single 50 mg oral dose of dolutegravir (AW, 25 mg/tablet) under fasted or fed conditions, including low-fat (7% fat/300 kcal), moderate-fat (30% fat/600 kcal), and high-fat (53% fat/870 kcal) meals. After administration under fasted conditions and with a low-fat, moderate-fat, and high-fat meal, the plasma dolutegravir $AUC_{0-\infty}$ values were 50.3, 66.7, 71.0, and 83.6 μg·h/mL, respectively, the C_{max} values were 2.65, 3.88, 4.03, and 4.44 μg/mL, respectively. The least-squares mean ratios of $AUC_{0-\infty}$ for low-fat, moderate-fat, and high-fat meals vs. fasting (90% CI) were 1.33 (1.21, 1.45), 1.41 (1.29, 1.55), and 1.66 (1.52, 1.82), respectively, and the least-squares mean ratios of C_{max} were 1.46 (1.34, 1.60), 1.52 (1.39, 1.66), and 1.67 (1.53, 1.83), respectively. The times to C_{max} (t_{max} [median]) were 3, 4, and 5 hours, respectively.

4.(i).A.(2) Food effect study (5.3.3.4, Study ING112941 [July 2009 to September 2009])

A three-period, crossover study[35)] was conducted in foreign healthy adult men and women (12 subjects included in pharmacokinetic assessment) to assess the effect of a high-fat meal (53% fat/869 kcal) on the pharmacokinetics of a single 50 mg oral dose of a dolutegravir tablet formulation (AP, 25 mg/tablet). As a result, following administration under fasted conditions and after a high-fat meal, the plasma dolutegravir $AUC_{0-\infty}$

[34)] Subjects who completed Part A were enrolled.
[35)] There was a washout of at least 5 days between treatments. In this study, drug interactions with omeprazole were also assessed [see "4.(ii).A.(4) Drug interaction studies"].

values were 34.7 and 67.2 μg·h/mL, respectively, the C_{max} values were 1.84 and 3.39 μg/mL, respectively. The least-squares mean ratios of $AUC_{0-\infty}$ and C_{max} for fed administration vs. fasted administration (90% CI) were 1.94 (1.63, 2.30) and 1.84 (1.55, 2.19), respectively.

4.(i).B Outline of prior assessment by PMDA

4.(i).B.(1) Food effect

Although the dosage and administration section of the proposed package insert states that dolutegravir may be taken with or without food, food increased the $AUC_{0-\infty}$ and C_{max} of plasma dolutegravir. PMDA asked the prior assessment requestor to explain whether the timing of taking dolutegravir relative to meals should be specified.

The prior assessment requestor explained as follows:

The solubility of dolutegravir sodium was 0.021, 0.170, and 0.239 mg/mL at pH 1.2, 5.0, and 6.5 (the physiological pH range), respectively, and the dissolution rates[36] of the tablets were 5% to 80% (i.e., ≤85%) at 15 or 20 minutes. Dolutegravir sodium was therefore considered to be poorly soluble and slow dissolution in the gastrointestinal tract was expected and it was considered that food may affect the BA of dolutegravir. However, a high-fat meal (53% fat/870 kcal) increased the C_{max} and AUC up to approximately 1.7-fold in Study ING113674, and the total calorie and fat content of meals in foreign late phase II and phase III studies[37] were not expected to exceed those of a high-fat meal in Study ING113674. The timing of taking dolutegravir relative to meals was therefore not specified in these study plans. These studies assessed the relationship between dolutegravir exposure and the occurrence of the most common adverse events such as diarrhoea, headache, nausea, and abdominal pain. As a result, no association was shown, and these adverse events were considered unrelated to increased dolutegravir exposure. In an early phase II study (ING111521), the clinical dose of dolutegravir (50 mg QD) under fasted conditions appeared to be on the plateau of the exposure-efficacy (the change from baseline to Day 11 in plasma HIV-1 RNA) relationship after 10 days of monotherapy. Thus, the prior assessment requestor considered that dolutegravir may be taken without regard to meals, also from an efficacy and safety point of view.

Food was shown to increase plasma dolutegravir concentrations, and the possibility that food affects the efficacy and safety of dolutegravir cannot be denied. However, there was no association between increased plasma dolutegravir concentrations and adverse events, and the clinical dose of dolutegravir (50 mg QD) under fasted conditions also appeared to be on the plateau of the exposure-efficacy relationship. PMDA therefore accepted the above explanation by the prior assessment requestor.

---

[36] Media of pH 1.2, 4.5, and 6.8 and paddle speeds were 900 mL 0.1 M HCl (0.25% w/v SDS) and 100 rpm; 900 mL USP acetate buffer and 50 rpm; and 900 mL 0.01 M phosphate buffer (0.25% w/v SDS) and 50 rpm, respectively.

[37] In Study ING114467, Atripla as a comparator [EFV/tenofovir disoproxil fumarate (TDF)/emtricitabine (FTC)] was to be administered under fasted conditions at bedtime and taking account of the double-blind comparative design of the study, all study drugs were to be administered in the same manner. The timing of taking dolutegravir or a comparator was not specified in other studies.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The following pharmacokinetic data were submitted: the results from 1 phase I study in Japanese healthy adult subjects, 7 phase I studies in foreign healthy adult subjects, 1 QT/QTc study in foreign healthy adult subjects, 16 pharmacokinetic studies in foreign healthy adult subjects, 2 pharmacokinetic studies in foreign subjects with hepatic or renal impairment, and 8 phase II and III studies in foreign patients.

4.(ii).A.(1) Healthy adult subject studies

4.(ii).A.(1).1) Phase I study in Japanese healthy adult subjects (5.3.3.3, Study ING115381 [April 2011 to May 2011])

The pharmacokinetics of plasma dolutegravir following a single oral dose of dolutegravir 50 mg in Japanese healthy adult men and women (10 subjects included in pharmacokinetic assessment) under fasted conditions were evaluated. The AUC from time zero to the time of the last quantifiable concentration (AUC_{0-t}) and $AUC_{0-\infty}$ were 41.87 and 43.38 μg·h/mL, respectively. The C_{max}, the plasma dolutegravir concentration at 24 hours post-dose (C_{24h}), and the plasma concentration at the time of the last quantifiable concentration (C_t) were 2.14, 0.67, and 0.068 μg/mL, respectively. The t_{max} (median [range]) was 3.00 (2.00-4.00) hours, the $t_{1/2}$ was 14.6 hours, and the apparent oral clearance (CL/F) was 1.15 L/h.

4.(ii).A.(1).2) Phase I studies in foreign healthy adult subjects

4.(ii).A.(1).2).(a) Single-dose studies (5.3.3.1, Study ING111207 [November 2007 to February 2008]; 5.3.3.4, Study ING112941 [July 2009 to September 2009])

The pharmacokinetics of plasma dolutegravir were evaluated following single oral suspension doses of 2, 5, 10, 25, 50, and 100 mg in foreign healthy adult men and women (16 subjects included in pharmacokinetic assessment [8 subjects per cohort]) under fasted conditions.

The results are shown in Table 18 and plasma dolutegravir exposures increased dose-proportionally over the tested dose range of 2 to 100 mg.

Table 18. Pharmacokinetic parameters of plasma dolutegravir following single oral doses of 2 to 100 mg

Dose	2 mg	5 mg	10 mg	25 mg	50 mg	100 mg
N	8	7	8	8	6	5
C_{max} (μg/mL)	0.23 (20)	0.66 (20)	1.23 (9)	2.76 (12)	4.56 (21)	8.14 (12)
t_{max} (h) [a)]	0.63 (0.25-1.00)	0.50 (0.50-1.50)	0.63 (0.25-1.50)	0.75 (0.50-1.50)	1.25 (0.50-3.00)	1.00 (0.75-3.00)
$AUC_{0-\infty}$ (μg.h/mL)	2.78 (26)	8.87 (27)	14.6 (21)	35.2 (30)	73.2 (19)	136 (24)
$t_{1/2}$ (h)	12.7 (20)	14.3 (25)	12.7 (9)	12.7 (21)	14.2 (19)	14.7 (23)
C_{24h} (μg/mL)	0.04 (41)	0.13 (28)	0.20 (34)	0.47 (41)	1.06 (27)	1.80 (33)

Geometric mean (CV%)
a) Median (Range)

The pharmacokinetics of plasma dolutegravir were evaluated following a single oral suspension dose of 250 mg in foreign healthy adult men and women (8 subjects included in pharmacokinetic assessment) under fasted conditions. The $AUC_{0-\infty}$ was 278 μg·h/mL. The C_{24h} and C_{max} were 4.08 and 14.1 μg/mL, respectively. The $t_{1/2}$

was 14.5 hours. The t_{max} (median [range]) was 2.5 (1.50-4.00) hours.

4.(ii).A.(1).2).(b) Repeat-dose study (5.3.3.1, Study ING111322 [February 2008 to June 2008])

Foreign healthy adult men and women (26 subjects included in pharmacokinetic assessment) received oral suspension doses of dolutegravir 10, 25, and 50 mg [38)] QD under fasted conditions for 10 days. The pharmacokinetics of plasma dolutegravir were evaluated.

The results are shown in Table 19 and plasma concentrations of dolutegravir reached steady state by approximately 5 days of dosing.

Table 19. Pharmacokinetic parameters of plasma dolutegravir following 10-day oral administration of 10 to 50 mg

Dose		10 mg	25 mg (+ Midazolam) [b)]	50 mg
N		8	10	8
Day 1	C_{max} (μg/mL)	1.24 (12)	2.66 (21)	4.52 (20)
	t_{max} (h) [a)]	0.50 (0.50-1.00)	1.00 (0.50-2.00)	0.75 (0.50-1.00)
	AUC_{0-24h} (μg.h/mL)	11.8 (7)	31.0 (21)	53.9 (23)
	$AUC_{0-\infty}$ (μg.h/mL)	15.8 (12)	43.1 (28)	75.8 (28)
	$t_{1/2}$ (h)	11.8 (19)	12.6 (17)	12.6 (14)
	C_{24h} (μg/mL)	0.23 (19)	0.65 (33)	1.18 (32)
Day 10	C_{max} (μg/mL)	1.47 (24)	3.09 (26)	6.16 (15)
	t_{max} (h) [a)]	0.50 (0.25-2.00)	1.00 (0.50-2.00)	1.00 (0.50-2.00)
	$AUC_{0-\tau}$ (μg.h/mL)	16.7 (15)	38.4 (23)	76.8 (19)
	C_τ (μg/mL)	0.35 (20)	0.84 (33)	1.64 (25)

Geometric mean (CV%)
$AUC_{0-\tau}$, AUC over the dosing interval; C_τ, trough concentration
a) Median (Range)
b) Midazolam 3 mg was co-administered on Day 10.

4.(ii).A.(1).2).(c) Mass balance study (5.3.3.1, Study ING111853 [February 2009 to April 2009])

A mass balance study was conducted in foreign healthy adult men (6 subjects included in pharmacokinetic assessment). Subjects received a single oral suspension dose of dolutegravir (^{14}C-dolutegravir) 20 mg under fasted conditions.

By 144 hours post-dose, 95.6% of the administered radioactivity was recovered, with 64.0% in feces and 31.6% in urine. The blood/plasma concentration ratios between 0.5 hours to 72 hours post-dose ranged from 0.441 to 0.535, and the ratio of plasma dolutegravir $AUC_{0-\infty}$ to total plasma radiocarbon $AUC_{0-\infty}$ ranged from 0.95 to 0.99, demonstrating that dolutegravir is the predominant circulating compound in plasma.

In feces, 53.1% of the dose was excreted unchanged and metabolites M13 (cysteine conjugate) (1.8%) and M1 (N-dealkylation) (1.3%) were detected. In urine, 31.6% of the administered radioactivity was excreted and metabolites M3 (ether glucuronide conjugate) (18.9%), M1 (N-dealkylation) (3.6%), and M7 (oxidation at the benzylic carbon) (3.0%) etc. were detected and unchanged dolutegravir represented <1% of the dose.

[38)] Midazolam 3 mg was co-administered on Day 10 in the 25 mg group only [see "4.(ii).A.(4) Drug interaction studies"].

4.(ii).A.(1).2).(d) Distribution to female and male genital tracts (5.3.3.1, Study ING115465 [August 2011 to April 2012], Study ING116195 [December 2011 to May 2012])

Dolutegravir 50 mg QD was administered orally for 5 to 7 days to foreign healthy adult female subjects (8 subjects included in pharmacokinetic assessment) and the pharmacokinetics in the genital tract were evaluated. The $AUC_{0\text{-}24h}$ values in cervicovaginal fluid, cervical tissue, and vaginal tissue were 6%, 10%, and 9%, respectively, of the plasma $AUC_{0\text{-}24h}$ at steady state.

Dolutegravir 50 mg QD was administered orally for 8 days to foreign healthy adult men (12 subjects included in pharmacokinetic assessment) and the pharmacokinetics in the genital tract were evaluated. The $AUC_{0\text{-}24h}$ values in semen and rectal mucosal tissue were 7% and 17%, respectively, of the plasma $AUC_{0\text{-}24h}$ at steady state.

4.(ii).A.(1).2).(e) Effects of dolutegravir on renal function (5.3.4.1, Study ING114819 [October 2010 to December 2010])

Foreign healthy adult men and women (25 subjects included in pharmacokinetic assessment) took dolutegravir 50 mg QD or BID orally for 14 days. Dolutegravir decreased creatinine clearance (CLcr) by 10% at 50 mg QD and 14% at 50 mg BID, but had no effect on glomerular filtration rate (GFR) or effective renal plasma flow (ERPF).

4.(ii).A.(2) Patient studies

4.(ii).A.(2).1) Treatment-naïve or treatment-experienced, INSTI-naïve patients (5.3.4.2, Study ING111521 [June 2008 to August 2008], Study ING116070 [started in January 2012, ongoing], 5.3.5.1, Study ING112276 [started in July 2009, ongoing], Study ING113086 [started in October 2010, ongoing], Study ING111762 [started in October 2010, ongoing])

Dolutegravir tablets 2, 10, and 50 mg QD were administered orally for 10 days to HIV-infected, treatment-naïve or treatment-experienced, INSTI-naïve, foreign patients (26 subjects included in pharmacokinetic assessment) under fasted conditions. The plasma pharmacokinetics were evaluated.

The results are shown in Table 20 and steady state was reached by Day 7.

Table 20. Pharmacokinetic parameters of dolutegravir following 10-day oral administration of 2 to 50 mg

Dose	2 mg	10 mg	50 mg
N	9	7	10
C_{max} (μg/mL)	0.22 (25)	0.80 (23)	3.34 (16)
t_{max} (h) [a)]	1.00 (0.42-3.00)	1.48 (0.50-3.00)	2.00 (0.97-4.00)
$AUC_{0\text{-}\tau}$ (μg.h/mL)	2.56 (15)	10.1 (20)	43.4 (20)
C_τ (μg/mL)	0.04 (50)	0.19 (25)	0.83 (26)

Geometric mean (CV%)
a) Median (Range)

The reductions in plasma HIV RNA (mean) in the dolutegravir 2, 10, and 50 mg QD groups were 1.51, 2.03, and 2.46 $\log_{10}$ copies/mL, respectively. As antiviral response was found best associated with a pharmacokinetic

parameter C_τ, the EC_{90} was estimated at 0.32 μg/mL based on the E_{max} model describing the relationship between reduction in plasma HIV RNA from baseline to Day 11 and C_τ[39)].

Dolutegravir tablets 10, 25, or 50 mg or EFV 600 mg was administered orally QD in combination with ABC/3TC 600/300 mg or TDF/FTC 300/200 mg for 96 weeks to HIV-infected, treatment-naïve foreign patients (45 subjects included in pharmacokinetic assessment [15 subjects per group]) and the pharmacokinetics were evaluated. The plasma pharmacokinetic parameters at Week 2 are shown in Table 21.

Table 21. Pharmacokinetic parameters following repeat oral doses of 10 to 50 mg

Dose	10 mg	25 mg	50 mg
N	15	15	15
C_{max} (μg/mL)	1.10 (37)	1.71 (43)	3.40 (27)
t_{max} (h) [a)]	2.00 (2.0-4.0)	2.00 (2.0-8.0)	2.00 (1.9-4.0)
$AUC_{0-\tau}$ (μg.h/mL)	16.0 (40)	23.1 (48)	48.1 (40)
C_τ (μg/mL)	0.30 (71)	0.54 (67)	1.20 (62)

Geometric mean (CV%)
a) Median (Range)

Dolutegravir 50 mg was administered orally in combination with ABC/3TC 600/300 mg for 96 weeks to HIV-infected, treatment-naïve, foreign male patients (11 subjects included in pharmacokinetic assessment) and the pharmacokinetics were evaluated. At Week 2, the dolutegravir concentration in the cerebral spinal fluid (median [range]) was 0.0182 (0.0040-0.0232) μg/mL, which was 0.11% to 0.66% of the plasma concentration (3.36 μg/mL).

Dolutegravir 50 mg QD or RAL 400 mg BID was administered orally in combination with ABC/3TC 600/300 mg or TDF/FTC 300/200 mg for 96 weeks to HIV-infected, treatment-naïve, foreign patients (399 subjects included in pharmacokinetic assessment). The average pre-dose plasma concentration ($C_{0,\,avg}$) at Week 48 was 1.18 μg/mL. The $C_{0,avg}$ values at Week 48 in the dolutegravir + ABC/3TC (165 subjects) and dolutegravir + TDF/FTC (234 subjects) groups were 1.16 and 1.19 μg/mL, respectively.

Dolutegravir 50 mg QD or RAL 400 mg BID was administered orally in combination with background therapy for 96 weeks to HIV-infected, antiretroviral treatment-experienced, INSTI-naïve, foreign patients (337 subjects included in pharmacokinetic assessment). The $C_{0,\,avg}$ at Week 24 was 0.856 μg/mL. The $C_{0,\,avg}$ at Week 24 by subgroup is shown in Table 22.

39) Based on the data from Study ING111521, PK-PD analysis was performed to explore the relationships between reduction in plasma HIV RNA from baseline to Day 11 and pharmacokinetic parameters (C_τ, $C_{\tau,\,avg}$, C_{min}, C_0, $AUC_{0-\tau}$, C_{max}). The E_{max} model was described by the following equation.
PD Response = $E_{max} * C_\tau / (EC_{50} + C_\tau)$ [E_{max} = 2.6 log, EC_{50} = 35.68 ng/mL]

Table 22. $C_{0,avg}$ (μg/mL) at Week 24 by subgroup

Baseline HIV-1 RNA		
>5×10^4 copies/mL (N = 100)		≤5×10^4 copies/mL (N = 237)
0.843 (129)		0.862 (146)
HBV or HCV co-infection status		
HBV co-infected patients (N = 15)	HCV co-infected patients (N = 28)	Hepatitis negative (N = 277)
1.30 (65)	0.777 (87)	0.857 (140)
Co-administration of metabolic (CYP3A4/UGT) inducers such as tipranavir (TPV)/ritonavir (RTV) and EFV		
Inducers co-administered (N = 16)		Inducers not co-administered (N = 268)
0.169 (209)		0.774 (119)

Geometric mean (CV%)

4.(ii).A.(2).2) INSTI-experienced patients (5.3.5.2, Study ING112961 [started in August 2009, ongoing], Study ING112574 [started in May 2011, ongoing])

Dolutegravir 50 mg QD or BID was administered orally for 96 weeks to HIV-infected, INSTI-experienced foreign patients [48 subjects included in pharmacokinetic assessment (dolutegravir QD, 25 subjects; dolutegravir BID, 23 subjects)]. The pharmacokinetics of plasma dolutegravir on Day 10 and at Weeks 4 and 24 were evaluated (Table 23).

Table 23. Pharmacokinetic parameters of plasma dolutegravir following oral administration of dolutegravir QD or BID

Dose		50 mg QD	50 mg BID
N		25	23
Day 10	C_{max} (μg/mL)	3.04 (38)	5.41 (40)
	t_{max} (h) [a)]	2.97 (1.97-7.92)	2.00 (0.00-7.87)
	$AUC_{0\text{-}24h}$ (μg.h/mL)	36.5 (53)	93.4 (50)
	C_{τ} (μg/mL)	0.69 (91)	2.72 (70)
Week 4	C_0 (μg/mL)	0.57 (100)	2.55 (63)
Week 24	C_0 (μg/mL)	0.38 (114)	2.38 (69)

Geometric mean (CV%)
a) Median (Range)

Dolutegravir 50 mg BID was administered orally in combination with background therapy for 24 weeks to HIV-infected, INSTI-experienced, foreign patients (178 subjects included in pharmacokinetic assessment) and the pharmacokinetics of plasma dolutegravir were evaluated. The $C_{0,\,avg}$ at Week 24 was 2.35 μg/mL. The $C_{0,\,avg}$ at Week 24 by subgroup is shown in Table 24.

Table 24. $C_{0,avg}$ (μg/mL) at Week 24 by subgroup

Baseline HIV-1 RNA		
>10^5 copies/mL (N = 40)		≤10^5 copies/mL (N = 138)
2.45 (80)		2.33 (67)
HBV or HCV co-infection status		
HBV co-infected patients (N = 10)	HCV co-infected patients (N = 25)	Hepatitis negative (N = 141)
2.97 (89)	2.06 (57)	2.41 (67)
Co-administration of metabolic (CYP3A4/UGT) inducers such as TPV/RTV and EFV		
Inducers not co-administered (N = 98)		Inducers co-administered (N = 8)
2.34 (68)		2.21 (30)

Geometric mean (CV%)

PPK analysis was performed using plasma concentrations obtained from 3 foreign clinical studies in HIV-infected, antiretroviral treatment-experienced patients (ING112961, ING112574, ING111762) (574 subjects,

2289 sampling points). Significant factors were identified as follows: body weight, smoking status, albumin, and concomitant use of metabolic inducers on CL/F, body weight and albumin on V/F, and gender and concomitant use of metal-cation containing products on BA.

4.(ii).A.(2).3) Pediatric patients (5.3.5.2, Study ING112578 [started in April 2011, ongoing])

Dolutegravir tablets 35 mg (10-mg tablet and 25-mg tablet) or 50 mg (50-mg tablet)[40] QD was administered orally for 24 weeks to HIV-infected, antiretroviral treatment-experienced, INSTI-naïve, foreign pediatric patients aged ≥6 months and <18 years[41] (10 subjects included in pharmacokinetic assessment). The pharmacokinetics of plasma dolutegravir up to Day 10 were evaluated. The $AUC_{0-\tau}$ was 46 μg·h/mL and the C_{τ} and C_{max} were 0.90 and 3.49 μg/mL, respectively.

4.(ii).A.(3) Intrinsic factor pharmacokinetic studies

4.(ii).A.(3).1) Pharmacokinetic study in subjects with hepatic impairment (5.3.3.3, Study ING113097 [November 2010 to June 2011])

This study evaluated the pharmacokinetics following a single oral dose of dolutegravir 50 mg in foreign healthy adult men and women and foreign male and female subjects with moderate hepatic impairment (Child-Pugh grade B) (8 subjects/group included in pharmacokinetic assessment).

The pharmacokinetic parameters of plasma dolutegravir in healthy adult subjects and subjects with moderate hepatic impairment are shown in Table 25. The least-squares mean ratios of C_{max} and AUC_{0-t} for subjects with moderate hepatic impairment vs. healthy adult subjects (90% CI) were 1.02 (0.75, 1.37) and 1.06 (0.75, 1.48), respectively.

Table 25. Pharmacokinetic parameters of plasma dolutegravir following single dose administration to healthy adult subjects or subjects with moderate hepatic impairment

	Subjects with moderate hepatic impairment	Healthy adult subjects
N	8	8
C_{max} (μg/mL)	1.78 (17)	1.80 (49)
C_{24h} (μg/mL)	0.59 (36)	0.57 (44)
$AUC_{0-\infty}$ (μg.h/mL)	38.5 (30)	37.3 (47)
AUC_{0-t} (μg.h/mL)	36.7 (27)	35.5 (48)
CL/F (L/hr)	1.30 (30)	1.34 (47)
Vz/F (L)	29.1 (18)	28.7 (50)
$t_{1/2}$ (h)	15.5 (19)	14.9 (24)
t_{max} (h) [a]	4.00 (2.0-5.0)	3.00 (1.0-4.0)

Geometric mean (CV%)
Vz/F: apparent volume of distribution after oral administration at terminal phase
a) Median (Range)

4.(ii).A.(3).2) Pharmacokinetic study in subjects with renal impairment (5.3.3.3, Study ING113125 [June 2011 to April 2012])

This study evaluated the pharmacokinetics of plasma dolutegravir following a single oral dose of dolutegravir

[40] Pediatric patients were to receive dolutegravir at approximately 1.0 mg/kg according to weight-based fixed doses: 20 mg for 15-20 kg, 25 mg for 20-30 kg, 35 mg for 30-40 kg, and 50 mg for ≥40 kg. In this study, 9 subjects received dolutegravir 50 mg and 1 subject received dolutegravir 35 mg.
[41] Pediatric patients of 12 to <18 years old were actually enrolled.

50 mg in foreign healthy adult men and women and foreign male and female subjects with severe renal impairment (CLcr <30 mL/min) under fasted conditions (8 subjects/group included in pharmacokinetic assessment).

The pharmacokinetic parameters of plasma dolutegravir in healthy adult subjects and subjects with severe renal impairment are shown in Table 26. The least-squares mean ratios of C_{max} and AUC_{0-t} for subjects with severe renal impairment vs. healthy adult subjects (90% CI) were 0.77 (0.53, 1.13) and 0.61 (0.38, 0.98), respectively.

Table 26. Pharmacokinetic parameters following single dose administration of dolutegravir to healthy adult subjects or subjects with severe renal impairment

	Subjects with severe renal impairment	Healthy adult subjects
N	8	8
C_{max} (µg/mL)	1.50 (34)	1.86 (45)
$AUC_{0-\infty}$ (µg.h/mL)	23.5 (48)	37.1 (58)
AUC_{0-t} (µg.h/mL)	22.6 (47)	35.3 (58)
CL/F (L/hr)	2.12 (48)	1.35 (58)
Vz/F (L)	38.8 (43)	29.9 (44)
$t_{1/2}$ (h)	12.7 (31)	15.4 (15)

Geometric mean (CV%)

4.(ii).A.(4) Drug interaction studies (5.3.3.4, Study ING113099 [May 2011 to November 2011], Study ING115696 [September 2011 to October 2011], Study ING115697 [March 2012 to May 2012], Study ING1115698 [December 2011], Study ING111405 [October 2008 to December 2008], Study ING111602 [January 2009 to March 2009], Study ING111603 [October 2008 to December 2008], Study ING111604 [August 2008 to October 2008], Study ING111854 [April 2009 to June 2009], Study ING111855 [December 2011 to March 2012], Study ING112934 [April 2009 to May 2009], Study ING112941 [July 2009 to September 2009], Study ING113068 [September 2010 to November 2010], Study ING113096 [February 2010 to April 2010], Study ING114005 [March 2010 to May 2010], Study LAI116181 [November 2011 to February 2012])

Sixteen foreign clinical studies were conducted to evaluate drug interactions with dolutegravir.

The ratios of the pharmacokinetic parameters (C_τ or C_{24h}, AUC, C_{max}) of dolutegravir or co-administered drugs (co-administration/monotherapy) and their 90% confidence intervals are shown in Table 27 and Table 28.

Table 27. Effects of dolutegravir on pharmacokinetic parameters of co-administered drugs

Co-administered drug	Dosage regimen		N	Pharmacokinetic parameters of co-administered drug		
	Co-administered drug	Dolutegravir		C_τ or C_{24h}	AUC	C_{max}
Midazolam	3 mg single dose	25 mg QD (suspension)	10	NA	0.95 (0.82, 1.10)	NA
TDF	300 mg QD 5 days	50 mg QD 5 days	15	1.19 (1.04-1.35)	1.12 (1.01-1.24)	1.09 (0.97-1.23)
Methadone	Individualized dose (16-150 mg QD) 5 days	50 mg BID 5 days	11	Total 0.99 (0.91, 1.07)	0.98 (0.91, 1.06)	1.00 (0.94, 1.06)
				R-methadone 0.95 (0.89, 1.02)	0.95 (0.89, 1.02)	0.97 (0.91, 1.03)
				S-methadone 1.02 (0.93, 1.12)	1.01 (0.93, 1.09)	1.03 (0.97, 1.10)
Oral contraceptives [a)]	Norgestimate 0.25 mg 21 days	50 mg BID 21 days	15	0.93 (0.85, 1.03)	0.98 (0.91, 1.04)	0.89 (0.82, 0.97)
	Ethinyl estradiol 0.035 mg 21 days	50 mg BID 21 days	15	1.02 (0.93, 1.11)	1.03 (0.96, 1.11)	0.99 (0.91, 1.08)
RPV	25 mg QD 5 days	50 mg QD 5 days	16	1.21 (1.07, 1.38)	1.06 (0.98, 1.16)	1.10 (0.99, 1.22)

Least-squares mean ratio (90% CI), NA, not available; QD, once daily; BID, twice daily
TDF, Tenofovir disoproxil fumarate; RPV, Rilpivirine
a) Norgestimate and ethinyl estradiol were administered as a combination product (Ortho-Cyclen).

Table 28. Effects of co-administered drugs on pharmacokinetic parameters of dolutegravir

Co-administered drug	Dosage regimen		N	Pharmacokinetic parameters of dolutegravir		
	Co-administered drug	Dolutegravir		C_τ or C_{24h}	AUC	C_{max}
TDF	300 mg QD 5 days	50 mg QD 5 days	15	0.92 (0.82-1.04)	1.01 (0.91-1.11)	0.97 (0.87-1.08)
DRV/RTV	600/100 mg BID 14 days	30 mg QD 14 days	15	0.62 (0.56-0.69)	0.78 (0.72-0.85)	0.89 (0.83-0.97)
LPV/RTV	400/100 mg BID 14 days	30 mg QD 14 days	15	0.94 (0.85-1.05)	0.97 (0.91-1.04)	1.00 (0.94-1.07)
ETR	200 mg BID 14 days	50 mg QD 14 days	15	0.12 (0.09-0.16)	0.29 (0.26-0.34)	0.48 (0.43-0.54)
ETR/LPV/RTV	200/400/100 mg BID 14 days	50 mg QD 14 days	8	1.28 (1.13-1.45)	1.11 (1.02-1.20)	1.07 (1.02-1.13)
ETR/DRV/RTV	200/600/100 mg BID 14 days	50 mg QD 14 days	9	0.63 (0.52-0.76)	0.75 (0.69-0.81)	0.88 (0.78-1.0)
Multivitamins	1 tablet QD	50 mg single dose	16	0.68 (0.56-0.82)	0.67 (0.55-0.81)	0.65 (0.54-0.77)
Maalox	20 mL	50 mg single dose	16	0.26 (0.21-0.31)	0.26 (0.22-0.32)	0.28 (0.23-0.33)
	20 mL (2 hours after dolutegravir administration)	50 mg single dose	16	0.70 (0.58-0.85)	0.74 (0.62-0.90)	0.82 (0.69-0.98)
ATV/RTV	300/100 mg QD 14 days	30 mg QD 14 days	12	2.21 (1.97-2.47)	1.62 (1.50-1.74)	1.34 (1.25-1.42)
ATV	400 mg QD 14 days	30 mg QD 14 days	12	2.80 (2.52-3.11)	1.91 (1.80-2.03)	1.50 (1.40-1.59)
Omeprazole	40 mg QD 5 days	50 mg single dose	12	0.95 (0.75-1.21)	0.97 (0.78-1.20)	0.92 (0.75-1.11)
TPV/RTV	500/200 mg BID 5 days	50 mg QD 5 days	14	0.24 (0.21-0.27)	0.41 (0.38-0.44)	0.54 (0.50-0.57)
EFV	600 mg QD 14 days	50 mg QD 14 days	12	0.25 (0.18-0.34)	0.43 (0.35-0.54)	0.61 (0.51-0.73)

Co-administered drug	Dosage regimen		N	Pharmacokinetic parameters of dolutegravir		
	Co-administered drug	Dolutegravir		C_τ or C_{24h}	AUC	C_{max}
FPV/RTV	700/100 mg BID 10 days	50 mg QD 10 days	12	0.51 (0.41-0.63)	0.65 (0.54-0.78)	0.76 (0.63-0.92)
Rifampicin	600 mg QD 14 days	50 mg BID [a)] 14 days	11	1.22 (1.01, 1.48)	1.33 (1.15, 1.53)	1.18 (1.03, 1.37)
	600 mg QD 14 days	50 mg BID [b)] 14 days	11	0.28 (0.23, 0.34)	0.46 (0.38, 0.55)	0.57 (0.49, 0.65)
Rifabutin	300 mg QD 14 days	50 mg QD 14 days	9	0.70 (0.57, 0.87)	0.95 (0.82, 1.10)	1.16 (0.98, 1.37)
Prednisone	60 mg QD (taper) 10 days	50 mg QD 10 days	12	1.17 (1.06, 1.28)	1.11 (1.03, 1.20)	1.06 (0.99, 1.14)
Boceprevir	800 mg TID 10 days	50 mg QD 10 days	13	1.08 (0.91, 1.28)	1.07 (0.95, 1.20)	1.05 (0.96, 1.15)
Telaprevir	750 mg TID 10 days	50 mg QD 10 days	15	1.37 (1.29, 1.45)	1.25 (1.20, 1.31)	1.19 (1.11, 1.26)
RPV	25 mg QD 5 days	50 mg QD 5 days	16	1.22 (1.15, 1.30)	1.12 (1.05, 1.19)	1.13 (1.06, 1.21)

Least-squares mean ratio (90% CI), TID, thrice daily
DRV, Darunavir; RTV, Ritonavir; LPV, Lopinavir; ETR, Etravirine; ATV, Atazanavir; TPV, Tipranavir; EFV, Efavirenz; FPV, Fosamprenavir; RPV, Rilpivirine
a) Comparison between dolutegravir 50 mg BID + rifampicin vs. dolutegravir 50 mg QD.
b) Comparison between dolutegravir 50 mg BID + rifampicin vs. dolutegravir 50 mg BID.

4.(ii).A.(5) TQTc study (5.3.4.1, Study ING111856 [September 2009 to December 2009])

A single-blind, three-treatment, three-period, crossover study was conducted in foreign healthy adult men and women (42 subjects included in pharmacokinetic assessment) to evaluate the effect of dolutegravir on the QT/QTc interval. Subjects received a single dose of placebo or dolutegravir (suspension) 250 mg or moxifloxacin 400 mg as a positive control.

The largest difference between dolutegravir and placebo in time-matched change from baseline in the corrected QT interval (QTcF) (90% CI) was 1.99 (-0.55, 4.53) msec at 4 hours post-dose, which was below 10 msec, as defined by the ICH E14 criteria. Thus, it was considered that up to 250 mg of dolutegravir does not prolong the QTcF interval. The largest difference between moxifloxacin and placebo in time-matched change from baseline in QTcF (90% CI) was 9.58 (7.05, 12.11) msec at 4 hours post-dose.

4.(ii).B Outline of prior assessment by PMDA

4.(ii).B.(1) Plasma concentrations in patients receiving other anti-HIV agents or with renal impairment

Plasma dolutegravir concentrations were lowered when co-administered with other drugs and in subjects with renal impairment in clinical pharmacology studies. PMDA asked the prior assessment requestor to explain whether dose adjustment of dolutegravir is needed.

The prior assessment requestor explained as follows:

Based on the results of the PK-PD analysis assessing the relationship between dolutegravir C_τ and reduction in plasma HIV RNA in a repeat oral dose study in foreign patients with HIV infection[39)], the EC_{90} was estimated at 0.32 μg/mL. In Study ING112276, the C_τ values at 10 mg QD and 50 mg QD were 0.30 and 1.20 μg/mL, respectively. Thus, a reduction of ≤75% in C_τ was not considered clinically significant and efficacy (antiviral response) was defined as dolutegravir Cτ (geometric mean) of ≥0.3 μg/mL or a ≤75% reduction in dolutegravir Cτ at 50 mg QD (geometric mean) or the ratio of dolutegravir Cτ of 0.25. According to such criteria, whether

dose adjustment would be required was considered, based on the 90% confidence interval of the geometric mean ratio of dolutegravir C_τ. As a result, based on the relationship between C_τ change and reduction in plasma HIV RNA, the prior assessment requestor considered that concomitant use of ETR with dolutegravir should not be recommended and that dolutegravir dose should be adjusted when co-administered with TPV/RTV, EFV, or RIF. On the other hand, decreases in plasma dolutegravir concentrations when co-administered with other drugs in drug interaction studies and in subjects with severe renal impairment were not considered clinically significant due to a ≤75% reduction in C_τ. Clinical data on co-administration of dolutegravir with TPV/RTV or EFV were obtained from Study ING111762 and patients on these metabolic inducers (N = 16) showed dolutegravir C_τ of 0.169 μg/mL (CV%, 209%) as well as a 14% lower antiviral response rate compared to patients not on these inducers. Dolutegravir C_τ following co-administration of dolutegravir 50 mg BID with these inducers is estimated at 1.20 μg/mL, which is higher than the geometric mean C_0 observed in Study ING111762 (0.856 μg/mL). Therefore, it is expected that dolutegravir 50 mg BID in combination with TPV/RTV or EFV would demonstrate comparable antiviral response as observed in Study ING111762. No drug interaction study of nevirapine (NVP) or dolutegravir was performed. However, as co-administration with NVP has the potential to decrease plasma dolutegravir concentrations due to enzyme induction, dolutegravir dose adjustment to 50 mg BID is recommended, as in the case of EFV.

In Study ING112574, a small number of INSTI-resistant patients (N = 8) received dolutegravir 50 mg BID in combination with EFV or TPV/RTV. Dolutegravir C_τ in these subjects was similar to that in other subjects not on these inducers. The response rate at Week 24 in these subjects was 75% (6 of 8 subjects), which was higher than that in the overall population (63%). Therefore, no dose adjustment of dolutegravir is needed. Co-administration of LPV/RTV or DRV/RTV with dolutegravir attenuated the metabolic enzyme induction by ETR in Study ING112934. Thus dolutegravir may be co-administered with ETR without dose adjustment if the patient is receiving concomitant protease inhibitors including LPV/RTV and DRV/RTV. Though no drug interaction study was performed, as ATV/RTV also has the potential to attenuate the metabolic enzyme induction by ETR, dolutegravir may be co-administered with ETR without dose adjustment if the patient is receiving concomitant ATV/RTV.

Taking into account that co-administration with ATV or ATV/RTV increases plasma dolutegravir concentrations, PMDA asked the prior assessment requestor to explain the effect of increased dolutegravir exposure on safety.

The prior assessment requestor explained as follows:
As for the safety of increased dolutegravir exposure when co-administered with ATV or ATV/RTV, co-administration with ATV or ATV/RTV increased blood dolutegravir concentrations, but the incidence of adverse events was unaffected in Studies ING111762 and ING112574. Thus, increased dolutegravir exposure when co-administered with ATV is not considered clinically significant and no dose adjustment of dolutegravir is needed when co-administered with ATV or ATV/RTV.

PMDA considers as follows:
Dolutegravir concentrations may be reduced substantially by concomitant drugs or depending on the patient's condition, which raises concerns about the efficacy of dolutegravir and resistance development in terms of drug exposure, and the association between increased dolutegravir exposure and safety should also be further investigated. However, based on the above explanation by the prior assessment requestor, the proposed dolutegravir dosage regimen showed a certain level of efficacy and there is currently no major concern about drug resistance and safety is not affected significantly. Therefore, the dose adjustment recommendations proposed by the prior assessment requestor are acceptable at present. It is necessary to collect and analyze post-marketing information on efficacy, resistance development, and safety etc. in patients receiving specific concomitant drugs for whom a dose adjustment is recommended and in patients with renal impairment.

The above conclusions will be finalized, taking account of discussions at the prior assessment meeting.

4.(ii).B.(2) Transporter-mediated drug interactions
Co-administration of dolutegravir with dofetilide is contraindicated in the foreign labelings. PMDA asked the prior assessment requestor to explain whether a precautionary statement concerning co-administration with drugs that are substrates for transporters involved in the pharmacokinetics of dofetilide (e.g. metformin) should be included.

The prior assessment requestor explained as follows:
Taking account of the *in vitro* IC_{50} of dolutegravir (1.97 μM) in a cell line expressing the transporter and changes in serum creatinine observed after administration of dolutegravir, dolutegravir may increase dofetilide and metformin exposure. However, based on comparison with the *in vitro* inhibition parameter of cimetidine for which co-administration with dofetilide is contraindicated, doltegravir is expected to have a smaller impact on metformin exposure than cimetidine. Therefore, the likelihood of clinically relevant interactions with drugs that are substrates for the transporter involved in the renal excretion of dofetilide, such as metformin, should be lower with dolutegravir than with cimetidine.

In foreign countries, co-administration of dolutegravir with dofetilide, a class III antiarrhythmic agent, is contraindicated for the following reasons: dofetilide has a very narrow therapeutic window (1-3.5 ng/mL) and is known to be associated with dose-related proarrhythmia, especially serious adverse events including torsade de pointes; and as cimetidine, trimethoprim, ketoconazole, etc. increase plasma dofetilide concentrations by 13% to 97%, co-administration of these drugs with dofetilide is contraindicated.Cco-administration of dolutegravir with dofetilide should also be contraindicated. On the other hand, metformin is a hypoglycemic agent with a wide therapeutic window (0.6-2 μg/mL) and no dose adjustment etc. is advised for cimetidine, trimethoprim, ketoconazole, etc. when co-administered with metformin. Thus, there is no need to contraindicate co-administration of dolutegravir with metformin.

Because dofetilide is not marketed in Japan, the precautionary statement will not be included in the package insert. Co-administration with pilsicainide should be contraindicated for the following reaons: pilsicainide with a similar elimination profile to that of dofetilide is marketed in Japan; ventricular tachycardia, sinus arrest, and ventricular fibrillation etc. have been reported as clinically significant adverse reactions to pilsicainide; and pilsicainide's therapeutic window is narrow (0.2-0.9 μg/mL). Since metformin is started at a lower dose and gradually increased according to blood glucose levels and since hypoglycemia associated with increased systemic exposure is unlikely to occur, it should be stated in the package insert that co-administration with dolutegravir may increase metformin plasma concentrations.

PMDA considers as follows:
PMDA understands the prior assessment requestor's explanation that as pilsicainide has a narrow therapeutic window and a similar renal elimination profile to that of dofetilide, co-administration with dolutegravir may increase pilsicainide plasma concentrations. On the other hand, although the magnitude of the effect of dolutegravir on pilsicainide plasma concentrations is unknown at present, no drugs (including cimetidine, which is considered to have a greater effect on plasma metformin concentrations, and cetirizine, which is one of OCT2 inhibitors including dolutegravir) are contraindicated with pilsicainide and there have so far been no serious safety problems that would contraindicate co-administration of these drugs with pilsicainide. Thus, there is no need to contraindicate co-administration of dolutegravir with pilsicainide. However, it should be noted that dolutegravir has the potential to affect blood concentrations of co-administered drugs via drug-drug interactions mediated by transporters involved in renal excretion, e.g. OCT2 and/or MATEs. Based on the above, the "Precautions for Concomitant Use" section of the package insert should state that co-administration with dolutegravir may increase pilsicainide plasma concentrations and that patients receiving dolutegravir in combination with pilsicainide should be carefully monitored, particularly for the possible occurrence and exacerbation of ventricular tachycardia, sinus arrest, and ventricular fibrillation etc. These events have been reported as clinically significant adverse reactions to pilsicainide.

The above conclusions will be finalized, taking account of discussions at the prior assessment meeting.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The data from clinical studies in HIV-1 infected patients (4 phase II studies and 7 phase III studies) were submitted in the application. The data from 27 phase I studies in foreign healthy adult subjects were also submitted. Furthermore, the data from 2 phase I studies in foreign subjects with renal or hepatic impairment and 1 phase I study in Japanese healthy adult subjects were submitted.

As the main efficacy and safety evaluation data, the results from 2 phase II studies in HIV-1 infected patients (ING112276, ING112961) and 4 phase III studies in HIV-1 infected patients (ING113086, ING111762,

ING114467, ING112574) were submitted. An overview of these studies is presented in Table 29. The results from these studies are summarized in this section.

Table 29. List of efficacy and safety studies

Study identifier (Phase)	Study design	Study population	Dosage regimen of study drug (No. of treated subjects)	Treatment duration	Primary efficacy endpoint	Results
Pivotal efficacy and safety studies						
ING113086 (III)	Randomized, double-blind, active-controlled	HIV-1 infected, treatment-naïve, adult patients	(1) Dolutegravir 50 mg QD or (2) RAL 400 mg BID + 2 NRTIs (ABC/3TC or TDF/FTC) [411 for both (1) and (2)]	96 wks	Proportion of patients with HIV-RNA <50 copies/mL at Week 48	(1) 361/411 (88%) (2) 351/411 (85%)
ING114467 (III)	Randomized, double-blind, active-controlled	HIV-1 infected, treatment-naïve, adult patients	(1) Dolutegravir 50 mg QD+ABC/3TC (2) EFV/TDF/FTC [a] QD [(1) 414, (2) 419]	96 wks	Proportion of patients with HIV-RNA <50 copies/mL at Week 48 (Snapshot)	(1) 364/414 (88%) (2) 338/419 (81%)
ING111762 (III)	Randomized, double-blind, active-controlled	HIV-1 infected, treatment-experienced, INSTI-naïve, adult patients	(1) Dolutegravir 50 mg QD or (2) RAL 400 mg BID + background therapy [(1) 354, (2) 361]	48 wks	Proportion of patients with HIV-RNA <50 copies/mL at Week 24	(1) 281/354 (79%) (2) 252/361 (70%)
ING112574 (III)	Single-arm	HIV-1 infected, INSTI-experienced, adult patients	Dolutegravir 50 mg BID + failing background therapy (to Day 8) followed by Dolutegravir 50 mg BID + optimized background therapy (from Day 8 onwards) (183)	24 wks	Change from baseline in HIV-RNA at Day 8, Proportion of patients with HIV-RNA <50 copies/mL at Week 24	Proportion of patients with HIV-RNA <50 copies/mL at Week 24 72/114 (63%)
Supportive efficacy and safety studies						
ING112961 (II)	Single-arm	HIV-1 infected, treatment-experienced, adult patients with RAL resistance	Dolutegravir 50 mg QD (Cohort I) or BID (Cohort II) + failing background therapy (10 days) followed by (1) Cohort I: Dolutegravir 50 mg QD + optimized background therapy (from Day 11 onwards) (27) or (2) Cohort II: Dolutegravir 50 mg BID + optimized background therapy (from Day 11 onwards) (24)	(1) 96 wks, (2) 48 wks	Proportion of patients with HIV-RNA <400 copies/mL at Day 11 or ≥0.7 $\log_{10}$ copies/mL below baseline value	(1) 9/27 (33%) (2) 17/24 (71%)
ING112276 (II)	Randomized, double-blind, active-controlled	HIV-1 infected, treatment-naïve, adult patients	Dolutegravir [(1)10, (2) 25, (3) 50] mg or (4) EFV 600 mg + (ABC/3TC or TDF/FTC) [(1) 53, (2) 51, (3) 51, (4) 50]	96 wks 24 wks	Proportion of patients with HIV-RNA <50 copies/mL at Week 16	(1) 51/53 (96%) (2) 47/51 (92%) (3) 46/51 (90%) (4) 30/60 (60%)

a) EFV/TDF/FTC 600/300/200 mg: the combination product Atripla (unapproved in Japan)

4.(iii).A.(1) Phase II studies

4.(iii).A.(1).1) Foreign phase II study in HIV-1 infected, foreign adult patients (5.3.5.2, Study ING112961 [started in August 2009, ongoing]) (Data cutoff date, November 2011)

A single-arm study was conducted in HIV-1 infected, antiretroviral treatment-experienced, foreign adult patients with RAL resistance (target sample size, Cohort I, 30 subjects; Cohort II, 20 subjects) at a total of 16 sites in 5 countries including Spain to evaluate the efficacy and safety of dolutegravir.

Subjects in Cohort I were to receive dolutegravir 50 mg QD in addition to their failing antiretroviral regimen (subjects with current RAL virologic failure substituted RAL with dolutegravir 50 mg QD or subjects with historical RAL virologic failure added dolutegravir 50 mg QD to their failing regimen) for 10 days and, from Day 11 onwards, in combination with optimized background therapy including at least one fully active agent. Subjects in Cohort II were to receive dolutegravir 50 mg BID in the same manner as in Cohort I (administered through Week 96).

In Cohort I, all of 27 subjects enrolled into the study received study drug and were included in the Intent-to-treat Exposed Population (ITT-E) and used for the safety and efficacy analyses. In Cohort II, all of 24 subjects enrolled into the study received study drug and were included in the ITT-E population and used for the safety and efficacy analyses.

The primary efficacy endpoint of the proportion of subjects with Day 11 HIV-1 RNA <400 copies/mL or reduced by ≥0.7 $\log_{10}$ copies/mL from baseline was 78% (21 of 27 subjects) in Cohort I and 96% (23 of 24 subjects) in Cohort II.

As for safety, the incidences of adverse events were 96% (26 of 27 subjects) in Cohort I and 96% (23 of 24 subjects) in Cohort II. Adverse events reported by ≥3 subjects and those for which a causal relationship to study drug could not be denied (adverse drug reactions) are shown in Table 30.

Table 30. Adverse events reported by ≥3 subjects and adverse drug reactions

	Cohort I		Cohort II	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Mean duration of treatment	60 weeks (Median 86 weeks)		49 weeks (Median 49 weeks)	
No. of evaluable subjects	N = 27		N = 24	
No. of subjects with event	26 (96)	7 (26)	23 (96)	10 (42)
Diarrhoea	5 (19)	2 (7)	9 (38)	1 (4)
Bronchitis	4 (15)	-	4 (17)	-
Pyrexia	4 (15)	-	4 (17)	-
Asthenia	4 (15)	-	2 (8)	-
Cough	2 (7)	-	4 (17)	-
Headache	4 (15)	-	2 (8)	1 (4)
Insomnia	5 (19)	1 (4)	1 (4)	-
Abdominal pain upper	2 (7)	-	3 (13)	-
Constipation	3 (11)	-	2 (8)	-
Arthralgia	4 (15)	-	-	-
Fatigue	1 (4)	1 (4)	3 (13)	-
Gastrooesophageal reflux disease	3 (11)	1 (4)	1 (4)	-
Myalgia	4 (15)	-	-	-
Sinus congestion	-	-	3 (13)	-
Abdominal pain	3 (11)	-	-	-
Pollakiuria	-	-	3 (13)	1 (4)

n (%)

Two subjects in Cohort I (immunoblastic lymphoma and brain tumor, 1 subject each) and 1 subject in Cohort II (completed suicide) died and a causal relationship to study drug was denied for these cases. Serious adverse events occurred in 6 subjects in Cohort I (neurosyphilis, febrile bone marrow aplasia, inflammation, immunoblastic lymphoma, uterine leiomyoma, brain mass, renal failure acute, and dyspnoea, 1 subject each) and 6 subjects in Cohort II (gastroenteritis viral, subcutaneous abscess, anaemia, chest discomfort, diabetes mellitus, haemochromatosis, hypoalbuminaemia, hypokalaemia, demyelinating polyneuropathy, hepatic

fibrosis, and completed suicide, 1 subject each). Adverse events leading to discontinuation occurred in 2 subjects in Cohort I (febrile bone marrow aplasia and brain mass, 1 subject each) and 2 subjects in Cohort II (anaemia, hypoalbuminaemia, hypokalaemia, and completed suicide, 1 subject each).

4.(iii).A.(1).2) Foreign phase II study in HIV-1 infected, foreign adult patients (5.3.5.1, Study ING112276 [started in July 2009, ongoing]) (Data cut-off date, September 2011)

A randomized, double-blind, parallel-group study[42)] was conducted in HIV-1 infected, treatment-naïve, foreign adult patients (target sample size, 200 [50 subjects/group]) at a total of 34 sites in 6 countries including Spain to select the optimal dose of dolutegravir in combination with 2 NRTIs (ABC/3TC or TDF/FTC) and evaluate its efficacy and safety. Existing therapy (EFV + ABC/3TC or EFV + TDF/FTC) served as the control arm.

Dolutegravir (10, 25, 50 mg QD) or EFV 600 mg QD was to be administered orally in combination with background therapy (ABC/3TC 600/300 mg or TDF/FTC 300/200 mg) for 96 weeks.

Of 208 randomized subjects, 205 subjects who received study drug (53 subjects in the dolutegravir 10 mg group, 51 subjects in the dolutegravir 25 mg group, 51 subjects in the dolutegravir 50 mg group, 50 subjects in the EFV group) were included in the ITT-E population and used for the safety and efficacy analyses.

The primary efficacy endpoint of the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 16 using the Time to Loss of Virologic Response (TLOVR) algorithm[43)] was 96% (51 of 53 subjects) in the dolutegravir 10 mg group, 90% (46 of 51 subjects) in the dolutegravir 25 mg group, 92% (47 of 51 subjects) in the dolutegravir 50 mg group, and 58% (29 of 50 subjects) in the EFV group.

As for safety, the incidences of adverse events were 94% (50 of 53 subjects) in the dolutegravir 10 mg group, 90% (46 of 51 subjects) in the dolutegravir 25 mg group, 90% (46 of 51 subjects) in the dolutegravir 50 mg group, and 92% (46 of 50 subjects) in the EFV group. The incidences of adverse drug reactions were 49% (26 of 53 subjects) in the dolutegravir 10 mg group, 37% (19 of 51 subjects) in the dolutegravir 25 mg group, 55% (28 of 51 subjects) in the dolutegravir 50 mg group, and 62% (31 of 50 subjects) in the EFV group. Adverse events and/or adverse drug reactions reported by ≥10% of subjects in any group are shown in Table 31.

[42)] Existing therapy (EFV + ABC/3TC or EFV + TDF/FTC) was given in an open-label manner.
[43)] Appendix B (Time to loss of virologic response algorithm, 2002) of FDA Guidance for industry; HIV RNA Measurements

Table 31. Adverse events and/or adverse drug reactions reported by ≥10% of subjects in any group

	Adverse events				Adverse drug reactions			
	Dolutegravir			EFV	Dolutegravir			EFV
	10 mg	25 mg	50 mg	600 mg	10 mg	25 mg	50 mg	600 mg
No. of evaluable subjects	N = 53	N = 51	N = 51	N = 50	N = 53	N = 51	N = 51	N = 50
No. of subjects with event	50 (94)	46 (90)	46 (90)	46 (92)	26 (49)	19 (37)	28 (55)	31 (62)
Diarrhoea	7 (13)	9 (18)	9 (18)	7 (14)	4 (8)	4 (8)	5 (10)	3 (6)
Nausea	10 (19)	7 (14)	6 (12)	6 (12)	7 (13)	6 (12)	6 (12)	3 (6)
Nasopharyngitis	8 (15)	8 (16)	6 (12)	5 (10)	-	2 (4)	-	1 (2)
Headache	7 (12)	7 (14)	9 (18)	3 (6)	2 (4)	4 (8)	5 (10)	2 (4)
Dizziness	2 (4)	3 (6)	3 (6)	11 (22)	2 (4)	0	3 (6)	9 (18)
Insomnia	0	7 (14)	6 (12)	6 (12)	0	0	3 (6)	5 (10)
Cough	5 (9)	4 (8)	6 (12)	2 (4)	1 (2)	-	-	-
Depression	3 (6)	6 (12)	2 (4)	6 (12)	-	-	-	1 (2)
Influenza	5 (9)	5 (10)	4 (8)	3 (6)	-	-	-	-
Rash	5 (9)	3 (6)	3 (6)	6 (12)	2 (4)	0	2 (1)	5 (10)
Bronchitis	5 (9)	2 (4)	2 (4)	5 (10)	1 (2)	-	-	-
Fatigue	3 (6)	3 (6)	2 (4)	6 (12)	1 (2)	3 (6)	1 (2)	4 (8)
Upper respiratory tract infection	2 (4)	3 (6)	6 (12)	1 (2)	1 (2)	-	-	-

n (%)

One subject in the dolutegravir 10 mg group died (multiple severe injuries due to road traffic accident) and its causal relationship to study drug was denied. The incidences of serious adverse events in the dolutegravir 10 mg, 25 mg, and 50 mg and EFV groups were 6% (3 of 53 subjects), 2% (1 of 51 subjects), 6% (3 of 51 subjects), and 8% (4 of 50 subjects), respectively. Adverse events leading to discontinuation occurred in 1 subject in the dolutegravir 10 mg group (multiple injuries and road traffic accident), 1 subject in the dolutegravir 25 mg group (dyspepsia), 2 subjects in the dolutegravir 50 mg group (Burkitt's lymphoma and lipoatrophy, 1 subject each), and 5 subjects in the EFV group (abnormal dreams [3 subjects]; insomnia, suicide attempt, drug intolerance, fatigue, and drug hypersensitivity, 1 subject each).

4.(iii).A.(2) Phase III studies

4.(iii).A.(2).1) Foreign phase III study in HIV-1 infected, foreign adult patients (5.3.5.1, Study ING113086 [started in October 2010, ongoing]) (Data cut-off date, January 2013)

A randomized, double-blind, parallel-group study was conducted in HIV-1 infected, treatment-naïve, foreign adult patients (target sample size, 822 [411 subjects/group]) at a total of 100 sites in 9 countries including Spain to evaluate the efficacy and safety of dolutegravir in combination with 2 NRTIs. RAL + 2 NRTIs served as the control arm.

Dolutegravir 50 mg QD or RAL 400 mg BID was to be administered orally in combination with FTC/TDF (200/300 mg) or ABC/3TC (600/300 mg) QD as background therapy for 96 weeks.

Of 827 randomized subjects (413 subjects in the dolutegravir group, 414 subjects in the RAL group), 822 subjects (411 subjects each) received study drug and were included in the ITT-E population and used for the safety and efficacy analyses.

The primary efficacy endpoint of the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48[44] was 88% (361 of 411 subjects) in the dolutegravir group and 85% (351 of 411 subjects) in the RAL group; the treatment difference (95% CI) was 2.5 (-2.2, 7.1)%[45] and the lower limit of the 95% confidence interval was above the pre-specified non-inferiority margin (-10%), therefore establishing the non-inferiority of dolutegravir to RAL. The proportions of subjects with HIV-1 RNA <50 copies/mL at Week 96 [44] were 81% (332 of 411 subjects) in the dolutegravir group and 76% (314 of 411 subjects) in the RAL group; the treatment difference (95% CI) was 4.5 (-1.1, 10.0)%.

As for safety, the incidences of adverse events were 85% (349 of 411 subjects) in the dolutegravir group and 85% (349 of 411 subjects) in the RAL group. The incidences of adverse drug reactions were 30% (124 of 411 subjects) in the dolutegravir group and 29% (121 of 411 subjects) in the RAL group. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either group are shown in Table 32.

Table 32. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either group

	Adverse events		Adverse drug reactions	
	Dolutegravir	RAL	Dolutegravir	RAL
No. of evaluable subjects	N = 411	N = 411	N = 411	N = 411
No. of subjects with event	349 (85)	349 (85)	124 (30)	132 (29)
Nausea	60 (15)	56 (14)	40 (10)	45 (11)
Nasopharyngitis	55 (13)	58 (14)	-	-
Diarrhoea	57 (14)	55 (13)	16 (4)	17 (4)
Headache	56 (14)	55 (13)	19 (5)	16 (4)
Upper respiratory tract infection	34 (8)	30 (7)	-	-
Syphilis	22 (5)	27 (7)	-	-
Dizziness	24 (6)	25 (6)	11 (3)	16 (4)
Pyrexia	23 (6)	25 (6)	-	-
Back pain	21 (5)	26 (6)	-	2 (<1)
Bronchitis	24 (6)	22 (5)	-	-
Fatigue	22 (5)	24 (6)	4 (<1)	11 (3)
Cough	23 (6)	22 (5)	-	2 (<1)
Depression	26 (6)	19 (5)	1 (<1)	1 (<1)
Insomnia	25 (6)	19 (5)	6 (1)	2 (<1)
Sinusitis	25 (6)	17 (4)	-	-
Rash	19 (5)	22 (5)	6 (1)	7 (2)
Anogenital warts	17 (4)	23 (6)	-	-
Influenza	16 (4)	24 (6)	-	-
Anxiety	17 (4)	22 (5)	1 (<1)	2 (<1)
Pharyngitis	22 (5)	14 (3)	1 (<1)	-
Oropharyngeal pain	19 (5)	16 (4)	-	1 (<1)
Vomiting	16 (4)	19 (5)	10 (2)	7 (2)
Respiratory tract infection	19 (5)	12 (3)	-	1 (<1)

n (%)

Two deaths occurred (1 subject in the dolutegravir group [a victim of homicide], 1 subject in the RAL group [completed suicide]) and a causal relationship to study drug was denied for both cases.

The incidences of serious adverse events were 10% (41 of 411 subjects) in the dolutegravir group and 12% (48

[44] FDA Snapshot (MSDF) algorithm

[45] Based on Cochran-Mantel Haenszel stratified analysis adjusting for baseline HIV-1 RNA (≤100,000 copies/mL vs. >100,000 copies/mL) and background therapy (ABC/3TC vs. TDF/FTC).

of 411 subjects) in the RAL group. Serious adverse drug reactions occurred in 3 subjects in the dolutegravir group (drug hypersensitivity, arrhythmia, and hepatitis, 1 subject each) and 5 subjects in the RAL group (convulsion, 2 subjects; aphasia, hypersensitivity, diarrhoea, and blood creatine phosphokinase increased, 1 subject each).

Adverse events leading to discontinuation occurred in 10 subjects in the dolutegravir group (hepatitis C and ALT increased, 2 subjects each; AST increased, blood alkaline phosphatase increased, blood bilirubin increased, liver function test abnormal, nausea, vomiting, hepatitis, confusional state, drug hypersensitivity, dizziness, headache, rash, arrhythmia, feeling abnormal, and a victim of homicide, 1 subject each) and 10 subjects in the RAL group (hepatitis C, abscess, atypical mycobacterial infection, influenza, lymphadenitis viral, ALT increased, AST increased, blood creatine phosphokinase increased, nausea, tongue haematoma, hepatitis, hepatotoxicity, completed suicide, suicide attempt, hypersensitivity, convulsion, drug eruption, lymphadenopathy, intentional overdose, and myalgia, 1 subject each).

4.(iii).A.(2).2) Foreign phase III study in HIV-1 infected, foreign adult patients (5.3.5.1, Study ING114467 [started in February 2011, ongoing]) (Data cut-off date, May 2013)

A randomized, double-blind, parallel-group study was conducted in HIV-1 infected, treatment-naïve, foreign adult patients (target sample size, 788 [394 subjects/group]) at a total of 136 sites in 12 countries including Spain to evaluate the efficacy and safety of dolutegravir in combination with ABC/3TC (dolutegravir/ABC/3TC). Atripla (EFV/TDF/FTC) served as the control arm.

Dolutegravir 50 mg plus ABC/3TC (600/300 mg) or Atripla (EFV/TDF/FTC 600/300/200 mg) QD was to be administered orally for 96 weeks.

Of 844 randomized subjects (422 subjects in the dolutegravir/ABC/3TC group, 422 subjects in the Atripla group), 833 subjects who received study drug (414 subjects in the dolutegravir/ABC/3TC group, 419 subjects in the Atripla group) were included in the ITT-E population and used for the safety and efficacy analyses.

The primary efficacy endpoint of the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 [44)] was 88% (364 of 414 subjects) in the dolutegravir/ABC/3TC group and 81% (338 of 419 subjects) in the Atripla group; the treatment difference (95% CI) was 7.4 (2.5, 12.3)%[46)] and the lower limit of the 95% confidence interval was above the pre-specified non-inferiority margin (-10%), therefore establishing the non-inferiority of dolutegravir/ABC/3TC to Atripla. The proportions of subjects with HIV-1 RNA <50 copies/mL at Week 96 [44)] were 77% (319 of 414 subjects) in the dolutegravir/ABC/3TC group and 70% (293 of 419 subjects) in the Atripla group; the treatment difference (95% CI) was 7.3 (1.4, 13.3)%.

[46)] Based on Cochran-Mantel Haenszel stratified analysis adjusting for baseline HIV-1 RNA (≤100,000 copies/mL vs. >100,000 copies/mL) and CD4+ T-lymphocyte count (≤200 cells/mm^3 vs. >200 cells/mm^3).

As for safety, the incidences of adverse events in the dolutegravir/ABC/3TC and Atripla groups were 91% (376 of 414 subjects) and 94% (394 of 419 subjects), respectively, and the incidences of adverse drug reactions were 44% (184 of 414 subjects) and 67% (282 of 419 subjects), respectively. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either group are shown in Table 33.

Table 33. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either group

	Adverse events		Adverse drug reactions	
	Dolutegravir/ABC/ 3TC	Atripla	Dolutegravir/ABC/ 3TC	Atripla
No. of evaluable subjects	N = 414	N = 419	N = 414	N = 419
No. of subjects with event	376 (91)	394 (94)	184 (44)	282 (67)
Dizziness	40 (10)	153 (37)	29 (7)	139 (33)
Diarrhoea	84 (20)	83 (20)	23 (6)	35 (8)
Nasopharyngitis	74 (18)	66 (16)	1 (<1)	-
Headache	63 (15)	63 (15)	24 (6)	31 (7)
Nausea	65 (16)	61 (15)	44 (11)	49 (12)
Fatigue	63 (15)	53 (13)	29 (7)	28 (7)
Insomnia	69 (17)	46 (11)	41 (10)	25 (6)
Abnormal dreams	31 (7)	73 (17)	27 (7)	66 (16)
Upper respiratory tract infection	50 (12)	53 (13)	-	1 (<1)
Rash	19 (5)	60 (14)	4 (<1)	34 (8)
Cough	36 (9)	36 (9)	1 (<1)	2 (<1)
Depression	31 (7)	34 (8)	12 (3)	14 (3)
Anxiety	26 (6)	30 (7)	4 (<1)	11 (3)
Bronchitis	28 (7)	26 (6)	-	-
Pyrexia	26 (6)	27 (6)	-	4 (<1)
Vomiting	26 (6)	24 (6)	9 (2)	11 (3)
Back pain	30 (7)	18 (4)	-	-
Arthralgia	23 (6)	20 (5)	3 (<1)	1 (<1)
Oropharyngeal pain	27 (7)	16 (4)	-	1 (<1)
Syphilis	18 (4)	25 (6)	-	-
Anogenital warts	27 (7)	16 (4)	1 (<1)	-
Gastroenteritis	21 (5)	17 (4)	-	-
Sinusitis	22 (5)	15 (4)	-	-
Somnolence	9 (2)	24 (6)	7 (2)	18 (4)
Influenza	22 (5)	10 (2)	2 (<1)	1 (<1)
Pain in extremity	22 (5)	10 (2)	1 (<1)	-

n (%)

Two subjects in the Atripla group died (renal failure and disseminated intravascular coagulation, 1 subject each) and a causal relationship to study drug could not be denied for renal failure. Serious adverse events occurred in 44 subjects (11%) in the dolutegravir/ABC/3TC group and 51 subjects (12%) in the Atripla group. Events for which a causal relationship to study drug could not be denied occurred in 1 subject in the dolutegravir/ABC/3TC group (drug hypersensitivity) and 9 subjects in the Atripla group (suicidal ideation and syncope, 2 subjects each; bipolar I disorder, depression, visual hallucination, homicidal ideation, paranoia, hypersensitivity, and renal failure, 1 subject each).

Adverse events leading to discontinuation occurred in 14 subjects in the dolutegravir/ABC/3TC group (rash, 2 subjects; abnormal dreams, depression, insomnia, nightmare, depressed level of consciousness, memory impairment, hypersensitivity, drug hypersensitivity, pulmonary tuberculosis, tuberculosis, renal failure, jaw fracture, subdural haematoma, and colon cancer, 1 subject each) and 52 subjects in the Atripla group (dizziness,

8 subjects; fatigue, 7 subjects; abnormal dreams, depression, and headache, 5 subject each; anxiety and nausea, 4 subjects each; insomnia, sleep disorder, somnolence, drug eruption, hypersensitivity, and vertigo, 3 subjects each; nightmare, alopecia, and decreased appetite, 2 subjects each; affect lability, bipolar I disorder, disorientation, visual hallucination, mental disorder, paranoia, suicidal ideation, withdrawal syndrome, cerebrovascular accident, disturbance in attention, hyperaesthesia, hypersomnia, loss of consciousness, neurotoxicity, rash, cold sweat, rash generalised, rash maculo-papular, asthenia, irritability, oedema peripheral, pyrexia, dyspepsia, gastrointestinal pain, lip swelling, vomiting, aspergillosis, hepatitis C, septic shock, renal failure, renal failure chronic, anaemia, disseminated intravascular coagulation, ovarian cancer, cough, pneumonia aspiration, respiratory distress, blood creatinine increased, and arthralgia, 1 subject each).

4.(iii).A.(2).3) Foreign phase III study in HIV-1 infected, foreign adult patients (5.3.5.1, Study ING111762 [started in October 2010, ongoing]) (Data cut-off date, February 2013)

A randomized, double-blind, parallel-group study was conducted in HIV-1 infected, antiretroviral treatment-experienced, INSTI-naïve, foreign adult patients (target sample size, 688 [344 subjects/group]) at a total of 156 sites in 19 countries including the US to evaluate the efficacy and safety of dolutegravir in combination with background therapy. RAL served as the control arm.

Dolutegravir 50 mg QD or RAL 400 mg BID was to be administered orally in combination with background therapy for 48 weeks.

Of 724 randomized subjects (360 subjects in the dolutegravir group, 364 subjects in the RAL group), 719 subjects who received study drug (357 subjects in the dolutegravir group, 362 subjects in the RAL group) were included in the safety analysesdolutegravir. Of the 719 subjects, 4 subjects enrolled at sites that failed to comply with GCP (3 subjects in the dolutegravir group, 1 subject in the RAL group) were excluded. As a result, 715 subjects (354 subjects in the dolutegravir group, 361 subjects in the RAL group) were included in the Modified ITT-E (mITT-E) population and used for the efficacy analyses. After completion of 48 weeks of treatment, subjects randomized to the dolutegravir group had the option of continuing to receive study drug in an open label phase, while subjects randomized to the RAL group were discontinued from the study and received marketed RAL with background therapy.

The primary efficacy endpoint of the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48[44)] was 71% (251 of 354 subjects) in the dolutegravir group and 64% (230 of 361 subjects) in the RAL group; the treatment difference (95% CI) was 7.4 (0.7, 14.2)%[47)] and the lower limit of the 95% confidence interval was above the pre-specified non-inferiority margin (-12%), therefore establishing the non-inferiority of dolutegravir to RAL. At the time of submission of the prior assessment data, the proportions of subjects with HIV-1 RNA <50 copies/mL at Week 24 were presented, which were 79% (281 of 354 subjects) in the dolutegravir group

[47)] Based on Cochran-Mantel Haenszel stratified analysis adjusting for baseline HIV-1 RNA (≤50,000 copies/mL vs. >50,000 copies/mL), DRV/r use without primary PI mutations (yes vs. no), and baseline phenotypic susceptibility score with full sensitivity only (PSSf) of background regimen (≤2 vs. >2).

and 70% (252 of 361 subjects) in the RAL group[44], with a treatment difference (95% CI) of 9.7 (3.4, 15.9)%[47].

As for safety, the incidences of adverse events were 78% (280 of 357 subjects) in the dolutegravir group and 79% (286 of 362 subjects) in the RAL group. The incidences of adverse drug reactions were 20% (73 of 357 subjects) in the dolutegravir group and 23% (85 of 362 subjects) in the RAL group. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either group are shown in Table 34.

Table 34. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either group

	Adverse events		Adverse drug reactions	
	Dolutegravir	RAL	Dolutegravir	RAL
No. of evaluable subjects	N = 357	N = 362	N = 357	N = 362
No. of subjects with event	280 (78)	286 (79)	73 (20)	85 (23)
Diarrhoea	71 (20)	64 (18)	29 (8)	21 (6)
Upper respiratory tract infection	38 (11)	29 (8)	-	-
Headache	33 (9)	31 (9)	7 (2)	7 (2)
Nausea	29 (8)	29 (8)	13 (4)	16 (4)
Cough	33 (9)	24 (7)	1 (<1)	1 (<1)
Influenza	24 (7)	25 (7)	-	-
Nasopharyngitis	23 (6)	22 (6)	1 (<1)	0
Urinary tract infection	26 (7)	18 (5)	-	-
Vomiting	20 (6)	20 (6)	8 (2)	11 (3)
Fatigue	15 (4)	24 (7)	4 (1)	10 (3)
Rash	19 (5)	18 (5)	5 (1)	6 (2)
Arthralgia	10 (3)	18 (5)	-	-
Abdominal pain upper	17 (5)	5 (1)	6 (2)	0

n (%)

Three subjects in the RAL group died (metastatic adenocarcinoma, multi-organ failure, cervix carcinoma) and a causal relationship to study drug was denied for all events.

Serious adverse events occurred in 33 subjects (9%) in the dolutegravir group (suicidal ideation, 4 subjects [1%]; pneumonia, alcohol withdrawal syndrome, depression, suicide attempt, pancreatitis, hepatitis, rhabdomyolysis, and renal failure acute, 2 subjects each [<1%]; gastroenteritis, bronchitis, gastroenteritis viral, histoplasmosis disseminated, joint abscess, Legionella infection, lower respiratory tract infection, lung infection, parvovirus infection, pneumonia viral, toxoplasmosis, tuberculosis liver, mental status changes, alcohol abuse, abdominal pain, pancreatitis relapsing, rectal haemorrhage, hepatotoxicity, liver disorder, back pain, myositis, disseminated intravascular coagulation, methaemoglobinaemia, hyperkalaemia, metastatic neoplasm, alcohol poisoning, fibula fracture, overdose, upper limb fracture, cerebrovascular disorder, nephrolithiasis, respiratory distress, angina pectoris, pyrexia, and immune reconstitution inflammatory syndrome, 1 subject each [<1% each]) and 42 subjects (12%) in the RAL group (pneumonia, 4 subjects; postoperative wound infection, anaemia, dehydration, and cerebrovascular accident, 2 subjects each; gastroenteritis, anal ulcer, bronchopneumonia, cellulitis, cytomegalovirus oesophagitis, disseminated tuberculosis, extrapulmonary tuberculosis, gangrene, gas gangrene, genital herpes, infection, infective myositis, intervertebral discitis, orchitis, pneumonia staphylococcal, progressive multifocal leukoencephalopathy, subcutaneous abscess, wound infection, wound

infection staphylococcal, suicidal ideation, mental status changes, anxiety, depression suicidal, substance abuse, pancreatitis, anal ulcer, intestinal obstruction, oral mucosal blistering, pancreatitis acute, small intestinal obstruction, hepatitis, hepatotoxicity, acute hepatic failure, arthritis, intervertebral disc protrusion, coagulation factor deficiency, hyperglycaemia, lactic acidosis, adenocarcinoma, cervix carcinoma, immunoblastic lymphoma, vulval neoplasm, headache, renal failure acute, alveolar proteinosis, dyspnoea, epistaxis, sinus disorder, aortic arteriosclerosis, arteriosclerosis, hypertension, malignant hypertension, peripheral arterial occlusive disease, cardiomyopathy, coronary artery disease, non-cardiac chest pain, sarcoidosis, cervical dysplasia, uterine haemorrhage, iridocyclitis, blood alkaline phosphatase increased, and rash pruritic, 1 subject each [<1%]). Events for which a causal relationship to study drug could not be denied occurred in 2 subjects in the dolutegravir group (hepatotoxicity, myositis, and renal failure acute, 1 subject each) and 4 subjects in the RAL group (pancreatitis, hepatitis, suicidal ideation, and rash pruritic, 1 subject each).

Adverse events leading to discontinuation occurred in 7 subjects in the dolutegravir group (renal failure acute, 2 subjects; hepatotoxicity, liver disorder, tuberculosis liver, transaminases increased, back pain, myositis, and drug hypersensitivity, 1 subject each) and 13 subjects in the RAL group (hepatotoxicity, acute hepatic failure, hepatitis, extrapulmonary tuberculosis, Helicobacter gastritis, progressive multifocal leukoencephalopathy, gastrooesophageal reflux disease, nausea, oral mucosal blistering, pancreatitis, adenocarcinoma, cervix carcinoma, immunoblastic lymphoma, renal failure acute, blood alkaline phosphatase increased, coagulation factor deficiency, lactic acidosis, suicidal ideation, epistaxis, and rash pruritic, 1 subject each).

4.(iii).A.(2).4) Foreign phase III study in HIV-1 infected, foreign adult patients (5.3.5.1, Study ING112574 [started in May 2011, ongoing]) (Data cut-off date, December 2012)

A single-arm study was conducted in HIV-1 infected, foreign adult patients with treatment failure on an INSTI-containing regimen (target sample size, ≥100[48)]) at a total of 78 sites in 7 countries including Spain to evaluate the efficacy and safety of dolutegravir in combination with optimized background therapy.

Dolutegravir 50 mg BID was to be administered orally with failing background therapy to Day 8 and thereafter with optimized background therapy including at least one fully active agent through Week 24. After completion of 24 weeks of treatment, subjects were to continue to receive dolutegravir until dolutegravir is locally approved and commercially available.

All of 183 subjects enrolled into the study were included in the ITT-E population and used for the safety and efficacy analyses.

The primary efficacy endpoint of the change from baseline in HIV-1 RNA at Day 8 (95% CI) was -1.43 (-1.52, -1.34) $\log_{10}$ copies/mL. The proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 [44)] was 69% (126 of 183 subjects).

[48)] The initial target sample size was 100, which was changed to 150 to 200.

As for safety, the incidence of adverse events was 80% (147 of 183 subjects) and the incidence of adverse drug reactions was 27% (50 of 183 subjects). Adverse events and/or adverse drug reactions reported by ≥5% of subjects are shown in Table 35.

Table 35. Adverse events and/or adverse drug reactions reported by ≥5% of subjects

	Adverse events	Adverse drug reactions
No. of evaluable subjects	N = 183	
No. of subjects with event	161 (88)	50 (27)
Diarrhoea	30 (16)	10 (5)
Cough	19 (10)	-
Headache	19 (10)	9 (5)
Nausea	19 (10)	11 (6)
Pyrexia	15 (8)	1 (<1)
Bronchitis	14 (8)	-
Fatigue	14 (8)	4 (2)
Upper respiratory tract infection	14 (8)	-
Rash	13 (7)	4 (2)
Asthenia	11 (6)	-
Back pain	11 (6)	-
Injection site reaction	11 (6)	-
Insomnia	11 (6)	3 (2)
Nasopharyngitis	11 (6)	-
Arthralgia	10 (5)	2 (1)
Rhinitis	10 (5)	-
Pruritus	9 (5)	-

n (%)

One death occurred (progressive multifocal leukoencephalopathy, 1 subject), but its causal relationship to study drug was denied. Serious adverse events occurred in 31 subjects (pneumonia, 4 subjects; progressive multifocal leukoencephalopathy, pleural effusion, and dehydration. 2 subjects each; cytomegalovirus infection, cytomegalovirus viraemia, Epstein-Barr virus infection, febrile infection, gastroenteritis viral, herpes ophthalmic, herpes zoster, lung infection, oesophageal candidiasis, pneumococcal sepsis, septic shock, streptococcal sepsis, viral infection, cholecystitis acute, cholelithiasis, hepatic cirrhosis, hepatitis acute, hyperbilirubinaemia, cerebrovascular accident, convulsion, nerve compression, syncope, constipation, dysphagia, haematochezia, parotid gland enlargement, rectal haemorrhage, Bowen's disease, Hodgkin's disease recurrent, squamous cell carcinoma, acute respiratory failure, productive cough, pulmonary embolism, atrial flutter, cardiac failure congestive, chest pain, pyrexia, renal failure, renal failure acute, drug eruption, pruritus, rash, immune reconstitution inflammatory syndrome, ALT increased, ovarian mass, and hypertensive emergency, 1 subject each). A causal relationship to study drug could not be denied for hyperbilirubinaemia, ALT increased, syncope, and rash (1 subject each).

Adverse events leading to discontinuation occurred in 6 subjects (3%) (ALT increased, 2 subjects; AST increased, blood creatine phosphokinase increased, liver function test abnormal, drug eruption, pruritus, rash, cholelithiasis, and paraesthesia, 1 subject each).

4.(iii).B Outline of prior assessment by PMDA

4.(iii).B.(1) Efficacy

Taking account of the following discussions, PMDA concluded that the efficacy of dolutegravir in the treatment of HIV-1 infection was demonstrated. However, PMDA considers that it is necessary to continue to collect information on the long-term efficacy of dolutegravir in ongoing foreign clinical studies and appropriately provide information to healthcare professionalsmedical practice as soon as the obtained information is organized.

4.(iii).B.(1).1) HIV-1 infected, antiretroviral treatment-naïve patients

The prior assessment requestor explained the efficacy of dolutegravir in HIV-1 infected, treatment-naïve patients as follows:

In foreign phase III studies in HIV-1 infected, treatment-naïve patients (ING113086, ING114467), the results of the primary efficacy endpoint (the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 [44)]) and virologic failures (protocol-defined virologic failure [PDVF]) [49)] are shown in Table 36. Treatment differences in the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 (95% CI) were 2.5 (-2.2, 7.1)% between the dolutegravir and RAL groups (ING113086) and 7.4 (2.5, 12.3)% between the dolutegravir/ABC/3TC and Atripla groups (ING114467). The lower limit of the 95% confidence interval was above the pre-specified non-inferiority margin (-10.0) in both studies, therefore establishing the non-inferiority of dolutegravir to RAL and the non-inferiority of dolutegravir/ABC/3TC to Atripla.

Table 36. Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 and virologic failures (ITT-E population)

	Study ING113086		Study ING114467	
	Dolutegravir 50 mg QD	RAL 400 mg BID	Dolutegravir (50 mg)/ABC/3TC QD	Atripla (EFV/TDF/FTC 600/200/300 mg) QD
No. of evaluable subjects	N = 411	N = 411	N = 414	N = 419
Proportion of subjects with HIV-1 RNA <50 copies/mL	361 (88%)	351 (85%)	364 (88%)	338 (81%)
Treatment difference (95% CI)	2.5 (-2.2, 7.1)% [a)]		7.4 (2.5, 12.3)% [b)]	
Virologic failure	20 (5%)	31 (8%)	21 (5%)	26 (6%)
HIV-1 RNA ≥50 copies/mL at Week 48	8 (2%)	5 (1%)	6 (1%)	5 (1%)
Discontinued for lack of efficacy	5 (1%)	13 (3%)	7 (2%)	9 (2%)
Discontinued before achieving HIV-1 RNA <50 copies/mL (for reasons other than lack of efficacy)	2 (<1%)	11 (3%)	8 (2%)	12 (3%)
Change in ART	5 (1%)	2 (<1%)	—	—

n (%)

a) Based on Cochran-Mantel Haenszel stratified analysis adjusting for baseline HIV-1 RNA (≤100,000 copies/mL vs. >100,000 copies/mL) and background therapy (ABC/3TC vs. TDF/FTC).

b) Based on Cochran-Mantel Haenszel stratified analysis adjusting for baseline HIV-1 RNA (≤100,000 copies/mL vs. >100,000 copies/mL) and CD4+ T-lymphocyte count (≤200 cells/mm^3 vs. >200 cells/mm^3).

PMDA concluded that dolutegravir 50 mg QD in combination with background therapy demonstrated its efficacy in HIV-1 infected, treatment-naïve patients, because phase III studies in HIV-1 infected, treatment-naïve patients (ING113086, ING114467) established the non-inferiority of dolutegravir to RAL and the non-inferiority of dolutegravir/ABC/3TC to Atripla for the primary endpoint of the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48dolutegravir. PMDA confirmed that there were no major differences in the proportion of subjects with HIV-1 RNA <50 copies/mL between Weeks 48 and 96.

49) Subjects with HIV-1 RNA ≥50 copies/mL at or after Week 24.

4.(iii).B.(1).2) HIV-1 infected, antiretroviral treatment-experienced, INSTI-naïve patients

The prior assessment requestor explained the efficacy of dolutegravir in HIV-1 infected, antiretroviral treatment-experienced, INSTI-naïve patients as follows:

In a phase III study in HIV-1 infected, treatment-experienced, INSTI-naïve patients (ING111762), dolutegravir 50 mg QD or RAL 400 mg BID was administered in combination with optimized background therapy. The results of the primary endpoint of the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 and virologic failures[44] are shown in Table 37. The difference between the dolutegravir and RAL groups in the primary endpoint (95% CI) was 7.4 (0.7, 14.2)%.

Table 37. Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 and virologic failures in HIV-1 infected, antiretroviral treatment-experienced, INSTI-naïve patients (Study ING111762 [mITT-E population])

	Dolutegravir 50 mg QD	RAL 400 mg BID
No. of evaluable subjects	N = 354	N = 361
Proportion of subjects with HIV-1 RNA <50 copies/mL	251 (71%)	230 (64%)
Treatment difference (95% CI)	7.4 (0.7, 14.2)% [a]	
Virologic failure	71 (20%)	100 (28%)
HIV-1 RNA ≥50 copies/mL at Week 24	35 (10%)	48 (13%)
Discontinued for lack of efficacy	19 (5%)	35 (10%)
Discontinued before achieving HIV-1 RNA <50 copies/mL (for reasons other than lack of efficacy)	7 (2%)	7 (2%)
Change in ART	10 (3%)	10 (3%)

n (%)
a) Based on Cochran-Mantel Haenszel stratified analysis adjusting for baseline HIV-1 RNA (≤50,000 copies/mL vs. >50,000 copies/mL), DRV/r use without primary PI mutations, and baseline phenotypic susceptibility score with full sensitivity only (PSSf) of background regimen (≤2 vs. >2).

PMDA concluded as follows:

The difference between the dolutegravir and RAL groups in the primary efficacy endpoint of the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 (95% CI) was 7.4 (0.7, 14.2)% and the lower limit of the 95% confidence interval was above the pre-specified non-inferiority margin (-12%), therefore establishing the non-inferiority of dolutegravir to RAL. The efficacy of dolutegravir 50 mg QD in combination with background therapy in HIV-1 infected, treatment-experienced, INSTI-naïve patients was thus demonstrated.

4.(iii).B.(1).3) HIV-1 infected, INSTI-experienced patients

The prior assessment requestor explained about HIV-1 infected, INSTI-experienced patients as follows:

Two primary efficacy endpoints were selected for a phase III study in HIV-1 infected patients with treatment failure on an INSTI-containing regimen (ING112574). The results are shown in Table 38. The change from baseline in HIV-1 RNA at Day 8 (95% CI) was -1.43 (-1.52, -1.34) $\log_{10}$ copies/mL, showing HIV-1 RNA reduction associated with dolutegravir. The proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24[44] was 69% (126 of 183 subjects). The above findings showed a certain level of efficacy of dolutegravir and indicated that dolutegravir will become a treatment option for HIV-1 infected, INSTI-experienced patients.

Table 38. Results of efficacy endpoints in HIV-1 infected, INSTI-experienced patients and virologic failures (Study ING112574 [mITT-E population])

	Dolutegravir 50 mg BID + background therapy (N = 183)
Change from baseline in HIV-1 RNA at Day 8 (log_{10} copies/mL)	-1.43 (95% CI, -1.52, -1.34)
Proportion of patients with HIV-1 RNA <50 copies/mL at Week 24 (FDA Snapshot [MSDF] algorithm [mITT-E population])	126 (69)
Virologic failure	50 (27)
HIV-1 RNA ≥50 copies/mL at Week 24	28 (15)
Discontinued for lack of efficacy	9 (5)
Discontinued before achieving HIV-1 RNA <50 copies/mL (for reasons other than lack of efficacy)	3 (2)
Change in ART	10 (5)

n (%)

This study (ING112574) was a single-arm study. PMDA asked the prior assessment requestor to explain the efficacy of dolutegravir in HIV-1 infected patients with treatment failure on an INSTI-containing regimen, based on the results of this study.

The prior assessment requestor explained as follows:
HIV-1 infected patients with treatment failure on an INSTI-containing regimen were considered to have an extensive antiretroviral treatment history and limited options for effective background therapy. Selecting a specific comparator was therefore difficult and thus a single-arm design was employed. As a result, the change from baseline in HIV-1 RNA at Day 8 was -1.43 log_{10} copies/mL. There was a reduction in viral load with dolutegravir also in patients with treatment failure, and the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 was 69% (126 of 183 subjects). Therefore, dolutegravir 50 mg BID is considered clinically useful in patients with limited treatment options.

The primary endpoints for Study ING112574 were the change from baseline in HIV-1 RNA at Day 8 and "the proportion of subjects with HIV-1RNA <50 copies/mL at Week 24" and the data up to Week 24 have been reported. PMDA asked the prior assessment requestor to explain the long-term efficacy of dolutegravir in these patients.

The prior assessment requestor explained as follows:
Study ING112574 is ongoing and the 48-week data are available for 114 initially enrolled subjects. The proportions of these subjects with HIV-1 RNA <50 copies/mL at Weeks 24 and 48 were 64% (73 of 114 subjects) and 56% (64 of 114 subjects), respectively, which indicated that dolutegravir generally remained effective for 48 weeks.

PMDA considers as follows:

As explained by the prior assessment requestor, the results from Study ING112574 in HIV-1 infected patients with treatment failure on an INSTI-containing regimen indicated that a certain level of efficacy of dolutegravir 50 mg BID can be expected also in patients with treatment failure on an INSTI-containing regimen. However, the efficacy of dolutegravir is considered to be influenced by HIV-1 IN mutations and patient characteristics including background antiretroviral agents. Therefore, the impact of patient characteristics is discussed in "4.(iii).B.(1).4) Impact of patient characteristics on efficacy" and IN mutations are discussed in "4.(iii).B.(1).5) Development of resistance mutations and its impact on efficacy".

4.(iii).B.(1).4) Impact of patient characteristics on efficacy

The prior assessment requestor explained as follows:

Table 39 shows efficacy (the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48[44)]) by patient characteristics (gender, background regimen (NRTI), baseline HIV-1 RNA, baseline CD4+ T-lymphocyte count, race, age) in phase III studies conducted in HIV-1 infected, treatment-naïve patients (ING113086, ING114467). There was no particular impact of gender, background regimen, or race on the efficacy of dolutegravir. The results were similar between the dolutegravir and control groups.

Table 39. Proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48 by patient characteristics in phase III studies (ING113086, ING114467) [ITT-E population]

	Study ING113086		Study ING114467	
	Dolutegravir 50 mg	RAL 400 mg	Dolutegravir (50 mg)/ABC/3TC	Atripla
No. of evaluable subjects	N = 411	N = 411	N = 414	N = 419
Gender				
Female	53/63 (84)	46/56 (82)	57/67 (85)	47/63 (75)
Male	308/348 (89)	305/355 (86)	307/347 (88)	291/356 (82)
Background NRTIs				
ABC/3TC	145/169 (86)	142/164 (87)	364/414 (88)	
TDF/FTC	216/242 (89)	209/247 (85)		338/419 (81)
Baseline HIV-1 RNA (copies/mL)				
<100,000	267/297 (90)	264/295 (89)	253/280 (90)	238/288 (83)
≥100,000	94/114 (82)	87/116 (75)	111/134 (83)	100/131 (76)
Baseline CD4+ T-lymphocyte count (cells/mm^3)				
<50	5/8 (62)	0/6 (0)	9/13 (69)	12/14 (86)
50 to <200	38/47 (81)	34/44 (77)	36/44 (82)	36/48 (75)
200 to <350	128/144 (89)	118/139 (85)	143/163 (88)	126/159 (79)
350 to <500	111/126 (88)	123/136 (90)	116/131 (89)	105/128 (82)
≥500	79/86 (92)	76/86 (88)	60/63 (95)	59/70 (84)
Race				
Caucasian	306/346 (88)	301/352 (86)	255/284 (90)	238/285 (84)
Black/African American	41/49 (84)	33/39 (85)	80/98 (82)	74/99 (75)
Other than the above	14/16 (88)	17/20 (85)	29/32 (91)	25/34 (74)
East Asian only	2/2	6/6	2/2	1/2
Age				
<50 years of age	324/370 (88)	312/365 (85)	319/361 (88)	302/375 (81)
≥50 years of age	37/41 (90)	39/46 (85)	45/53 (85)	36/44 (82)

n (%)

In addition, the prior assessment requestor explained as follows:

Table 40 shows efficacy (the proportion of patients with HIV-1 RNA <50 copies/mL at Week 48 or 24) by

patient characteristics (gender, baseline HIV-1 RNA, baseline CD4+ T-lymphocyte count, race, age)[50] conducted in phase III studies in HIV infected, antiretroviral treatment-experienced patients (ING111762, ING112574). In Study ING112574, there was a trend for diminished efficacy in patients with high viral load or low CD4+ T-lymphocyte count at baseline in HIV-infected patients with treatment failure on an INSTI-containing regimen.

Table 40. Proportion of subjects with HIV-1 RNA <50 copies/mL by patient characteristics in phase III studies (ING111762 [Week 48], ING112574 [Week 24]) [mITT-E or ITT-E population]

	Study ING111762		Study ING112574
	Dolutegravir 50 mg QD	RAL 400 mg BID	Dolutegravir 50 mg BID
No. of evaluable subjects	N = 354	N = 361	N = 183
Gender			
Female	79/107 (74)	74/123 (60)	30/42 (71)
Male	172/247 (70)	156/238 (66)	96/141 (68)
Baseline HIV-1 RNA (copies/mL)			
<100,000	212/287 (74)	198/288 (69)	112/142 (79)
≥100,000	39/67 (58)	32/73 (44)	14/41 (34)
Baseline CD4+ T-lymphocyte count (cells/mm^3)			
<50	33/62 (53)	30/59 (51)	19/50 (38)
50 to <200	77/111 (69)	76/125 (61)	41/60 (68)
200 to <350	64/82 (78)	53/79 (67)	32/34 (94)
350 to <500	41/56 (73)	42/59 (71)	21/24 (88)
≥500	36/43 (84)	29/39 (74)	13/15 (87)
Race			
White	133/178 (75)	125/175 (71)	91/130 (70)
Black/African American	98/143 (69)	92/160 (58)	32/49 (65)
Other than the above	20/32 (63)	13/25 (52)	3/4 (75)
East Asian only	3/6	3/4	N/A
Age			
<50 years of age	196/269 (73)	172/277 (62)	80/110 (73)
≥50 years of age	55/85 (65)	58/84 (69)	46/73 (63)

n (%)

PMDA considers as follows:

Subgroup analyses of foreign phase III studies (ING113086, ING114467, ING111762, ING112574) showed that the proportion of subjects with HIV-1 RNA <50 copies/mL was lower in patients with high HIV-1 RNA levels or low CD4+ T-lymphocyte count at baseline among HIV-infected patients with treatment failure on an INSTI-containing regimen. Thus, information concerning clinical study results by patient characteristics (baseline HIV-1 RNA and CD4+ T-lymphocyte count) should be appropriately provided. Post-marketing data on efficacy in these patients should continue to be collected, and healthcare professionals should be appropriately informed when new findings have become available.

4.(iii).B.(1).5) Development of resistance mutations and its impact on efficacy

4.(iii).B.(1).5).(a) Emergence of resistant viruses in HIV-1 infected, treatment-naïve patients

The prior assessment requestor explained as follows:

Virologic failures in the dolutegravir groups of phase III studies conducted in HIV-1 infected, treatment-naïve patients (ING113086, ING114467) are shown in Table 41. The rates of virologic failures at Week 48 in the

[50] Since the number of patients who received ABC/3TC or TDF/FTC was <9 in both groups in Study ING111762 and only 2 patients received TDF/FTC only as background therapy in Study ING112574, the results by background NRTI are not presented.

dolutegravir groups were 5% (20 of 411 subjects) in Study ING113086 and 4% (18 of 414 subjects) in Study ING114467, which were similar to or lower than those in the control groups. Although no dolutegravir-associated resistance mutations were observed in any of the subjects, EFV- and RAL-associated resistance mutations emerged in the control groups of these studies.

Table 41. Virologic failures in HIV-1 infected, treatment-naïve patients

	Study ING113086				Study ING114467			
Treatment group	Dolutegravir 50 mg		RAL 400 mg BID		Dolutegravir (50 mg)/ABC/3TC		Atripla	
No. of evaluable subjects	N = 411		N = 411		N = 414		N = 419	
Time point	Week 48	Week 96	Week 48	Week 96	Week 48	Week 96	Week 48	Week 96
Protocol-defined virologic failure	20 (5)	22 (5)	28 (7)	29 (7)	18 (4)	25 (6)	17 (4)	25 (6)
Treatment-emergent mutations in subjects with genotypic/phenotypic data								
Subjects with emergent INSTI resistance mutations	0/8	0/10	1/18 [a)]	1/20 [a)]	0/7 [c)]	0/13 [c)]	0/7	0/10
Subjects with emergent NNRTI resistance mutations	-	-	-	-	0/9	0/17	4/9 [d)]	6/12 [d)]
Subjects with emergent NRTI resistance mutations	0/12	0/14	4/19 [b)]	4/20 [b)]	0/9	0/17	1/9 [e)]	1/12 [e)]

n (%)
a) T97A, E138D, V151I, and N155H
b) A62V (2 subjects), K65R/E, and M184I/V
c) An IN substitution at Week 24 (1 subject) E157Q/P
d) K101E/N (3 subjects) and G190A (2 subjects) plus K101N (2 subjects) at Week 96
e) K65R

PMDA confirmed that no dolutegravir-associated resistance mutations emerged in foreign phase III studies (ING113086, ING114467).

4.(iii).B.(1).5).(b) Resistant viruses in HIV-1 infected, treatment-experienced patients

Table 42 shows virologic failures (PDVF)[51)] in a foreign phase III study conducted in HIV-1-infected, treatment-experienced, INSTI-naïve patients (ING111762) and in a foreign phase III study conducted in HIV-1 infected, INSTI-experienced patients (ING112574). In Study ING111762, emergent INSTI resistance mutations were detected in 2 of 9 subjects with resistance data in the dolutegravir group and in 9 of 27 subjects with resistance data (33%) in the RAL group.

In Study ING112574, the rate of virologic failures was 23% (26 of 114 subjects) and of whom 16 subjects (62%) had a Q148 mutation detected at baseline. Of the 26 subjects with PDVF, 25 subjects had baseline and PDVF resistance data for analysis and 13 of the 25 subjects had treatment-emergent INSTI resistance mutations detected at the time of virologic failure.

[51)] HIV-1 RNA 400 copies/mL at or after Week 24 in Study ING111762; and a <0.5 $\log_{10}$ copies/mL decrease in HIV-1 RNA and HIV-1 RNA 400 copies/mL at Day 8 and HIV-1 RNA 400 copies/mL at or after Week 24 (from Day 9 onwards) in Study ING112574.

Table 42. Virologic failures in HIV-infected, treatment-experienced, INSTI-naïve or INSTI-experienced patients

	HIV-1 infected, treatment-experienced, INSTI-naïve adult patients				HIV-1 infected, INSTI-experienced adult patients	
Study identifier	ING111762				ING112574	
Treatment group	Dolutegravir 50 mg QD		RAL 400 mg BID		Dolutegravir 50 mg BID	
No. of evaluable subjects	N = 354		N = 361		N = 114	N = 183
Time point	Week 24	Week 48	Week 24	Week 48	At the time of submission of prior assessment data	Week 24 for all subjects
Protocol-defined virologic failure	14 (4)	21 (6)	34 (9)	45 (12)	26 (23)	36 (20)
Treatment-emergent mutations in subjects with genotypic/phenotypic data						
Subjects with emergent INSTI resistance mutations	2/9 [a)]	4/17 [b)]	9/27 [c)]	16/38 [d)]	13/25 [e)]	16/31 [f)]

n (%)
a) R263K (2 subjects)
b) T97A, E138T/A, V151I, and R263K (2 subjects)
c) L68V, L74M, E92Q, T97A (3 subjects), G140A/S (2 subjects), Y143R/H/C (3 subjects), Q148H/R (3 subjects), V151I (2 subjects), N155H (5 subjects), E157Q, and G163K
d) L68V, L74M, E92Q, T97A (4 subjects), G140A/S (3 subjects), Y143R/H/C (5 subjects), Q148H/R (5 subjects), V151I (2 subjects), N155H (9 subjects), E157Q, and G163K (2 subjects)
e) E92Q (2 subjects), T97A (6 subjects), E138A/K (5 subjects), G140S (2 subjects), Y143H, S147G, Q148H/K/R (4 subjects), and N155H
f) L74M, E92Q (2 subjects), T97A (8 subjects), E138A/K/T (7 subjects), G140S (2 subjects), Y143H, S147G, Q148H/K/R (4 subjects), N155H, and E157Q

Moreover, in a foreign phase II study (ING112961) and a foreign phase III study (ING112574) in HIV-1 infected, INSTI-experienced patients, the proportion of subjects with HIV-1 RNA <50 copies/mL[44)] by baseline INSTI resistance mutation category[52)] is shown in Table 43.

Table 43. Proportion of subjects with HIV-1 RNA <50 copies/mL by baseline resistance mutation category in HIV-infected, INSTI-experienced patients

Baseline factors	Study ING112961	Study ING112574	
	Week 48/TLOVR (Time to Loss of Virologic Response)	Week 24/Snapshot (MSDF)	
	Cohort II dolutegravir 50 mg BID + BR (N = 24)	Dolutegravir 50 mg BID + BR (N = 114)	Dolutegravir 50 mg BID + BR (N = 183)
INSTI resistance			
Q148 + ≥2	1/2 (50)	0/12	5/21 (24)
Q148 + 1	4/8 (50)	10/20 (50)	19/32 (59)
Mixture or ≥2 primary resistance mutations	1/1 (100)	3/5 (60)	4/8 (50)
N155	6/6 (100)	18/21 (86)	29/33 (88)
Y143	4/6 (67)	10/15 (67)	21/28 (75)
Other	1/1 (100)	N/A	N/A

n (%)

In a foreign phase III study in HIV-1 infected, INSTI-experienced patients (ING112574), diminished virologic responses at Week 24 were observed in patients with Q148 mutations. PMDA asked the prior assessment requestor to explain the clinical relevance of dolutegravir therapy in patients harboring virus with Q148 mutations.

The prior assessment requestor explained as follows:
An analysis of a foreign phase III study in HIV-1 infected, INSTI-experienced patients (ING112574)[53)] showed

[52)] INSTI resistance mutations list: T66A, T66I, E92Q, E92V, T66K, Y143C, Y143H, Y143R, Q148H, Q148K, Q148R, and N155H were defined as primary resistance mutations. H51Y, L68V, L68I, L74I, L74M, L74R, Q95A, T97A, G118R, E138A, E138K, E138T, G140A, G140C, G140S, P145S, S147G, V151I, V151L, S153F, S153Y, E157Q, G163K, G163R, G193E, and R263K were classified as other resistance mutations.
[53)] Based on Week 24 data for all subjects, Week 24 virologic outcome population (161 subjects).

that in patients with Q148 mutations, virologic response at Week 24 decreased with increasing number of secondary mutations[54]. Among 60 subjects with no primary INSTI resistance mutations detected at baseline, the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 was 78% (47 of 60 subjects), demonstrating the efficacy of dolutegravir. In the baseline mutation category Q148 + 1 secondary mutation[54], the proportion of subjects with HIV-1 RNA <50 copies/mL was 65% (20 of 31 subjects), indicating that dolutegravir 50 mg BID has clinical benefits for patients with Q148 + 1 secondary mutation.

On the other hand, in the Q148 + ≥2 secondary mutations category[54], the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 was 25% (4 of 16 subjects), indicating that the activity of dolutegravir may be compromised. Thus, it is necessary to consider other treatments as well prior to the use of dolutegravir in patients with Q148 + ≥2 secondary mutations.

PMDA considers as follows:
In a foreign phase III study in HIV-1 infected, treatment-experienced, INSTI-naïve patients (ING111762), the rate of virologic failures was not markedly higher in the dolutegravir group than in the RAL group.

However, virologic response at Week 24 decreased with increasing number of secondary mutations in subjects with Q148 mutations in a foreign phase III study conducted in HIV-1 infected, INSTI-experienced adult patients (ING112574). It is therefore important to take measures such as resistance testing prior to the use of dolutegravir in patients who have experienced virologic failure on a regimen containing INSTI with cross-resistance.

In the foreign phase III study (ING112574), the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 was low at 24% (4 of 16 subjects) in the baseline INSTI resistance mutation category Q148 + ≥2 secondary mutations. Dolutegravir may thus be inferior in efficacy to similar drugs in patients with such mutations, depending on the pattern of resistance mutations; this information should be provided. Post-marketing data on the association between resistance at baseline and efficacy should continue to be collected.

The above conclusions by PMDA will be finalized, taking account of discussions at the prior assessment meeting.

4.(iii).B.(2) Safety

PMDA evaluated the safety of dolutegravir based on the submitted data from foreign phase II studies (ING112276, ING112961) and foreign phase III studies (ING113086, ING114467, ING111762, ING112574), taking account of the discussions presented below. As a result, PMDA concluded that dolutegravir is generally tolerable. Since there are currently no data from clinical studies in Japanese patients treated with dolutegravir, post-marketing data on the safety of dolutegravir in Japanese patients should be collected.

[54] L74I, E138A/K/T, and G140A/C/S (with or without primary resistance mutations other than Q148 mutations)

4.(iii).B.(2).1) Overview of safety

The prior assessment requestor explained an overview of the safety of dolutegravir as follows:

Table 44 shows adverse events occurring in the dolutegravir and control groups of phase III studies (ING113086 and ING114467, Week 96) and in a phase IIb study (ING112276, Week 48) conducted in HIV-1 infected, treatment-naïve patients.

Table 44. Adverse events reported by ≥5% of subjects in the dolutegravir group (HIV-1 infected, treatment-naïve patients)

Event term	Study ING112276		Study ING113086		Study ING114467		Total Dolutegravir
	Dolutegravir	EFV	Dolutegravir	RAL	Dolutegravir/ABC/3TC	Atripla	
No. of evaluable subjects	N = 155	N = 50	N = 411	N = 411	N = 414	N = 419	N = 980
Any event	142 (92)	46 (92)	349 (85)	349 (85)	376 (91)	394 (94)	867 (88)
Diarrhoea	25 (16)	7 (14)	57 (14)	55 (13)	84 (20)	83 (20)	166 (17)
Nausea	23 (15)	7 (14)	60 (15)	56 (14)	65 (16)	61 (15)	148 (15)
Nasopharyngitis	22 (14)	5 (10)	55 (13)	58 (14)	74 (18)	66 (16)	151 (15)
Headache	23 (15)	3 (6)	56 (14)	55 (13)	63 (15)	63 (15)	142 (14)
Insomnia	13 (8)	6 (12)	25 (6)	19 (5)	69 (17)	46 (11)	107 (11)
Fatigue	8 (5)	6 (12)	22 (5)	24 (6)	63 (15)	53 (13)	93 (9)
Upper respiratory tract infection	11 (7)	1 (2)	34 (8)	30 (7)	50 (12)	53 (13)	95 (10)
Dizziness	8 (5)	11 (22)	24 (6)	25 (6)	40 (13)	153 (37)	72 (7)
Cough	15 (10)	2 (4)	23 (6)	22 (5)	36 (9)	36 (9)	74 (8)
Depression	11 (7)	6 (12)	26 (6)	19 (5)	31 (7)	34 (8)	68 (7)
Pyrexia	11 (7)	4 (8)	23 (6)	25 (6)	26 (6)	27 (6)	60 (6)
Abnormal dreams	3 (2)	4 (8)	13 (3)	8 (2)	31 (7)	73 (17)	47 (5)
Bronchitis	9 (6)	5 (10)	24 (6)	22 (5)	28 (7)	26 (6)	61 (6)
Back pain	8 (5)	4 (8)	21 (5)	26 (6)	30 (7)	18 (4)	59 (6)
Influenza	14 (9)	3 (6)	16 (4)	24 (6)	22 (5)	10 (2)	52 (5)
Rash	11 (7)	6 (12)	19 (5)	22 (5)	19 (5)	60 (14)	49 (5)
Syphilis	5 (3)	4 (8)	22 (5)	27 (7)	18 (4)	25 (6)	45 (5)
Sinusitis	7 (5)	4 (8)	25 (6)	17 (4)	22 (5)	15 (4)	54 (6)
Anogenital warts	3 (2)	0	17 (4)	23 (6)	27 (7)	16 (4)	47 (5)
Pharyngitis	7 (5)	2 (4)	22 (5)	14 (3)	11 (3)	14 (3)	40 (4)
Oropharyngeal pain	6 (4)	1 (2)	19 (5)	16 (4)	27 (7)	16 (4)	52 (5)
Respiratory tract infection	7 (5)	3 (6)	19 (5)	12 (3)	9 (2)	3 (1)	35 (4)
Anxiety	5 (3)	3 (6)	17 (4)	22 (5)	26 (6)	30 (7)	48 (5)
Vomiting	6 (4)	1 (2)	16 (4)	19 (5)	26 (6)	24 (6)	48 (5)
Arthralgia	6 (4)	1 (2)	10 (2)	14 (3)	23 (6)	20 (5)	39 (4)
Gastroenteritis	2 (1)	2 (4)	18 (4)	18 (4)	21 (5)	17 (4)	41 (4)
Pain in extremity	3 (2)	0	7 (2)	10 (2)	22 (5)	10 (2)	32 (3)

n (%)

Table 45 shows adverse events occurring in foreign phase II and III studies conducted in HIV-infected, treatment-experienced, INSTI-naïve or INSTI-experienced patients (ING112961, ING111762, ING112574). Events observed in the dolutegravir group were similar to those in the RAL group. Most of the events were mild to moderate in severity.

Table 45. Adverse events reported by ≥5% of subjects in the dolutegravir group (≥3 subjects in Study ING112961) (HIV-1 infected, treatment-experienced patients)

Event term	Study ING111762		Study ING112574	Study ING112961	Total Dolutegravir
	Dolutegravir	RAL	Dolutegravir	Cohort II Dolutegravir	
No. of evaluable subjects	N = 357	N = 362	N = 183	N = 24	N = 564
Any event	280 (78)	286 (79)	161 (88)	23 (96)	464 (82)
Diarrhoea	71 (20)	64 (18)	30 (16)	9 (38)	110 (20)
Upper respiratory tract infection	38 (11)	29 (8)	14 (8)	2 (8)	54 (10)
Headache	33 (9)	31 (9)	19 (10)	2 (8)	54 (10)
Nausea	29 (8)	29 (8)	19 (10)	2 (8)	50 (9)
Cough	33 (9)	24 (7)	19 (10)	4 (17)	56 (10)
Urinary tract infection	26 (7)	18 (5)	6 (3)	2 (18)	34 (6)
Influenza	24 (7)	25 (7)	3 (2)	0	27 (5)
Nasopharyngitis	23 (6)	22 (6)	11 (6)	0	34 (6)
Fatigue	15 (4)	24 (7)	14 (2)	3 (13)	32 (6)
Vomiting	20 (6)	20 (6)	7 (4)	2 (8)	29 (5)
Rash	19 (5)	18 (5)	13 (7)	1 (4)	33 (6)
Arthralgia	10 (3)	18 (5)	10 (5)	0	20 (4)
Abdominal pain upper	17 (5)	5 (1)	-	3 (13)	20 (4)
Pyrexia	7 (2)	6 (2)	15 (8)	4 (17)	26 (5)
Bronchitis	12 (3)	14 (4)	14 (8)	4 (17)	30 (5)
Asthenia	4 (1)	6 (2)	11 (6)	2 (8)	17 (3)
Back pain	11 (3)	13 (4)	11 (6)	1 (4)	23 (4)
Injection site reaction	0	1 (<1)	11 (6)	2 (8)	13 (2)
Insomnia	12 (3)	14 (4)	11 (6)	1 (4)	24 (4)
Rhinitis	3 (<1)	3 (<1)	10 (5)	2 (8)	15 (3)
Pruritus	6 (2)	8 (2)	9 (5)	1 (4)	16 (3)
Constipation	9 (3)	6 (2)	7 (4)	2 (8)	18 (3)
Sinus congestion	6 (2)	3 (<1)	2 (1)	3 (13)	11 (2)
Pollakiuria	2 (<1)	4 (1)	-	3 (13)	5 (1)

n (%)

PMDA concluded as follows:

There were no major differences in the occurrence of adverse events between the dolutegravir and control groups in foreign phase II and III studies in HIV-infected, treatment-naïve patients (ING112276, ING113086, ING114467). There were also no major differences in adverse events between HIV-infected, antiretroviral treatment-experienced patients in foreign phase II and III studies (ING112961, ING111762, ING112574) and HIV-infected, treatment-naïve patients. Therefore, there should be no particular problem with the safety of dolutegravir. (a) Gastrointestinal symptoms and (b) liver function-related adverse events are discussed separately in the sections below.

4.(iii).B.(2).1).(a) Gastrointestinal symptoms

Treatment-related gastrointestinal irritation was observed in toxicity studies with dolutegravir and the most commonly reported gastrointestinal adverse events were diarrhoea and nausea in foreign phase II studies (ING112276, ING112961) and foreign phase III studies (ING113086, ING111762, ING114467, ING112574). PMDA asked the prior assessment requestor to explain the severity of these events and actions taken etc. and then explain whether these events can have a significant impact on the safety of patients.

The prior assessment requestor explained as follows:

Table 46 and Table 47 show the incidences of diarrhoea, nausea, and vomiting and actions taken in phase II (ING112276) and phase III (ING113086, ING114467) studies conducted in HIV-1 infected, treatment-naïve patients, a phase III study conducted in HIV-1 infected, treatment-experienced, INSTI-naïve patients (ING111762), and phase II (ING112961) and phase III (ING112574) studies in HIV-1 infected, INSTI-experienced patients. The incidences of gastrointestinal adverse events were similar between the dolutegravir and control groups, with no serious events occurring in the dolutegravir groups. Most subjects continued study treatment and the outcome was reported as “resolved” for most cases.

Based on the above, gastrointestinal adverse events following treatment with dolutegravir 50 mg QD or BID have no significant impact on the safety of patients.

Table 46. Summary of diarrhoea, nausea, and vomiting (HIV-1 infected, treatment-naïve patients)

	Study ING112276		Study ING113086		Study ING114467	
	Dolutegravir [e)]	EFV 600 mg	Dolutegravir 50 mg	RAL 400 mg	Dolutegravir (50 mg)/ABC/3TC	Atripla
No. of evaluable subjects	N = 155	N = 50	N = 411	N = 411	N = 414	N = 419
Gastrointestinal adverse events	44 (28)	12 (24)	116 (28)	102 (26)	135 (33)	147 (35)
Diarrhoea [a)]						
Adverse event	25 (16)	7 (14)	57 (14)	55 (13)	84 (20)	83 (20)
Adverse drug reaction	14 (56)	3 (43)	16 (28)	17 (31)	23 (27)	35 (42)
Serious	0	0	0	1 (2)	0	0
Outcome						
Resolved	23 (92)	6 (86)	49 (86)	48 (87)	78 (93)	74 (89)
Resolving	0	0	1 (2)	1 (2)	1 (1)	1 (1)
Not resolved	1 (4)	1 (14)	8 (14)	4 (7)	9 (11)	7 (8)
Resolved with sequelae	1 (4)	1 (14)	1 (2)	2 (4)	0	4 (5)
Action taken						
Study drug continued	24 (96)	6 (86)	57 (100)	53 (96)	83 (99)	83 (100)
Dose interrupted	0	1 (14)	0	2 (4)	1 (1)	0
Others [b)]	1 (4)	0	0	1 (2)	0	1 (<1)
Nausea [c)]						
Adverse event	23 (15)	7 (14)	60 (15)	56 (14)	65 (16)	61 (15)
Adverse drug reaction	19 (83)	4 (57)	40 (67)	45 (80)	44 (68)	49 (80)
Serious	0	0	0	0	0	0
Outcome						
Resolved	20 (87)	7 (10)	55 (92)	50 (89)	57 (88)	52 (87)
Resolving	0	0	2 (3)	0	2 (3)	1 (2)
Not resolved	1 (4)	0	0	6 (11)	10 (15)	5 (8)
Resolved with sequelae	2 (9)	0	3 (5)	2 (4)	3 (5)	3 (5)
Action taken						
Study drug withdrawn	0	0	1 (2)	1 (2)	0	4 (7)
Study drug continued	23 (100)	6 (86)	59 (98)	54 (96)	65 (100)	57 (93)
Dose interrupted	0	1 (14)	0	1 (2)	0	1 (2)
Others [b)]	0	0	1 (2)	1 (2)	0	0
Vomiting [d)]						
Adverse event	6 (4)	1 (2)	16 (4)	19 (5)	26 (6)	24 (6)
Adverse drug reaction	3	0	10 (63)	7 (37)	9 (35)	11 (46)
Serious	0	0	0	0	0	0
Outcome						
Resolved	5	1	16 (100)	18 (95)	26 (100)	22 (92)
Resolving	0	0	1 (6)	0	0	0
Not resolved	0	0	0	1 (5)	0	2 (8)
Resolved with sequelae	1	0	0	0	0	3 (13)
Action taken						
Study drug withdrawn	0	0	1 (6)	0	0	1 (4)
Study drug continued	6	1	15 (94)	18 (95)	26 (100)	23 (96)
Dose interrupted	0	0	0	0	0	1 (4)
Others [b)]	0	0	1 (2)	1 (2)	0	0

n (%)
a) Events diagnosed as the adverse event term (PT) diarrhoea.
b) Actions taken for adverse events occurring after the completion of treatment.
c) Events diagnosed as the adverse event term (PT) nausea.
d) Events diagnosed as the adverse event term (PT) vomiting.
e) Dolutegravir 10 mg, 25 mg, and 50 mg groups combined.

Table 47. Summary of diarrhoea, nausea, and vomiting
(HIV-1 infected, antiretroviral treatment-experienced patients)

	Study ING111762		Study ING112961		Study ING112574
	Dolutegravir 50 mg	RAL 400 mg	Cohort I [e)]	Cohort II [f)]	Dolutegravir 50 mg BID
No. of evaluable subjects	N = 357	N = 362	N = 27	N = 24	N = 183
Gastrointestinal adverse events	97 (27)	85 (23)	9 (33)	10 (42)	45 (25)
Diarrhoea [a)]					
Adverse event	71 (20)	64 (18)	5 (19)	9 (38)	30 (16)
Adverse drug reaction	29 (41)	21 (33)	2	0	10 (33)
Serious	0	0	0	1	0
Outcome					
Resolved	65 (92)	53 (83)	5	7	26 (87)
Resolving	1 (1)	2 (3)	0	0	0
Not resolved	8 (11)	8 (13)	0	3	6 (20)
Resolved with sequelae	3 (4)	3 (5)	0	0	1 (3)
Action taken					
Study drug continued	70 (99)	63 (98)	5	9	30 (100)
Dose interrupted	1 (1)	0	0	0	0
Others [b)]	0	1 (2)	0	0	0
Nausea [c)]					
Adverse event	29 (8)	29 (8)	2	2	19 (10)
Adverse drug reaction	13 (45)	16 (55)	1	0	11 (58)
Serious	0	0	0	0	0
Outcome					
Resolved	24 (83)	23 (79)	1	1	18 (95)
Resolving	1 (3)	0	0	0	0
Not resolved	3 (10)	6 (21)	0	1	2 (11)
Resolved with sequelae	2 (7)	1 (3)	1	0	0
Action taken					
Study drug withdrawn	0	1 (3)	0	0	0
Study drug continued	28 (97)	27 (93)	2	2	19 (100)
Dose interrupted	1 (3)	0	0	0	0
Others [b)]	0	1 (3)	0	0	0
Vomiting [d)]					
Adverse event	20 (6)	20 (6)	1 (4)	2 (8)	7 (4)
Adverse drug reaction	8 (40)	11 (55)	1	0	2
Serious	0	0	0	0	0
Outcome					
Resolved	19 (95)	17 (85)	1	1	7
Resolving	0	0	0	0	0
Not resolved	2 (10)	3 (15)	0	1	0
Resolved with sequelae	0	0	0	0	0
Action taken					
Study drug continued	20 (100)	17 (85)	1	2	7
Dose interrupted	0	4 (20)	0	0	0
Others [b)]	0	0	0	0	0

n (%)
a) Events diagnosed as the adverse event term (PT) diarrhoea.
b) Actions taken for adverse events occurring after the completion of treatment.
c) Events diagnosed as the adverse event term (PT) nausea.
d) Events diagnosed as the adverse event term (PT) vomiting.
e) Cohort I: dolutegravir 50 mg QD + background therapy
f) Cohort II: dolutegravir 50 mg BID + background therapy

PMDA accepted the prior assessment requestor’s explanation.

4.(iii).B.(2).1).(b) Hepatobiliary disorders

The prior assessment requestor explained the occurrence of hepatobiliary disorders following administration of dolutegravir as follows:

Table 48 shows adverse events of hepatobiliary disorders[55] (hepatobiliary adverse events) in foreign phase II (ING112276) and phase III (ING113086, ING114467) studies conducted in HIV-1 infected, treatment-naïve patients. The incidences of hepatobiliary adverse events were similar between the dolutegravir and control groups. Most of the events were mild in severity.

Table 48. Hepatobiliary adverse events in HIV-1 infected, treatment-naïve patient population

Preferred term (PT)	Study ING112276		Study ING113086		Study ING114467	
	Dolutegravir [a]	EFV	Dolutegravir	RAL	Dolutegravir/ABC/3TC	Atripla
No. of evaluable subjects	N = 155	N = 50	N = 411	N = 411	N = 414	N = 419
No. of subjects with event	3 (2)	2 (4)	9 (2)	9 (2)	3 (<1)	3 (<1)
Autoimmune hepatitis	0	0	0	0	0	1 (<1)
Cholecystitis	0	0	1 (<1)	1 (<1)	0	1 (<1)
Cholelithiasis	1 (<1)	0	1 (<1)	0	3 (<1)	1 (<1)
Cholestasis	0	1 (2)	0	0	0	0
Hepatocellular injury	0	0	1 (<1)	0	0	0
Hepatic cyst	0	0	1 (<1)	0	0	0
Hepatic steatosis	1 (<1)	0	2 (<1)	3 (<1)	0	0
Hepatitis	0	0	1 (<1)	3 (<1)	0	0
Hepatitis toxic	0	0	0	2 (<1)	0	0
Hepatomegaly	1 (<1)	0	0	1 (<1)	0	0
Hepatotoxicity	0	0	0	1 (<1)	0	0
Hepatic lesion	0	0	1 (<1)	0	0	0
Hypertransaminasaemia	1 (<1)	1 (2)	0	0	0	0
Portal vein thrombosis	0	0	1 (<1)	0	0	0

n (%)

a) Dolutegravir 10 mg, 25 mg, and 50 mg groups combined.

Table 49 shows hepatobiliary adverse events occurring in a foreign phase III study conducted in HIV-1 infected, treatment-experienced, INSTI-naïve patients (ING111762) and in foreign phase II (ING112961) and phase III (ING112574) studies conducted in HIV-1 infected, INSTI-experienced patients. The incidences of hepatobiliary adverse events were similar between the dolutegravir and control groups.

[55] System Organ Class (SOC)

Table 49. Hepatobiliary adverse events in HIV-1 infected, antiretroviral treatment-experienced patients

	Study ING111762		Study ING112961		Study ING112574
	Dolutegravir 50 mg	RAL 400 mg	Cohort I [a)]	Cohort II [b)]	Dolutegravir 50 mg BID
No. of evaluable subjects	N = 357	N = 362	N = 27	N = 24	N = 183
No. of subjects with event	14 (4)	10 (3)	2 (7)	1 (4)	9 (5)
Jaundice	6 (2)	4 (1)	0	1 (4)	0
Cholelithiasis	1 (<1)	2 (<1)	0	0	1 (<1)
Hepatitis	2 (<1)	1 (<1)	0	0	0
Hepatotoxicity	1 (<1)	1 (<1)	0	0	0
Acute hepatic failure	0	1 (<1)	0	0	0
Bile duct stone	1 (<1)	0	0	0	0
Biliary colic	0	1 (<1)	0	0	0
Hepatocellular injury	2 (<1)	0	0	0	0
Liver disorder	1 (<1)	0	0	0	0
Hepatic steatosis	0	0	1 (4)	0	1 (<1)
Hepatomegaly	0	0	1 (4)	0	1 (<1)
Hepatic fibrosis	0	0	0	1 (4)	0
Hyperbilirubinaemia	0	0	0	1 (4)	1 (<1)
Portal hypertension	0	0	0	1 (4)	0
Cholecystitis	0	0	0	0	1 (<1)
Cholecystitis acute	0	0	0	0	1 (<1)
Hepatic cirrhosis	0	0	0	0	1 (<1)
Hepatitis acute	0	0	0	0	1 (<1)
Hypertransaminasaemia	0	0	0	0	1 (<1)

n (%)
a) Cohort I: dolutegravir 50 mg QD + background therapy
b) Cohort II: dolutegravir 50 mg BID + background therapy

As shown in the above, the incidences of hepatobiliary disorders in the dolutegravir group were low and similar to those in the control group, and most of the events were mild in severity. Thus, at present hepatobiliary disorders are unlikely to become a major safety problem.

PMDA considers as follows:
In foreign clinical studies, the incidences of hepatobiliary disorders were low and similar between the dolutegravir and control groups, with only a few severe cases observed. Thus, there is no major problem at present. However, post-marketing data on hepatobiliary events should continue to be collected.

4.(iii).B.(2).2) Occurrence of hepatic adverse events in patients with hepatitis virus co-infection
PMDA asked the prior assessment requestor to explain the occurrence of adverse events of hepatic dysfunction in patients with underlying viral hepatitis.

The prior assessment requestor explained as follows:
In foreign phase II and III studies, the frequencies of abnormal liver function tests by hepatitis co-infection status in HIV-1 infected, treatment-naïve, treatment-experienced and INSTI-naïve, or INSTI-experienced patients are shown in Table 50 to Table 52. Grade 3 or 4 abnormal liver function tests were more frequent in subjects with hepatitis B and/or C virus co-infection at baseline than in subjects without co-infection. Most of the subjects were able to continue study treatment and liver function test values returned to normal after the completion of treatment.

Table 50. Frequencies of ALT, AST, and total bilirubin abnormalities by hepatitis co-infection status (HIV-1 infected, treatment-naïve patients in Study ING112276, Study ING113086, Study ING114467)

	Patients with hepatitis B and/or C virus co-infection			Patients without hepatitis B or C co-infection		
	Dolutegravir	RAL	Atripla	Dolutegravir	RAL	Atripla
No. of evaluable subjects	N = 90	N = 43	N = 30	N = 885	N = 363	N = 385
ALT						
Grade 1-4	34 (38)	20 (47)	11 (37)	116 (13)	62 (17)	64 (17)
Grade 3-4	5 (6)	2 (5)	0	8 (<1)	6 (2)	2 (<1)
AST						
Grade 1-4	30 (33)	21 (49)	10 (33)	144 (16)	69 (19)	63 (16)
Grade 3-4	3 (3)	1 (2)	2 (7)	15 (2)	9 (2)	9 (2)
Total bilirubin						
Grade 1-4	4 (4)	5 (12)	0	60 (7)	27 (7)	3 (<1)
Grade 3-4	0	0	0	3 (<1)	1 (<1)	1 (<1)

n (%)
Graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events VERSION 1.0, DECEMBER 2004; CLARIFICATION AUGUST 2009.

Table 51. Frequencies of ALT, AST, and total bilirubin abnormalities by type of co-infection (Treatment-experienced, INSTI-naïve patients in Study ING111762)

	Patients co-infected with hepatitis B virus		Patients co-infected with hepatitis C virus	
	Dolutegravir 50 mg QD	RAL 400 mg BID	Dolutegravir 50 mg QD	RAL 400 mg BID
No. of evaluable subjects	N = 17	N = 16	N = 32	N = 48
ALT				
Grade 1-4	5 (29)	4 (25)	9 (28)	18 (38)
Grade 3-4	4 (24)	0	2 (6)	2 (4)
AST				
Grade 1-4	6 (35)	7 (44)	9 (28)	17 (35)
Grade 3-4	4 (24)	0	2 (6)	1 (2)
Total bilirubin				
Grade 1-4	6 (35)	3 (19)	2 (6)	8 (17)
Grade 3-4	2 (12)	0	1 (3)	1 (2)

n (%)
BR = Background regimen
Graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events VERSION 1.0, DECEMBER 2004; CLARIFICATION AUGUST 2009.

Table 52. Frequencies of ALT, AST, and total bilirubin abnormalities by hepatitis co-infection status (INSTI-experienced patients in Study ING112961, Study ING112574)

	Dolutegravir 50 mg BID	
	Patients with hepatitis B and/or C virus co-infection	Patients without hepatitis B and/or C co-infection
No. of evaluable subjects	N = 46	N = 157
ALT		
Grade 1-4	11 (24)	25 (16)
Grade 3-4	2 (4)	4 (3)
AST		
Grade 1-4	15 (33)	30 (19)
Grade 3-4	0	3 (2)
Total bilirubin		
Grade 1-4	6 (13)	5 (3)
Grade 3-4	1 (2)	2 (1)

n (%)
Graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events VERSION 1.0, DECEMBER 2004; CLARIFICATION AUGUST 2009.

As shown in the above, dolutegravir is more likely to affect the liver function of patients with hepatitis virus co-infection compared to patients without co-infection, but most of the subjects with hepatic adverse events were able to continue treatment and recovered. Thus, there should be no major safety problem.

PMDA considers as follows:
There are no clinical data regarding HIV and hepatitis B and/or C virus co-infected patients with moderate to severe hepatic impairment (Child-Pugh grade B or C) in foreign clinical studies, and adverse events of hepatic dysfunction occurred more frequently in patients with hepatitis virus co-infection. This information should be included in the package insert. Furthermore, post-marketing data on the safety of dolutegravir in patients with hepatitis virus co-infection should continue to be collected.

4.(iii).B.(2).3) Safety in Asian patients
PMDA asked the prior assessment requestor to explain whether the safety of dolutegravir in Asian patients was characteristically different from that in other racial groups.

The prior assessment requestor explained as follows:
A total of 22 Japanese or East Asian patients were enrolled into foreign phase II and III studies, which included 10 East Asian patients in Study ING111762, 8 Japanese or East Asian patients (2 Japanese patients, 6 East Asian patients) in Study ING113086, and 4 Japanese or East Asian patients (2 Japanese patients, 2 East Asian patients) in Study ING114467. Due to the small number of Asian patients enrolled, the number of Asian patients treated with dolutegravir was limited, i.e. 15 (1.5%). Thus, a clinically meaningful analysis was difficult, but the safety profile was similar across the different racial groups enrolled into the studies and no individual events occurred with a markedly high incidence in Asian patients.

PMDA considers as follows:
Based on safety information to date, no characteristic events have been identified among Asian patients compared to other ethnic groups, but the number of dolutegravir-treated Asian patients including Japanese patients was very limited and post-marketing data on the safety of dolutegravir in Japanese patients should continue to be collected.

4.(iii).B.(3) Clinical positioning
PMDA asked the prior assessment requestor to explain the clinical positioning of dolutegravir.

The prior assessment requestor explained as follows:
Phase III studies in HIV-1 infected, treatment-naïve adult patients (ING113086, ING114467) established the non-inferiority of dolutegravir to RAL and the non-inferiority of dolutegravir/ABC/3TC to Atripla. A phase III study in HIV-1 infected, treatment-experienced, INSTI-naïve patients (ING111762) established the non-inferiority of dolutegravir to RAL. A phase III study in HIV-1 infected, INSTI-experienced patients (ING11254) showed a certain level of efficacy of dolutegravir. As for safety, the foreign phase III studies in HIV-1 infected, treatment-naïve or treatment-experienced, INSTI-naïve patients (ING113086, ING114467, ING111762) showed similar safety profile for the dolutegravir and control groups. The phase III study in HIV-1 infected, INSTI-experienced patients (ING112574) also showed a similar trend in terms of safety.

An additional foreign phase III study has been conducted. The purpose of the clinical study was to test the non-inferiority of dolutegravir to darunavir/ritonavir (DRV/RTV) in HIV-1 infected, treatment-naïve adult patients (ING114915)[56]. The primary endpoint of the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 48[44] was 90% (217 of 242 subjects) in the dolutegravir group and 83% (200 of 242 subjects) in the DRV/RTV group; the treatment difference (95% CI) was 7.1 (0.9, 13.2)% and the lower limit of the 95% confidence interval for the treatment difference was above the pre-specified non-inferiority margin (-12%), therefore establishing the non-inferiority of dolutegravir to DRV/RTV. As for safety, adverse events reported by ≥10% of subjects in the dolutegravir and DRV/RTV groups were diarrhoea (17% in the dolutegravir group, 29% in the DRV/RTV group), nausea (16% in the dolutegravir group, 18% in the DRV/RTV group), and headache (15% in the dolutegravir group, 10% in the DRV/RTV group).

Based on the above, dolutegravir will become a new option for the treatment of HIV infection in both treatment-naïve and -experienced patients.

PMDA considers as follows:
Foreign clinical studies in HIV-1 infected, treatment-naïve or treatment-experienced patients established the non-inferiority of dolutegravir to RAL and the non-inferiority of dolutegravir/ABC/3TC to Atripla (EFV/TDF/FTC). Safety analyses showed similar incidences of adverse events in the dolutegravir and control groups. Therefore, a dolutegravir-containing combination regimen can become a new treatment option for treatment-naïve or treatment-experienced patients with HIV infection.

4.(iii).B.(4) Indication
The indication proposed by the prior assessment requestor is “HIV infectious disease”.

PMDA considers as follows:
Clinical studies confirmed the efficacy of dolutegravir in HIV-1 infected patients only. Non-clinical studies demonstrated the activity against HIV-2 as well [see “3.(i).(1) Primary pharmacodynamics”]. Therefore, dolutegravir should be indicated for “HIV infectious” while it should also be advised that the activity against HIV-2 has been demonstrated in a non-clinical setting only.

The above conclusion will be finalized, taking account of discussions at the prior assessment meeting.

4.(iii).B.(5) Dosage and administration
The dosage and administration statement proposed by the prior assessment requestor is as follows: “Usually in adults, dolutegravir is orally given at a dose of 50 mg once daily. The drug may be given without regard to

[56] This study was initiated in October 2011 and efficacy data were not available at the time of submission of prior assessment data, but study data up to Week 48 were submitted during prior assessment.

meals. It should be given with other anti-HIV drugs." The section of precautions for dosage and administration states that "Dolutegravir is orally given at a dose of 50 mg twice daily in patients with integrase inhibitor resistance."

The prior assessment requestor explained the dosing rationale for each patient population as follows.

4.(iii).B.(5).1) Dosage and administration for HIV-infected, treatment-naïve adult patients and HIV-infected, antiretroviral treatment-experienced, INSTI-naïve adult patients

In a foreign early phase II study (ING111521), dolutegravir 2 mg, 10 mg, 50 mg, or placebo QD was administered for 10 days to HIV-1 infected, treatment-naïve patients and HIV-1 infected, treatment-experienced, INSTI-naïve patients. The reductions from baseline in HIV-1 RNA at Day 11 (mean ± SD) in the dolutegravir 2 mg, 10 mg, and 50 mg groups were -1.51 ± 0.58, -2.03 ± 0.49, and -2.46 ± 0.35 $\log_{10}$ copies/mL, respectively, with dose-dependent reductions in HIV-1 RNA observed. In a late phase II study (ING112276), dolutegravir 10 mg, 25 mg, or 50 mg QD was administered in combination with 2 NRTIs to HIV-1 infected, treatment-naïve patients, to assess the durability of virological response through Week 96. As a result, no apparent relationship was observed between dolutegravir dose and antiviral response, but 2 patients in the dolutegravir 10 mg group and 1 patient in the dolutegravir 25 mg group had virologic failure (rebound of HIV RNA ≥400 copies/mL) or virologic resistance. Thus, dolutegravir 50 mg QD was selected for phase III studies in HIV-1 infected, treatment-naïve patients and HIV-1 infected, treatment-experienced, INSTI-naïve patients. The foreign phase III studies established the non-inferiority of dolutegravir 50 mg QD to RAL and the non-inferiority of dolutegravir 50 mg QD/ABC/3TC to Atripla. Based on the above, dolutegravir 50 mg orally once daily is justified for HIV-infected, treatment-naïve patients and HIV-infected, treatment-experienced, INSTI-naïve patients.

4.(iii).B.(5).2) HIV-infected, INSTI-experienced adult patients

A foreign late phase II study (ING112961) was conducted in HIV-1 infected, INSTI-experienced adult patients to evaluate the efficacy and safety of dolutegravir 50 mg QD or BID. The proportions of subjects with HIV-1 RNA <50 copies/mL at Week 48 [44)] were 33% (9 of 27 subjects) in the dolutegravir 50 mg QD group and 71% (17 of 24 subjects) in the dolutegravir 50 mg BID group, demonstrating a higher response rate in the dolutegravir 50 mg BID group. Dolutegravir exposure was higher in the dolutegravir 50 mg BID group than in the dolutegravir 50 mg QD group [see "4.(ii) Summary of clinical pharmacology studies"]. Thus, dolutegravir 50 mg BID was selected for a foreign phase III study (ING112574). In the foreign phase III study, the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 was 69% (126 of 183 subjects), showing a certain level of efficacy. Based on the above, dolutegravir 50 mg orally twice daily is justified for HIV-infected, INSTI-experienced patients.

PMDA considers as follows:

In HIV-1 infected, treatment-naïve patients; HIV-1 infected, treatment-experienced, INSTI-naïve patients; and

HIV-1 infected, INSTI-experienced patients, foreign phase III studies were conducted using the dosage regimens selected based on the results from foreign phase II studies. As a result, the dolutegravir was shown to be effective and is considered tolerable in terms of safety.Therefore, there is no major problem with selecting dolutegravir 50 mg QD for HIV-infected, treatment-naïve or treatment-experienced, INSTI-naïve patients and dolutegravir 50 mg BID for HIV-infected, INSTI-experienced patients. Since the recommended dosage regimen of dolutegravir is different depending on prior treatment experience, the dosage and administration section should be presented as follows.

Usually in adults, dolutegravir is orally given as described below. It should be given with other anti-HIV drugs. 1. Treatment-naïve patients and patients who experienced treatment with other anti-HIV drugs than integrase inhibitors Dolutegravir is orally given at a dose of 50 mg once daily. 2. Patients who experienced treatment with an integrase inhibitor Dolutegravir is orally given at a dose of 50 mg twice daily

The above conclusions will be finalized, taking account of discussions at the prior assessment meeting.

4.(iii).B.(6) Special population

4.(iii).B.(6).1) Children

PMDA asked the prior assessment requestor to explain the efficacy and safety of dolutegravir in children and the pediatric development plan in Japan.

The prior assessment requestor explained as follows:

In a foreign phase I/II study (ING112578), 23 HIV-infected, treatment-experienced, INSTI-naïve pediatric patients (12 to <18 years) in Cohort I received dolutegravir QD at approximately 1 mg/kg for 24 weeks. A pharmacokinetic analysis of dolutegravir showed that the $AUC_{0\text{-}24h}$ and C_{24h} were 45.97 μg·hr/mL and 0.902 μg/mL, respectively. These values were similar to those following repeated doses of 50 mg QD in adults ($AUC_{0\text{-}24h}$, 48.1 μg·hr/mL; C_{24h}, 1.20 μg/mL). The efficacy analysis showed that the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 was 70% (16 of 23 subjects). As for safety, 96% of the subjects (22 of 24 subjects) experienced adverse events and most of the events were mild in severity. There were no Grade 3 or worse adverse events, no adverse events leading to discontinuation, or no adverse events considered related to dolutegravir (including serious adverse events). As in adults, mild non-progressive increases in serum creatinine were seen, but there were no dropouts, no Grade 3 or worse adverse events, or no urinary/renal adverse events considered related to dolutegravir.

Based on the above results, dolutegravir was approved as “an integrase inhibitor indicated in combination with

other antiretroviral agents for the treatment of HIV-1 infection in adults and children aged 12 years and older and weighing at least 40 kg" in the US in August 2013.

In Japan, no new cases of pediatric HIV infection (<15 years of age) were reported in 2012, and the number of cumulative cases since 2005 is 7[57]. As the necessary precautions to prevent mother-to-child transmission of HIV are followed strictly, pediatric HIV infection is unlikely to increase also in future. Therefore, currently, there is no pediatric development plan in Japan, but the development plan will be considered as needed while watching the trend in the number of HIV-infected pediatric patients in Japan.

PMDA considers as follows:
Efficacy and safety data of dolutegravir in children are insufficient. However, the available data from HIV-infected, treatment-experienced, INSTI-naïve pediatric patients suggested the efficacy of dolutegravir and no major safety problems were found. Therefore, there is no problem with selecting the same dosage regimen as that used for adults, for HIV-infected, treatment-experienced, INSTI-naïve pediatric patients aged 12 years and older and weighing at least 40 kg in Japan, as in the US. Since the currently available information on pediatric use is limited, the efficacy and safety of dolutegravir in children should be investigated via post-marketing surveillance. For children aged <12 years, the pediatric development of dolutegravir should be considered based on the results from ongoing foreign clinical studies and drug utilization in children in Japan.

The above conclusions will be finalized, taking account of discussions at the prior assessment meeting.

4.(iii).B.(7) Post-marketing investigations
The prior assessment requestor plans to participate in the HIV-related drug (HRD) joint survey and conduct an all-case post-marketing surveillance study as follows.

- Objective: To collect information on safety and efficacy in routine clinical settings.
- Planned sample size: Inclusion of all cases wherever possible.
  Survey period: The survey will begin on the launch date. All patients enrolled by the end of March, two years before the year of the completion of re-examination, will be surveyed until the completion of the re-examination period. In order to collect information on pregnant and nursing women, pregnant women from the drug use-results survey and spontaneously reported pregnancies will be surveyed.

PMDA considers the following information should continue to be collected via post-marketing surveillance.

- Efficacy and safety of dolutegravir in HIV-infected, Japanese patients (including efficacy by patient characteristics)
- Association between baseline HIV RNA or CD4+ lymphocyte count and efficacy
- Development of resistance to dolutegravir and cross-resistance

[57] The AIDS Annual Surveillance Report 2012 (from January 1 to December 31), MHLW's AIDS Surveillance Committee, May 22, 2013 (http://api-net.jfap.or.jp/status/2012/12nenpo/nenpo_menu.htm)

- Occurrence of hepatic adverse events and laboratory abnormalities associated with dolutegravir
- Occurrence of adverse events associated with dolutegravir in patients with hepatitis virus co-infection

The above conclusions by PMDA will be finalized, taking account of discussions at the prior assessment meeting.

III. Overall Evaluation

As a result of the above evaluation based on the submitted prior assessment data, PMDA has concluded that the efficacy and safety of dolutegravir were confirmed. A final conclusion on the following issues will be made, taking also account of discussions at the prior assessment meeting.

- Efficacy and safety of dolutegravir
- Clinical positioning of dolutegravir and indication
- Dosage and administration

Review Report (1)

February 19, 2014

I. Product Submitted for Registration

[Brand name] Tivicay Tablets 50 mg
[Non-proprietary name] Dolutegravir Sodium
[Applicant] ViiV Healthcare K.K.
[Date of application] December 5, 2013
[Dosage form/Strength] Tablets: Each tablet contains 52.6 mg of Dolutegravir Sodium (50 mg as Dolutegravir).
[Proposed indication] HIV infectious disease
[Proposed dosage and administration]

Usually in adults, dolutegravir is orally given at a dose of 50 mg once daily. The drug may be given without regard to meals. It should be given with other anti-HIV drugs.

II. Content of the Review

The Pharmaceuticals and Medical Devices Agency (PMDA) sought the expert advisors' comments based on the Prior Assessment Report (1) at the prior assessment meeting and at the Expert Discussion. The expert advisors for the prior assessment meeting and the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

PMDA's conclusions described in the Prior Assessment Report (1) were discussed and largely supported by the expert advisors. PMDA conducted an additional review of the following points and took necessary actions.

(1) Transporter-mediated drug interactions

PMDA concluded that interactions between dolutegravir and pilsicainide [see "Prior Assessment Report (1), 4.(ii).B.(2) Transporter-mediated drug interactions"] should be listed in the precautions for concomitant use section of the package insert and that co-administration of dolutegravir with pilsicainide need not be contraindicated at present. The expert advisors supported this conclusion, adding the following comments.

- Interactions between dolutegravir and pilsicainide may cause serious adverse events such as ventricular tachycardia, sinus arrest, and ventricular fibrillation. Careful monitoring of the patient's condition should therefore be advised.
- Information on abnormal ECGs etc. should also be collected actively via post-marketing surveillance.

Based on the above comments, PMDA instructed the applicant to list pilsicainide in the precautions for concomitant use section, to modify the proposed package insert to advise careful monitoring for the possible occurrence and exacerbation of ventricular tachycardia, sinus arrest, ventricular fibrillation etc. during co-administration of dolutegravir with pilsicainide, and to actively collect information on abnormal ECGs etc. via post-marketing surveillance. The applicant agreed to follow the instructions.

(2) Dosage and administration

The expert advisors made the following comment on the proposed dosage and administration section [see "Prior Assessment Report (1), 4.(iii).B.(5) Dosage and administration"].

- Based on the results from clinical studies, dosing recommendations should be presented by the presence or absence of INSTI resistance, instead of prior INSTI use.

Taking also account of the comment from the expert advisors and based on the submitted results from foreign clinical studies, PMDA instructed the applicant to modify the dosage and administration statement as shown below. The applicant agreed to follow the instruction.

Usually in adults, dolutegravir is orally given as described below. The drug may be given without regard to meals. It should be given with other anti-HIV drugs. 1. Treatment-naïve patients and patients who experienced treatment with other anti-HIV drugs than integrase inhibitors Dolutegravir is orally given at a dose of 50 mg once daily. 2. Patients with integrase inhibitor resistance Dolutegravir is orally given at a dose of 50 mg twice daily. In treatment-naïve patients who are aged 12 years or older weighing 40 kg or more, and pediatric patients who experienced treatment with other anti-HIV drugs than integrase inhibitors, dolutegravir may be orally given at a dose of 50 mg once daily.

(3) Draft risk management plan

Based on the review in the Prior Assessment Report (1) "4.(iii).B.(7) Post-marketing investigations" and comments from the expert advisors at the Expert Discussion, PMDA considers that the following additional points should be investigated via post-marketing surveillance.

- Interactions between dolutegravir and other drugs (including information on abnormal ECGs etc.)
- Safety of dolutegravir in patients with hepatitis virus co-infection

PMDA instructed the applicant to investigate the above points as well, to actively collect information on the measured pharmacokinetics of dolutegravir (if available) via post-marketing surveillance, and to evaluate the relationship between dolutegravir blood concentration and the occurrence of adverse drug reactions wherever possible.

The applicant agreed with the above and submitted a draft risk management plan.

Based on the above discussions, PMDA concluded that the safety specification and efficacy concerns as shown in Table 53 should be included in the current risk management plan and that additional pharmacovigilance activities and risk minimization activities as shown in Table 54 should be conducted. PMDA then accepted an outline of the draft drug use-results survey plan shown in Table 55.

Table 53. Safety specification and efficacy concerns of the risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
· Drug-induced hypersensitivity syndrome · Hepatic dysfunction (especially in patients with HBV or HCV co-infection) · Immune reconstitution inflammatory syndrome (IRIS)	· Muscular events (rhabdomyolysis, myopathy, etc.) · Drug-drug interactions mediated by transporters involved in renal excretion, OCT2 and/or MATEs	· Safety in HIV-infected Japanese patients · Chronic use · Pregnant or nursing women
Efficacy concerns		
· Efficacy in routine clinical settings · Long-term efficacy (including the development of drug resistance and cross-resistance)		

Table 54. Summary of additional pharmacovigilance activities and risk minimization activities in the risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
· Early Post-marketing Phase Vigilance · Drug use-results survey (all-case surveillance study)	· Provide information from Early Post-marketing Phase Vigilance.

Table 55. Outline of the draft drug use-results survey plan

Objective	To collect safety and efficacy data in routine clinical settings.
Survey method	Participate in the HRD joint survey and conduct an all-case surveillance study.
Patients to be surveyed	HIV-infected Japanese patients
Observation period	To be determined (The survey will begin on the launch date and patient enrollment will continue until the end of March of the 8th year). Conduct a drug use-results survey of all patients enrolled by the end of March, two years before the year of the completion of re-examination, based on the HRD joint survey method.
Planned sample size	Inclusion of all cases wherever possible.
Main information to be collected	Patient characteristics, concomitant drugs, HIV-RNA, CD4, and adverse events. The survey will also pay attention to the safety specification.

(4) Additional study data submitted

The applicant explained that results from two *in vitro* transporter studies became available after the submission of the prior assessment data, although the results were not included in the US NDA data package. These studies are outlined below:

(a) An *in vitro* study using cells expressing various transporters was performed. The IC_{50} values of dolutegravir for MRP4, OAT1, OAT3, MATE1, and MATE2-K-mediated transport were 84.4, 2.12, 1.97, 6.34, and 24.8 μM, respectively. An IC_{50} for BSEP-mediated transport could not be calculated.

(b) The effects of OAT1, OAT3, and MRP4 inhibition by dolutegravir on kidney tenofovir exposure were assessed using a physiologically based pharmacokinetic model [58)]. The results showed that co-

[58)] SimCYP™ was used for analysis.

administration with dolutegravir increases the C_{max} of tenofovir in renal proximal tubules by up to 1.4-fold but does not affect tenofovir renal clearance.

PMDA reviewed these study results that were not included in the clinical data package to support this application, but were additionally submitted.

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

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

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

As a result of the above review, PMDA has concluded that dolutegravir may be approved for the indication and dosage and administration as shown below, with the following conditions. As the product is an orphan drug, the re-examination period is 10 years. The drug substance and the drug product are both classified as powerful drugs. The product is not classified as a biological product or a specified biological product.

[Indication]
HIV infection

[Dosage and administration]
Usually in adults, dolutegravir is orally given as described below. The drug may be given without regard to meals. It should be given with other anti-HIV drugs.

1. Treatment-naïve patients and patients who experienced treatment with other anti-HIV drugs than integrase inhibitors
   Dolutegravir is orally given at a dose of 50 mg once daily.
2. Patients with integrase inhibitor resistance
   Dolutegravir is orally given at a dose of 50 mg twice daily.
   In treatment-naïve patients who are aged 12 years or older weighing 40 kg or more, and pediatric patients who experienced treatment with other anti-HIV drugs than integrase inhibitors, dolutegravir may be orally given at a dose of 50 mg once daily.

[Conditions for approval]

The applicant is required to:

1. Request physicians to fully explain to their patients that further efficacy and safety data are still being collected etc. and obtain their informed consent prior to the use of the product.
2. Submit the study data and analysis results from ongoing or planned foreign clinical studies promptly after the study completion.
3. Conduct a post-marketing surveillance study, covering all patients treated with the product in Japan as a rule, until the completion of the re-examination period, in order to collect and periodically report the drug utilization information (patient characteristics, efficacy and safety [including the efficacy and safety of the product in combination with other drugs], drug interaction data, etc.). Submit the survey results as application data for re-examination.