Report on the Deliberation Results

May 13, 2008

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

[Brand name]	Isentress Tablets 400 mg
[Non-proprietary name]	Raltegravir Potassium (JAN*)
[Applicant]	Banyu Pharmaceutical Co., Ltd.
[Date of application]	March 12, 2008

[Results of deliberation]
In the meeting held on April 30, 2008, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

In addition, the following conclusions were reached: the product is not classified as a biological product or a specified biological product, the re-examination period is 10 years, and the drug substance and the drug product are both classified as powerful drugs.

The conditions for approval for the product are as follows:
1. Since a pharmacokinetic study will be conducted in Japan, 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. Report the progress status of a Japanese pharmacokinetic study on a regular basis and submit the study data and analysis results promptly after the study completion. Also, as for ongoing or planned foreign clinical studies, submit the study data and analysis results promptly after the study completion.
3. Conduct a post-marketing survey 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 information on actual use of the product (patient background, 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)*

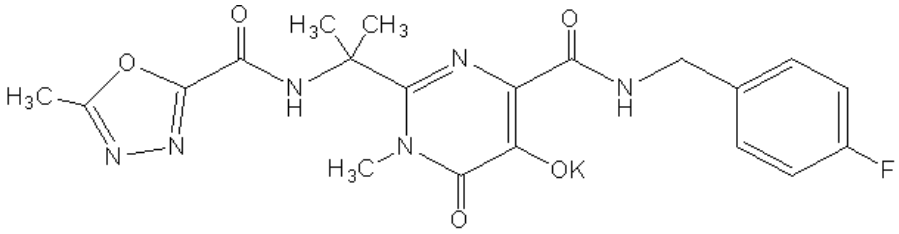
Review Report

April 14, 2008

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]	Isentress Tablets 400 mg
[Non-proprietary name]	Raltegravir Potassium
[Applicant]	Banyu Pharmaceutical Co., Ltd.
[Date of application]	March 12, 2008 (Application for marketing approval)
[Application classification]	1-(1) Drug with a new active ingredient
[Chemical structure]	Raltegravir Potassium



Molecular formula: $C_{20}H_{20}FKN_6O_5$
Molecular weight: 482.51

Chemical name:

Monopotassium 4-[(4-fluorobenzyl) carbamoyl]-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino}ethyl)-6-oxo-1,6-dihydropyrimidin-5-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 (Date of designation: November 26, 2007)

[Reviewing office] Office of New Drug I

Review Results

April 14, 2008

[Brand name] Isentress Tablets 400 mg

[Non-proprietary name] Raltegravir Potassium

[Applicant] Banyu Pharmaceutical Co., Ltd.

[Date of application] March 12, 2008

[Results of review]

(1) It has been determined that the submitted data have demonstrated the efficacy of the product in patients with documented resistance to at least 1 drug in each of the 3 classes (NRTI, NNRTI, PI) of currently licensed anti-HIV agents.

(2) Regarding the safety of the product, the submitted data indicate that there are no particular tolerability problems. However, since there are no Japanese data and the product has a novel mode of action and may cause unexpected adverse reactions, it is considered necessary to collect information carefully after the market launch.

(3) It is considered necessary to conduct a post-marketing clinical study to determine the pharmacokinetics of the product in Japanese subjects, evaluate the data appropriately as soon as they become available, and provide information.

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

[Indication] HIV infection

[Dosage and administration]

The usual adult dosage is 400 mg as raltegravir administered orally, twice daily with or without food. Isentress must be used in combination with other anti-HIV medicines.

[Conditions for approval]

1. Since a pharmacokinetic study will be conducted in Japan, 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. Report the progress status of a Japanese pharmacokinetic study on a regular basis and submit the study data and analysis results promptly after the study completion. Also, as for ongoing or

planned foreign clinical studies, submit the study data and analysis results promptly after the study completion.

3. Conduct a post-marketing survey 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 information on its actual use (patient background, 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)

February 27, 2008

[Intended brand name] Isentress Tablets 400 mg

[Prior assessment requestor] Banyu Pharmaceutical Co., Ltd.

[Non-proprietary name] Raltegravir Potassium

[Dosage form/Strength]

Each film-coated tablet contains 434.4 mg of raltegravir potassium (400 mg as raltegravir).

[Intended indication] HIV-1 infection

[Intended dosage and administration]

The usual adult dosage is 400 mg as raltegravir administered orally, twice daily with or without food. Isentress must be used in combination with other anti-HIV medicines.

[Date of preparatory meeting for prior assessment] December 3, 2007

[Items warranting special mention]

Orphan drug (Date of designation: November 26, 2007)

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: October 12, 2007

Date of approval in the EU: December 20, 2007

This prior assessment is based on the EU application dossier.

I. 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.

Raltegravir potassium is the first HIV integrase strand transfer inhibitor developed by Merck & Co., Inc., Whitehouse Station, N.J., U.S.A. and is claimed to have broad activity against various HIV-1 variants including those resistant to currently available anti-HIV drugs.

Highly active antiretroviral therapy (HAART) has enabled HIV infection to be managed as a chronic disease. On the other hand, as the number of patients treated with different combinations of anti-HIV drugs continues to grow, intolerance of complicated dosing regimens,

long-term toxicities, and multi-drug resistance have emerged as issues. Recent efforts, therefore, have been focused on the development of better-tolerated formulations and on combination regimens with improved tolerance and convenience to improve patients' compliance, an essential factor for treatment success.

For the development of raltegravir potassium, a phase I study was initiated in [redacted] 20[redacted] in [redacted] and 2 phase II studies in HIV treatment-naïve and HIV treatment-experienced patients were conducted. Then, 2 phase III studies in HIV treatment-experienced patients with documented resistance to at least 1 drug in each of the 3 classes [nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI), or protease inhibitors (PI)] of antiretroviral therapies were planned and are currently ongoing. Based on the results of interim analysis of these phase III studies, a new drug application for the product was filed in April 2007 in the US and approved in October 2007. Its EU marketing authorization was granted in December 2007 and the product has been approved in 30 countries worldwide as of December 2007.

In Japan, Banyu Pharmaceutical Co., Ltd. has requested pre-NDA evaluation of raltegravir potassium.

2. Physicochemical properties and specifications

2.(i) Drug substance

- The following physicochemical properties of the drug substance, i.e. raltegravir potassium have been investigated: description (appearance), solubility, hygroscopicity, pH, dissociation constant, thermal analysis (differential scanning calorimetry, thermogravimetry), partition coefficient, and polymorphic forms.

- The chemical structure of raltegravir potassium has been characterized by mass spectrum, ultraviolet-visible spectrum, infrared spectrum, nuclear magnetic resonance spectrum (^{1}H-NMR, ^{13}C-NMR), and single-crystal x-ray diffraction.

- The specifications for raltegravir potassium are proposed for description (appearance), identification (infrared spectrum, flame coloration), purity (related substances, residual solvents), water content, particle size, and content (assay).

- PMDA determined, based on the submitted stability data, that the proposed re-test period of 36 months for the drug substance when stored in double polyethylene bags

placed in fiber drums is acceptable.

2.(ii) Reference standard

- The specifications for reference material are proposed for description (appearance), identification (infrared spectrum, nuclear magnetic resonance spectrum [^{1}H-NMR]), purity (related substances, residual solvents), water content, and content (assay).

2.(iii) Drug product

- Isentress Tablet 400 mg is a film-coated tablet containing 434.4 mg of raltegravir potassium (400 mg as raltegravir). It contains microcrystalline cellulose, lactose monohydrate, calcium phosphate dibasic anhydrous, hypromellose, polyoxyethylene (196) polyoxypropylene (67) glycol, sodium stearyl fumarate, magnesium stearate, polyvinyl alcohol (partially hydrolyzed), Macrogol 4000, talc, titanium dioxide, red ferric oxide, and black iron oxide, as excipients.

- The specifications for the drug product are proposed for description (appearance), identification (near-infrared spectrometry, liquid chromatography), purity (related substances), uniformity of dosage units, microbial limits, dissolution, and content (assay).

- As for the uniformity of dosage unit test in the drug product specifications, the mass variation test, which is performed as an in-process control [redacted], is to be used as an alternative.

  The pre-NDA evaluation requestor explained about the mass variation test included as an in-process control as follows:
  The acceptance criterion for this test has been established so that [redacted]. It has also been established so that [redacted].

  PMDA determined that the acceptance criterion for mass variation has been established [redacted] appropriately and that [redacted]

[redacted].

Considering that it is necessary to clearly state that this in-process control test will be used as an alternative to the uniformity of dosage unit test in the specifications, PMDA instructed the pre-NDA evaluation requestor to set the specification appropriately.

- PMDA asked the pre-NDA evaluation requestor to explain how the specification limit for purity (Related Substance A) was established taking account of lot-to-lot variability and stability data.

  The requestor responded as follows:
  The levels of Related Substance A [redacted] when [redacted] lots were stored at [redacted]°C [redacted]%RH for [redacted] months were determined and based on these values, the increase in Related Substance A was estimated by [redacted]. As a result, the estimated increase in Related Substance A when sample was stored at [redacted]°C [redacted]%RH for up to [redacted] months, was [redacted]% as determined by [redacted] and [redacted]%. Related Substance A is an impurity derived from the drug substance manufacturing process and the specification limit for Related Substance A in the drug substance is [redacted]%. No increase has been observed during the manufacture of the drug product. It corresponds to [redacted]%." Based on the above, a specification limit of [redacted]% for Related Substance A, taking account of stability, has been established.

  PMDA accepted the above response.

- PMDA determined, based on the submitted stability data (the results of a long-term stability study up to 18 months were additionally submitted during the pre-NDA evaluation), that the proposed shelf-life of 30 months for the drug product when stored in HDPE bottles at room temperature is acceptable.

3. Non-clinical data

3.(i) Pharmacology

- Primary pharmacodynamic studies were conducted to investigate the inhibitory effect on HIV-1 integrase, *in vitro* antiviral activity against laboratory HIV-1 and HIV-2 isolates and clinical HIV-1 isolates, resistance development, and interactions with other antiviral drugs, etc. Safety pharmacology studies were conducted to determine the effects of raltegravir on the major organ systems (cardiovascular, central nervous, and respiratory systems) and the gastrointestinal system etc.

- The inhibitory effect of raltegravir on the DNA strand transfer activity of recombinant HIV-1 HXB2 integrase was evaluated in an *in vitro* assay. As a result, raltegravir concentration-dependently inhibited DNA strand transfer (50% inhibitory concentration [IC_{50} value], 10 nM). The inhibitory effects of raltegravir on the DNA polymerase and RNase H activities of HIV-1 reverse transcriptase and human DNA polymerases α, β, and γ were also investigated and the IC_{50} values of raltegravir were > 100, > 25, > 50, > 50, and > 50 (μM), respectively.

- Raltegravir was tested *in vitro* for the ability to inhibit replication of HIV-1 in MT4 human T-lymphoid cells infected with an HIV-1 laboratory isolate (H9IIIB) and the 95% inhibitory concentrations (IC_{95}) of raltegravir were 18.7 ± 14 nM (10% FBS-containing culture medium) and 31 ± 20 nM (50% NHS-containing culture medium). The IC_{95} values of raltegravir in mitogen-activated human peripheral blood mononuclear cells infected with primary clinical isolates of HIV-1 including isolates resistant to NNRTI and PI, were 6 to 50 nM (20% FBS-containing culture medium). The IC_{95} value of raltegravir in CEMx174 human lymphoid cells infected with an HIV-2 laboratory isolate was 6.3 nM (10% FBS-containing culture medium). (The anti-viral activity of raltegravir against other viruses such as HBV has not been investigated.)

- *In vitro* resistance selection study: The laboratory HIV-1 isolate (H9IIIB) was serially passaged 18 times in H9 cells in the presence of increasing concentrations of raltegravir (the starting raltegravir concentration for selection, 25 nM; the final concentration, 50 μM). Amino acid substitutions in HIV-1 integrase emerged with increasing passage number (Q148K [the raltegravir fold-change IC_{50} value increased approximately 46-fold], Q148K/E138A [the raltegravir fold-change IC_{50} value increased approximately 90-fold], and Q148K/E138A/G140A [the raltegravir

fold-change IC_{50} value increased approximately 508-fold]) and resistance to raltegravir evolved.

- *In vitro* sensitivity to raltegravir of HIV mutant viruses with amino acid substitutions selected with raltegravir or other integrase strand transfer inhibitors (InSTIs) is shown below.

Sensitivity to raltegravir of HIV mutant viruses with amino acid substitutions (Fold-change IC_{50} > 2 only)

Mutations in integrase	Raltegravir fold-change IC_{50} (mean ± SEM)
N155S	19 ± 4
F121Y/T125K	7 ± 2
T66I/L74M/V151I	5 ± 0.6
F121Y	3 ± 0.6
S153Y/N155S	3 ± 0
T125K/S153Y/N155S	3 ± 0.5
G140S/Q148H	521 ± 35
G140S/Q148R	405 ± 158
E92Q/N155H	64
Q148R	27 ± 10
Q148H	24 ± 11
N155H	13 ± 2.4
E92Q	3
Q148K/E138A/G140A	508 ± 153
Q148K/G140A	257 ± 2.5
Q148K/E138A	90 ± 12
Q148K	46 ± 9
E138A/G140A	4 ± 0.5
G140A	3 ± 0.5

Fold-change IC_{50} values with no SEM displayed represent single determinations.

- The results of genotypic and phenotypic analysis of integrase sequences isolated from subjects with virologic failure to raltegravir treatment (3 isolates) in a phase II study (Study 005) are as follows.

Amino acid changes from the baseline sequence	Raltegravir IC_{50} (nM)	Fold-Change IC_{50} (for virologic failure isolate)
G140S, Q148H	4861	211
N155H, D232N	300	18
L74I, F121N, I135V, V151I, K211R, D232N	> 160	> 8

- Based on the results of analysis of amino acid substitutions in the integrase of HIV-1 resistant to raltegravir *in vitro* or in clinical studies, it has been discussed that there are 2 primary pathways for acquiring resistance (Q148H/K/R or N155H), where the mutation Q148H/K/R or N155H is accompanied by one or more additional mutations (G140S, E92Q, L74I/M, E138A/K, G140A/S, or V151I, etc.). It has also been shown that Q148H/K/R or N155H decreases HIV susceptibility to raltegravir and addition of one or more amino acid mutations results in a further decrease in susceptibility to raltegravir.

- *In vitro* interactions of raltegravir with anti-HIV drugs from other classes: When raltegravir was combined with each of 18 antiviral agents from other classes (NRTI [zidovudine, zalcitabine, sanilvudine, abacavir, tenofovir, didanosine, lamivudine] and NNRTI [efavirenz, nevirapine, delavirdine], PI [indinavir, saquinavir, ritonavir, amprenavir, lopinavir, nelfinavir, atazanavir], or a fusion inhibitor [enfuvirtide]), additive or synergistic anti-HIV activity was observed at raltegravir concentrations of $\geq$ 3.125 to 9.375 nM.

- The "Pharmacology" section of the proposed package insert states that "raltegravir inhibits the catalytic activity of HIV integrase." PMDA asked the pre-NDA evaluation requestor to explain its specific mechanism of action (what chemical structure of raltegravir is responsible, how it acts on the catalytic active site of HIV integrase, or how it inhibits the catalytic activity).

  The pre-NDA evaluation requestor responded as follows:
  As co-crystal structure analysis of raltegravir with integrase has not been performed, the detailed binding mode is unknown. But based on the results of a biochemical study using an integrase inhibitor (DNA strand transfer inhibitor) with the same binding mode as raltegravir, a model where the oxygen atom in the central ring of raltegravir interacts with Mg^{2+} ions binding to the integrase active site has been proposed. In accordance with this model, other sites of raltegravir should make contact with amino acid residues in the vicinity of metal ions at the catalytic center. Raltegravir or other integrase inhibitor resistance mutations are located in the integrase active site and in the vicinity of amino acid residues coordinating a Mg^{2+} ion, which is a cofactor required for catalytic activity; this finding is also consistent with this model. Therefore, raltegravir is also considered to bind to the active site of HIV integrase or its vicinity.

  Although the binding mode of raltegravir with integrase is unknown at present, as raltegravir has been shown to inhibit the HIV DNA strand transfer in a non-clinical study, PMDA considers that the anti-HIV effect of raltegravir can be expected.

- PMDA asked the pre-NDA evaluation requestor to explain about foreign post-marketing information on resistance to raltegravir and a post-marketing surveillance plan in Japan.

The pre-NDA evaluation requestor responded as follows:

In foreign countries, it has recently been recognized that amino acid substitution at Y143, in addition to 2 primary pathways for acquiring resistance (Q148H/K/R or N155H), are clinically important.

Sensitivity to raltegravir of HIV mutant viruses with amino acid substitutions (Fold-change IC_{50} > 2 only)

Mutations in integrase	Raltegravir fold-change IC_{50} (mean ± SEM)
Y143R	16.5 ± 1.5
Y143R/T97A	461
Y143R/E92Q	65
L74I/F121N/V151I	63

The results of phenotypic resistance testing obtained from Study 005 after the submission of pre-NDA evaluation data

In the US, as post-marketing information on resistance to raltegravir, 3 primary pathways for acquiring resistance have been reported, but the collected data are limited. Thus, Merck & Co., Inc., Whitehouse Station, N.J., U.S.A. intends to report the information obtained from ongoing or planned clinical studies and pharmacovigilance activity (spontaneous adverse drug reaction reports on raltegravir resistance, literature reports on raltegravir resistance) in periodic safety update reports (PSUR). In Japan, while there is no plan to conduct a post-marketing surveillance study on raltegravir resistance, information on raltegravir resistance will be collected actively from the published literature and academic conferences and reported in periodic safety reports. Efforts will be made to obtain raltegravir resistance information from specialists as appropriate and the information will be transmitted to the medical institutions.

PMDA considers that although non-clinical and clinical studies have investigated the pattern of the emergence of HIV-1 integrase mutations, it is necessary to continue to collect information on resistance to raltegravir extensively also after the market launch and provide information appropriately.

3.(ii) Pharmacokinetics

- The non-clinical pharmacokinetics of raltegravir were studied in mice, rats, rabbits, and dogs following oral administration of raltegravir.

- The absolute bioavailability (BA) of raltegravir alone was 61.6% in rats and 70.0% in dogs. Following single dose administration of 40 to 240 mg/kg of raltegravir in rats, the pharmacokinetics were linear over the dose range of 40 to 120 mg/kg, but there was no further increase in exposure at > 120 mg/kg (saturation of absorption).

In dogs, the pharmacokinetics were linear over the 5 to 45 mg/kg dose range, but the increase in exposure was less than dose proportional when the dose was increased to 135 mg/kg (saturation of absorption).

- Raltegravir was distributed in the stomach, small intestine, liver, kidneys, and bladder at high concentrations at 30 minutes post-dose with limited distribution into other tissues (brain and lungs, etc.). Concentrations in all tissues declined steadily after reaching maximum concentrations and levels in most tissues were below the limit of quantitation (< 2 times the background radioactivity) by 24 hours post-dose.

- The plasma protein binding of raltegravir was 70% to 71% in mice, 73% to 75% in rats, 69% to 71% in dogs, and 82% to 83% in humans and was independent of raltegravir concentrations evaluated (2-10 μg/mL).

- In mice, rats, and dogs, raltegravir was excreted in urine and feces, primarily as the glucuronides (M2). In humans who had received a single dose of 200 mg of raltegravir, 51% and 32% of the dose were recovered in feces and urine, respectively, through 10 days post-dose. In urine, M2 and the parent compound accounted for 23% and 9% of the dose, respectively, while only the parent compound was detected in feces. In human plasma, the parent compound accounted for 70% of the total radioactivity and M2 was responsible for most of the remaining radioactivity. In humans, a significant fraction of the parent compound excreted in feces is likely derived from hydrolysis of M2 secreted in bile.

- The glucuronidation of raltegravir is catalyzed mainly by UGT1A1, but raltegravir did not inhibit UGT1A1 (or UGT2B7) at concentrations up to 50 μM. At concentrations up to 100 μM, raltegravir was not a potent inhibitor of any of the CYPs tested (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP2B6). It did not induce CYP3A4 and did not inhibit P-gp. [see “4.(ii).(4) Safety” for the association of UGT1A1 polymorphism with the pharmacokinetics and safety/efficacy of raltegravir in Japanese patients]

- In rats and dogs, about 50% to 74% and about 13% to 31% of the dose administered of raltegravir were excreted in feces and urine, respectively. In rats, the milk-to-plasma concentration ratios were 3.34 at 300 mg/kg/day and 2.55 at 600 mg/kg/day, demonstrating significant excretion of raltegravir into milk.

- An *in vitro* study of pharmacokinetic interactions between raltegravir and atazanavir (ATV) in rat liver microsomes indicated that ATV was a relatively potent inhibitor of the glucuronidation of raltegravir (IC_{50} = 2.2 μM). In an *in vivo* study in the rat, coadministration with 50 mg/kg dose of ATV increased the AUC, C_{max} and C_{8hr}, and $t_{1/2}$ of raltegravir (ATV 5 mg/kg had no effect). [see "4. (i) Human pharmacokinetics and pharmacodynamics" for the results of a study of interactions with ATV in humans]

- PMDA asked for the prior assessment requestor's view on the effects of the glucuronide of raltegravir excreted into bile on enterohepatic circulation.

  The prior assessment requestor responded as follows:
  In rats and dogs, it has been confirmed that raltegravir is eliminated predominantly via glucuronidation and raltegravir is found in bile mainly as the glucuronide. In humans, the majority of the dose is excreted in feces as the parent compound, a part of which is likely derived from the hydrolysis of the glucuronide in bile. The glucuronide of raltegravir is presumed to be excreted into bile also in humans. However, despite the fact that the glucuronate is excreted into bile, the plasma concentration-time profile has not clearly indicated enterohepatic circulation in any of the animal species studied, including humans. In a local absorption study in dogs, raltegravir was well-absorbed by oral and jejunal administration, but poorly absorbed by colonic administration, suggesting that raltegravir is significantly absorbed, in the upper gastrointestinal tract at least up to the upper small intestine. Enterohepatic circulation is not seen possibly because raltegravir may not be significantly absorbed in the lower small intestine and colon, where hydrolysis from the glucuronate conjugate to the parent compound should occur.

  PMDA considers as follows:
  Based on the results of the absorption site study in dogs, it is inferred that the major absorption site of raltegravir is the upper small intestine also in humans. Thus, deglucuronidation in the gastrointestinal tract is unlikely to affect enterohepatic circulation.

3.(iii) Toxicology

- Toxicity studies submitted include single-dose toxicity studies (mice, female rats, and dogs), repeated-dose toxicity studies (mice, rats, and dogs), genotoxicity studies, reproductive and developmental toxicity studies, and local tolerance studies, and carcinogenicity studies are ongoing. Raltegravir suspended or dissolved in 0.5% methylcellulose or polyethylene glycol/water (80:20) was orally administered. The vehicle used for raltegravir was administered to the control group.

- In single-dose toxicity studies, raltegravir was administered by oral gavage to mice, rats, and dogs.

- In a single oral dose toxicity study in mice (TT032616), raltegravir 1000, 1500, and 2000 mg/kg were administered to male and female mice. As a result, 1 out of 3 males in the 2000 mg/kg group died and decreased activity and bradypnea were noted in male and female mice at 1500 mg/kg. The approximate lethal doses were determined to be 2000 mg/kg/day for males and > 2000 mg/kg/day for females.

- In a single oral dose toxicity study in rats (TT032619), raltegravir 2000 mg/kg was administered to females only. As a result, no mortality occurred and there were no treatment-related effects. The approximate lethal dose was determined to be > 2000 mg/kg/day.

- In a single oral dose toxicity study in dogs (TT040080), 2 groups of female dogs received single escalating oral doses of raltegravir 100, 250, 500, and 1000 mg/kg. As a result, emesis was seen at ≥ 500 mg/kg.

- The following repeated-dose toxicity studies were conducted by administering raltegravir by oral gavage to mice, rats, and dogs.

- In an oral gavage repeated-dose toxicity study in mice (TT051023), vehicle and raltegravir (50, 500, 1000, 2500, and 5000 mg/kg/day) were administered to male and female mice for 14 weeks. Due to treatment-related effects, 7 out of 15 males and 6 out of 15 females in the 5000 mg/kg/day group, 9 out of 15 males and 8 out of 15 females in the 2500 mg/kg/day group, 5 out of 15 males and 7 out of 15 females in the 1000 mg/kg/day group, and 3 out of 15 males in the 500 mg/kg/day group were found dead or sacrificed early. Due to high mortalities at≥ 1000 mg/kg/day,

treatment was terminated and necropsy was performed for the remaining animals on Day 8 in the 5000 mg/kg/day group, on Day 27 for males and on Day 38 for females in the 2500 mg/kg/day group, and on Day 45 in the 1000 mg/kg/day group. The major findings were distended abdomen, laboured breathing, decreases in body weight gain, and decreased activity, etc. at ≧ 500 mg/kg/day. The prior assessment requestor has determined that histopathologically, mucosal erosion in the stomach and esophagitis observed in the 500 mg/kg/day group were related to an irritant effect of raltegravir. The no observed adverse effect level (NOAEL) was determined to be 50 mg/kg/day.

- Oral gavage repeated-dose toxicity studies in rats (TT040079, TT031190, TT046022)

  (a) 5-week oral toxicity study (TT040079)

  Vehicle and raltegravir (150, 300, 450, and 600 mg/kg/day) were administered. As a result, the major findings were increased ALT in females at 600 mg/kg/day, increased stomach mucosa inflammation in males at ≥ 300 mg/kg/day and in females at ≥ 450 mg/kg/day, and salivation and vacuolation of the nonglandular mucosa at the limiting ridge at all dose levels. The prior assessment requestor has determined that as salivation and the stomach mucosal findings are considered related to the irritation caused by raltegravir and the stomach mucosal findings were slight and local in nature, these effects are of no toxicological significance and that the NOAEL is 600 mg/kg/day for males and 450 mg/kg/day for females.

  (b) 14-week oral toxicity study (TT031190)

  Vehicle and raltegravir (30, 90, and 120 mg/kg/day) were administered. As a result, there were no treatment-related effects except for salivation observed in all dose groups. The NOAEL was determined to be 120 mg/kg/day.

  (c) 27-week oral toxicity study (TT046022)

  Vehicle and raltegravir (30, 120, and 90/600 mg/kg/day [the dose was increased from Day 59]) were administered. As a result, due to treatment-related effects, 3 out of 20 males and 1 out of 20 females in the 90/600 mg/kg/day group died. The major findings in the surviving animals were decreases in body weight gain, abnormal respiratory sounds, and inflammation of the nasopharynx, etc. in the 90/600 mg/kg/day group and salivation and vacuolation and vacuolar degeneration of the stomach mucosa in both males and females and inflammation of the nasopharynx in

males at ≥ 120 mg/kg.

The prior assessment requestor did not use salivation and the findings in the mucosa of the stomach and nose as the basis for determining the NOAEL because local tolerance studies as described later have demonstrated that such effects are associated with raltegravir irritation and the finding in the mucosa of the nose is likely caused by aspiration of the drug formulation to the nasal passages during gavage due to the biological features of the rat. Thus, the NOAEL for both males and females was determined to be 120 mg/kg/day.

Although it is difficult to say that the prior assessment requestor's decision not to consider the changes in the mucosa of the stomach and nose noted at ≥ 120 mg/kg/day as toxic findings has fully been explained, the irritation potential of raltegravir has been evaluated in local tolerance studies. Thus, PMDA accepted the decision not to use these changes as the basis for determining the NOAEL in view of the biological features of the rat. In addition, the possibility of the occurrence of inflammation in the stomach or the upper gastrointestinal tract in clinical use is considered very low for the following reasons: (a) Unlike the administration method in humans by which the drug is dissolved slowly, raltegravir was administered by catheter to rats and the drug came into contact with the gastric mucosa rapidly, (b) In a 1-year oral toxicity study in dogs having the stomach and upper gastrointestinal tract that are closer to those of humans, the local exposure was 7200 mg/m^2 at the NOAEL of raltegravir of 360 mg/kg/day, which is 13.5 times the human exposure at the recommended clinical dose, i.e. 532 mg/m^2, (c) To date, there have been no differences in the occurrence of adverse events involving the stomach and intestines between the raltegravir and placebo groups in clinical use.

- Oral gavage repeated-dose toxicity studies in dogs (TT049811, TT0469001)

  (a) 5-week oral toxicity study (TT049811)

  Vehicle and raltegravir (125, 250, and 500 mg/kg/day) were administered. As a result, there were no treatment-related effects except for emesis occurring within 30 minutes after dosing at ≥ 250 mg/kg/day. The NOAEL was determined to be 500 mg/kg/day.

  (b) 53-week oral toxicity study (TT049001)

  Vehicle and raltegravir (15, 90, and 5/360 mg/kg/day [the dose was increased after

Week 14]) were administered. As a result, there were no treatment-related effects except for emesis occurring within 30 minutes after dosing at 360 mg/kg/day. The NOAEL was determined to be 360 mg/kg/day.

- The reproductive toxicity of raltegravir was evaluated in fertility studies in rats (TT047420, TT057180) and prenatal and postnatal developmental toxicity studies in rats and rabbits (TT047090, TT047220). A juvenile toxicity study in rats (TT047420) was performed.

- Rat study of fertility and early embryonic development to implantation (TT047420, TT057180)
  Male rats were orally administered repeated doses of vehicle or raltegravir (100, 300, or 600 mg/kg/day) for 8 weeks from 4 weeks prior to mating and female rats were orally administered vehicle or raltegravir (150, 300, or 600 mg/kg/day) from 2 weeks before mating, during mating, and until gestation day 7. As a result, there were no treatment-related effects. The NOAEL for male and female general and reproductive toxicity and embryonic development was determined to be 600 mg/kg/day.

- Rat study for effects on embryo-fetal, prenatal, and postnatal development, including maternal function (TT047090)
  Female rats were orally administered repeated doses of vehicle or raltegravir (100, 300, or 600 mg/kg/day) from gestation day 6 to gestation day 20 (cesarean section group) or lactation day 20 (natural delivery group). As a result, an increased incidence of supernumerary ribs beyond the laboratory background incidence was observed in the F1 generation of the 600 mg/kg group. The NOAELs for the F0 and F1 generations were determined to be 600 mg/kg/day and 300 mg/kg/day, respectively.

- Embryo-fetal development study in rabbits (TT047220)
  Pregnant rabbits were orally administered repeated doses of vehicle or raltegravir (100, 500, or 1000 mg/kg/day) from gestation day 7 to gestation day 20. As a result, there were no treatment-related effects. The NOAELs for maternal general and reproductive toxicity and for the fetus were both determined to be 1000 mg/kg/day.

- Juvenile toxicity study in rats (TT057300)
  Juvenile rats were orally administered repeated doses of vehicle or raltegravir (50,

200, or 600 mg/kg/day) from postnatal day 5 to postnatal week 8. At ≥ 200 mg/kg, inflammation and nonglandular mucosal vacuolation in the stomach were noted, but these changes recovered after a 6-week recovery period. The NOAEL was determined to be 50 mg/kg/day.

- The genotoxic potential of raltegravir was investigated in bacterial reverse mutation tests (TT038029 etc.), alkaline elution/rat hepatocyte assays (TT038381 etc.), chromosomal aberration tests with CHO cells (TT038681 etc.), and a mouse micronucleus test (TT038619). As a result, these studies all produced negative results and no evidence of genotoxicity was observed.

- Carcinogenicity studies

  One-hundred-five-week carcinogenicity studies in mice and rats are ongoing and 81 weeks of assessment has been completed.

  (a) Carcinogenicity study in mice (TT051117)

  Male mice (50 animals) were orally administered repeated doses of vehicle or raltegravir (50, 100, or 250 mg/kg/day) and female mice (50 animals) were orally administered repeated doses of vehicle or raltegravir (50, 250, or 400 mg/kg/day) for 1 year. Among the deaths through Drug Week 81 (males, 14, 15, and 9 deaths, respectively; females, 8, 14, and 28 deaths, respectively), the deaths in the high dose females were caused by inflammation of the nose/trachea due to persistent reflux in the airway. Histomorphologic examination through Drug Week 76 has revealed no tumors of the mucosa of the nose or nasopharynx, whereas chronic inflammation, epithelial hyperplasia, and metaplasia of the mucosa of the nose and nasopharynx have been observed, which are consistent with those observed in the rat carcinogenicity study.

  (b) Carcinogenicity study in rats (TT056040)

  Male rats (50 animals) were orally administered repeated doses of vehicle or raltegravir (50, 150, or 300 mg/kg/day) and female rats (50 animals) were orally administered repeated doses of vehicle or raltegravir (50, 300, or 600 mg/kg/day) for 1 year. In many of the deaths through Drug Week 81 (males, 11, 15, and 16 deaths, respectively; females, 9, 13, and 23 deaths, respectively), histomorphologic examination through Drug Week 76 has revealed inflammation, epithelial hyperplasia, and squamous metaplasia following chronic irritation to the mucosa of

the nose and nasopharynx. Five squamous cell carcinomas of the mucosa of the nose and nasopharynx have been identified in high dose female animals and chondrosarcoma of the nose has been observed in one mid dose male rat. Concerning the nasal and nasopharyngeal mucosal tumors, the prior assessment requestor has discussed that the tumor lesions noted following treatment with raltegravir were due to chronic irritation because inflammation of the nasopharynx associated with raltegravir irritation was observed in male rats in the rat 27-week oral toxicity study (TT046022) and these tumors are consistent with the findings observed in Fisher rats treated with irritant chemicals.

PMDA accepted the prior assessment requestor's view. Then, PMDA asked for the prior assessment requestor's opinions on the potential for raltegravir to cause tumors in the stomach and on the safety in humans since the prior assessment requestor discussed that the nasal and nasopharyngeal mucosal tumors in the high dose group as shown in the preliminary results of the rat carcinogenicity study were due to inflammation caused by chronic irritation from raltegravir, and inflammation and degeneration in the stomach, which are similar to those in the mucosa of the nose and nasopharynx, have been observed in the rat 5-week oral toxicity study (TT040079) and rat 27-week oral toxicity study (TT046022).

The prior assessment requestor responded as follows:
The increased stomach inflammation and nonglandular mucosal vacuolation observed in the rat 5-week oral toxicity study (TT040079) are considered to have been caused by the drug's rapid contact with the gastric mucosa of the rat and mucosal surface irritation associated with the dosing procedure using a catheter. In the 27-week oral toxicity study (TT046022), glandular mucosal degeneration was noted after 6-month administration of raltegravir, which is considered attributable to local irritation from raltegravir as seen in the 5-week oral toxicity study. On the other hand, in a study where raltegravir was administered to dogs for 53 weeks at doses that were double the doses given to rats based on body surface area (TT049001), stomach inflammation etc. were not observed in the dogs having no forestomach.

As described above, the tumor lesions observed in this study are considered associated with chronic irritation from raltegravir. However, since humans have no forestomach as with dogs and raltegravir is taken in the form of a film-coated, solid tablet that is dissolved slowly in the upper gastrointestinal tract, inflammation of the

gastrointestinal tract is very unlikely to occur in humans.

Under the current situation where the carcinogenicity studies have not yet been completed, PMDA considers that it is important to monitor the results from the carcinogenicity studies and safety information in humans in future, since cancers have been reported in patients treated with raltegravir and the causality has been unknown; the tumors of the nose/nasopharynx as shown in the preliminary results of the rat carcinogenicity study seem to have been due to local deposition and/or aspiration of the drug in the mucosa of the nose/nasopharynx during dosing; and these tumors of the nose/nasopharynx are considered to be the expected outcome of chronic irritation and inflammation.

- Local tolerance studies (TT05551/TT05510, TT05545/TT05541, TT055509, TT045550/TT045556)
  In local tolerance studies, raltegravir was a moderate to severe irritant to the bovine cornea, but no evidence of irritation was observed in an *in vitro* human epidermal skin culture system, mouse skin, or rabbit skin.

- Phototoxicity study (TT062519)
  Vehicle, raltegravir (1000, 1500, and 2000 mg/kg/day), and chlorpromazine (positive control) were orally administered to female mice. As a result, raltegravir was not phototoxic.

- Hemolytic assay (TT064903, TT064905)
  Raltegravir was negative for *in vitro* hemolysis of rat, dog, or human erythrocytes.

- Intravenous single-dose toxicity study in rats (TT062521)
  Female rats received vehicle (0.9% isotonic sodium chloride solution) or raltegravir (100, 200, 400, 800, or 1600 mg/kg). As a result, since mortality occurred at ≥ 200 mg/kg, the approximate lethal dose was determined to be 200 mg/kg.

- Intravenous repeated-dose toxicity study in dogs (TT066030)
  Vehicle (0.9% isotonic sodium chloride solution) and raltegravir (30 and 100 mg/kg/day) were administered intravenously for 7 days. At 100 mg/kg/day, body weight loss, small increase in serum urea nitrogen levels, increases in ALT, ALP, and cholesterol, and slight renal tubular dilation were noted. The NOAEL was

determined to be 30 mg/kg.

- Toxicity study on an impurity (TT066055)
  In order to qualify an impurity in raltegravir (Related Substance B), raltegravir 30, 120, and 600 mg/kg/day (0.009, 0.036, and 0.18 mg/kg/day, respectively, as the impurity) were administered to male and female rats. As a result, no enhanced toxicities or no new toxicities were noted. [Note by PMDA: The details of the results of a toxicity study to qualify Related Substance A are being asked to the prior assessment requestor]

4. Clinical data

In the following text, the doses of the investigational drug are all expressed in terms of raltegravir, the active ingredient, though raltegravir potassium was actually administered.

4.(i) Human pharmacokinetics and pharmacodynamics

- Human pharmacokinetic data submitted include 2 single- and multiple-dose studies in healthy male adult subjects, 1 human ADME study, 3 pharmacokinetic studies in special populations, and 9 drug interaction studies, and as other studies, 1 QT/QTc study and 1 UGT1A1 polymorphism study. In addition, 3 biopharmaceutic studies including a food effect study were submitted.

- The effect of food on the pharmacokinetics of raltegravir was investigated in Study 028 using the Phase II/III/FMI formulation intended for marketing, Study 001 using the Phase I Lactose formulation, and Study 007 using the Phase I poloxamer formulation. There was little food effect on the pharmacokinetics of the Phase I Lactose formulation and the Phase I poloxamer formulation while dosing with a high-fat meal resulted in a 34% decrease in C_{max}, an 8.5-fold increase in C_{12hr}, and a 7.3-hour delay in T_{max} compared to fasted dosing in Study 028 using the Phase II/III/FMI formulation (an investigation of the effect of a standard high-fat meal on the pharmacokinetics of a single oral dose of 400 mg of raltegravir in 20 healthy adult subjects). The effect of food on the absorption phase observed in Study 028 was consistent with the results of population pharmacokinetic analysis (PPK analysis). However, the efficacy and safety of raltegravir potassium have been demonstrated in phase II and phase III studies where raltegravir potassium was administered without regard to food and the changes in the pharmacokinetic profile of the Phase II/III/FMI formulation intended for marketing following fed dosing

were not considered clinically meaningful (≥ 2-fold increase in AUC for safety, ≥ 60% decrease in C_{12hr} for efficacy).

- Coadministration with rifampicin (RFP), an UGT1A1 inducer, decreased raltegravir C_{12hr} by 61%, $AUC_{0-\infty}$ by 40%, and C_{max} by 38%. Caution should be used when coadministering raltegravir with strong inducers of UGT1A1, e.g. RFP.

- Coadministration with tipranavir/ritonavir (TPV/RTV) decreased raltegravir C_{12hr} by 55%, $AUC_{0-\infty}$ by 24%, and C_{max} by 18%, but the efficacy of raltegravir in combination with TPV/RTV has been confirmed in phase III studies (Study 018, Study 019). Thus, TPV/RTV may be coadministered with raltegravir without dose adjustment of raltegravir.

- Coadministration with ATV, a strong inhibitor of UGT1A1 or ATV/RTV increased raltegravir plasma levels (Coadministration with ATV resulted in a 1.53-fold increase in raltegravir C_{max}, a 1.72-fold increase in AUC, and a 1.95-fold increase in C_{min} and coadministration with ATV/RTV resulted in a 1.24-fold increase in C_{max}, a 1.41-fold increase in AUC, and a 1.77-fold increase in C_{min}). However, concomitant use of raltegravir with ATV/RTV was well-tolerated in phase II (Study 005) and phase III (Study 018, Study 019) studies. Thus, ATV/RTV may be coadministered with raltegravir without dose adjustment of raltegravir.

- Using plasma drug concentration data (785 subjects, 5634 sampling points) from phase I studies (Study 020, Study 025, Study 028), phase II studies (Study 004, Study 005), and phase III studies (Study 018, Study 019), PPK analysis was performed to evaluate the effects of the pre-selected covariates (CrCL, body weight, HIV RNA level, dose, gender, clinical trial phase, food status [fed/fasted]) on the pharmacokinetics of raltegravir. As a result, the statistically significant covariates were an effect of CrCL on CL/F of raltegravir and food status on duration of absorption of raltegravir. However, simulations predicted that CrCL has a modest magnitude of effect on AUC_{0-12h} and C_{12hr}. The simulations of food effect indicated no effect on AUC_{0-12h}, but an increase in C_{12hr} in the presence of food (a 6.8-fold increase compared to fasted state), which is consistent with the results of a phase I study (Study 028). It has been discussed that the predicted covariate effects are not clinically meaningful.

・ The potential for UGT1A1 polymorphism to affect the pharmacokinetics of raltegravir was investigated in Study 013 with 48 healthy adult subjects. According to the preliminary analysis of the pharmacokinetic parameters of 11 subjects (7 subjects with UGT1A1*28/*28, 4 subjects with UGT1A1*1/*1) ([redacted], 20[redacted]), the ratio of $AUC_{0-\infty}$ ([UGT1A1*28/*28]/[UGT1A1*1/*1]) (90% CI [confidence interval]) was 0.94 (0.36, 2.49), the ratio of C_{max} was 1.03 (0.27, 3.84), and the ratio of C_{12hr} was 2.51 (0.81, 7.82).

・ The results of a composite analysis across phase I to III studies (Studies 004, 014, 015, 017, 020, 025, 028) (the results of comparisons of pharmacokinetic parameters in Hispanic vs. black, Hispanic vs. white [Note by PMDA: Including Asian], and black vs. white [Note by PMDA: Including Asian]) indicate that there are no major differences in the pharmacokinetics of raltegravir among the different racial groups.

・ PMDA asked the prior assessment requestor to explain the reason for including Asian in the white population for the composite analysis to assess the effect of race on the pharmacokinetics of raltegravir and its appropriateness.

The prior assessment requestor responded as follows:
In the composite analysis, there was only 1 Asian subject, which was insufficient to analyze the Asian population as an independent subgroup. Therefore, for this analysis, it was decided to include 1 multiracial subject and 1 Asian subject in the white population, which accounted for most of the subjects in the phase I clinical studies of raltegravir. As a result, the pharmacokinetic parameters (AUC, C_{12hr}, and C_{max}) of the Asian subject were all within the variation ranges of the white population and there should be no problems with handling the Asian data as the white population data.

PMDA considers as follows:
The data from only 1 Asian subject are available and under the current situation, the prior assessment requestor can not determine based on the results of the composite analysis that race (black, white, and Hispanic subjects were included in the analysis) has no significant effect on the pharmacokinetics of raltegravir. However, at present, it is necessary to fully provide information about Asian pharmacokinetic data being very limited and then determine the pharmacokinetics of raltegravir in Japanese subjects promptly after approval. This point will be finalized taking also account of

the expert advisors' opinions.

4.(ii) Clinical efficacy and safety

4.(ii).(1) Submitted clinical study data

- For this prior assessment, 18 phase I studies in healthy subjects [a single-dose study, a multiple-dose study, a single-dose, crossover study to assess the cardiac safety of raltegravir potassium and moxifloxacin as positive control (Study 024), a drug interaction study with TMC125 (Study 026), and a bioequivalence study of the tablet formulations for clinical studies and the tablet formulation intended for marketing (Study 028)] were submitted. A study to assess the safety of raltegravir potassium in subjects with severe renal insufficiency (Study 015) and a study to assess the safety of raltegravir potassium in subjects with moderate hepatic insufficiency (Study 014) were submitted. Furthermore, in HIV-infected subjects, 2 phase II studies (Study 004, Study 005) and 2 phase III studies (Study 018, Study 019) were submitted (see the table below for the overview of phase II and phase III studies).

Overview of the phase II and phase III clinical studies

Protocol	Phase	Study population	Dosage regimen	Duration of treatment	Number of subjects	Primary efficacy endpoint	Major findings
004	IIa	Anti-HIV treatment-naïve, HIV-1-infected patients (≥ 18 years, HIV RNA ≥ 5000 copies/mL, CD4 cell count ≥ 100 cells/mm^3)	Part I Raltegravir 100, 200, 400, 600 mg BID vs. Placebo Part II Raltegravir 100, 200, 400, 600 mg BID + Tenofovir (TDF) + Lamivudine (3TC) vs Efavirenz (EFV) + TDF + 3TC	Part I 10 days Part II 48 weeks	Part I 35 Part II 169	Part I Change from baseline in HIV RNA (log_{10} copies/mL) on Day 10 Part II Proportion of patients with HIV RNA < 400 copies/mL at Week 24	Part I Raltegravir 100 mg BID group, -1.93; Raltegravir 200 mg BID group, -1.98; Raltegravir 400 mg BID group, -1.66; Raltegravir 600 mg BID group, -2.16; Placebo group, -0.17 Part II (Cohort II) Raltegravir 100 mg BID group, 93.9%; Raltegravir 200 mg BID group, 81.8%; Raltegravir 400 mg BID group, 100%; Raltegravir 600 mg BID group, 94.1%; EFV 600 mg QD group, 94.1%
005	IIb	HIV-1-infected patients with documented resistance to at least 1 drug in each of the 3 classes of anti-HIV agents (NRTI, NNRTI, PI) (≥ 18 years, HIV RNA ≥ 5000 copies/mL, CD4 cell count ≥ 50 cells/mm^3)	Raltegravir 200, 400, 600 mg BID + optimized background therapy (OBT) vs Placebo + OBT After 24 weeks of therapy, Raltegravir 400 mg BID	≥ 24 weeks (96 weeks after switched to Raltegravir 400 mg BID)	178	Change from baseline in HIV RNA (log_{10} copies/mL) at Week 24	Double-blind phase Substudy A Raltegravir 200 mg BID group, -1.83; Raltegravir 400 mg BID group, -1.76; Raltegravir 600 mg BID group, -1.74; Placebo group, -0.26 Substudy B Raltegravir 200 mg BID group, -1.73; Raltegravir 400 mg BID group, -2.11; Raltegravir 600 mg BID group, -2.07; Placebo group, -0.60
018	III	HIV-1-infected patients with documented resistance to at least 1 drug in each of the 3 classes of anti-HIV agents (NRTI, NNRTI, PI) (HIV RNA > 1000 copies/mL)	OBT + Raltegravir 400 mg BID OBT + Placebo	156 weeks	350	Proportion of patients with HIV RNA < 400 copies/mL at Week 16	Raltegravir 400 mg BID group, 78.1% Placebo group, 41.0%
019	III		OBT + Raltegravir 400 mg BID OBT + Placebo	156 weeks	349	Proportion of patients with HIV RNA < 400 copies/mL at Week 16	Raltegravir 400 mg BID group, 78.3% Placebo group, 43.2%

4.(ii).(2) Summary of the pivotal clinical studies

4.(ii).(2). 1) Study 018 (BENCHMRK-1)

An international, double-blind, randomized, comparative study in treatment-experienced, HIV-infected patients with documented resistance to at least 1 drug in each of the 3 classes of licensed anti-HIV agents (NRTI, NNRTI, PI) (HIV RNA > 1000 copies/mL) (target number of subjects: 230 subjects in the raltegravir 400 mg BID group and 115 subjects in the placebo group) was conducted at 65 sites in 12 foreign countries including Taiwan and Thailand from [redacted] 20[redacted] to [redacted] 20[redacted] (at 48-week data cutoff, the study is still ongoing) to evaluate the add-on effect of raltegravir 400 mg BID in combination with optimized background therapy (OBT).

Subjects were stratified by enfuvirtide (ENF) use in OBT and degree of resistance to

protease inhibitors (resistant to 1 PI or > 1 PI) at randomization (randomized in a 2:1 ratio to raltegravir or placebo).

Of the 500 enrolled patients, 352 patients (excluding the cases of inclusion criteria not met [132 patients], consent withdrawal [8 patients], protocol violations [5 patients], site closure [2 patients], and clinical adverse events [1 patient]) were randomized and excluding 2 patients who did not receive study drug, 350 patients (232 patients in the raltegravir 400 mg BID group, 118 patients in the placebo group) were included in the efficacy analysis population [modified-intention-to-treat (MITT)].

The primary efficacy endpoint, the proportion of patients with HIV RNA < 400 copies/mL at Week 16 was significantly higher in the raltegravir 400 mg BID group compared to the placebo group (see the table below). Also when NC = F approach (Non-Complete = Failure: Patients who prematurely discontinued the assigned treatment regardless of reasons were considered as failures thereafter) and OF approach (Observed Failure: Patients who prematurely discontinued the assigned treatment due to lack of efficacy were considered failures thereafter) were used, similar outcomes were obtained.

Virologic response (Study 018, TRD = F approach[1])

Proportion of patients with blood HIV RNA < 400 copies/mL								
	Week 16				Week 24			
Treatment group	n/N	% (95% CI)	Adjusted odds ratio [2] (95% CI)	*P*-value [2]	n/N	% (95% CI)	Adjusted odds ratio [2] (95% CI)	*P*-value [2]
Raltegravir 400 mg BID	178/228	78.1 (72.1, 83.3)	10.6 (5.6, 20.3)	< 0.001	119/158	75.3 (67.8, 81.8)	8.8 (4.2, 18.4)	< 0.001
Placebo	48/117	41.0 (32.0, 50.5)			32/81	39.5 (28.8, 51.0)		
Proportion of patients with blood HIV RNA < 50 copies/mL								
	Week 16				Week 24			
Treatment group	n/N	% (95% CI)	Adjusted odds ratio [2] (95% CI)	*P*-value [2]	n/N	% (95% CI)	Adjusted odds ratio [2] (95% CI)	*P*-value [2]
Raltegravir 400 mg BID	141/228	61.8 (55.2, 68.2)	5.0 (2.9, 8.8)	< 0.001	96/158	60.8 (52.7, 68.4)	4.1 (2.2, 7.8)	< 0.001
Placebo	39/117	33.3 (24.9, 42.6)			27/81	33.3 (23.2, 44.7)		
Proportion of patients with reduction from baseline in blood HIV RNA > 1.0 $\log_{10}$								
	Week 16				Week 24			
Treatment group	n/N	% (95% CI)	Adjusted odds ratio [2] (95% CI)	*P*-value [2]	n/N	% (95% CI)	Adjusted odds ratio [2] (95% CI)	*P*-value [2]
Raltegravir 400 mg BID	182/228	79.8 (74.0, 84.8)	10.0 (5.6, 17.7)	< 0.001	118/158	74.7 (67.2, 81.3)	6.2 (3.3, 11.8)	< 0.001
Placebo	40/117	34.2 (25.7, 43.5)			29/81	35.8 (25.4, 47.2)		
Proportion of patients with reduction from baseline in blood HIV RNA > 1.0 $\log_{10}$ or blood HIV RNA < 400 copies/mL								
	Week 16				Week 24			
Treatment group	n/N	% (95% CI)	Adjusted odds ratio [2] (95% CI)	*P*-value [2]	n/N	% (95% CI)	Adjusted odds ratio [2] (95% CI)	*P*-value [2]
Raltegravir 400 mg BID	197/228	86.4 (81.3, 90.6)	17.2 (8.7, 33.9)	< 0.001	128/158	81.0 (74.0, 86.8)	9.3 (4.5, 19.4)	< 0.001
Placebo	49/117	41.9 (32.8, 51.4)			35/81	43.2 (32.2, 54.7)		

1) Patients who prematurely discontinued the assigned treatment due to lack of efficacy or adverse experiences were considered as failures thereafter.
2) A logistic regression analysis adjusted for treatment group, the baseline HIV RNA level, enfuvirtide use in OBT in enfuvirtide -naïve patients, active PI in OBT determined by phenotypic resistance test, and darunavir use in OBT in darunavir-naïve patients.
n/N = (number of responders)/(number of patients)

The safety analyses included 350 patients treated with raltegravir 400 mg BID or placebo in the double-blind phase (232 patients in the raltegravir 400 mg BID group, 118 patients in the placebo group) and 54 patients who were identified as virologic failures at Week 16 or beyond and entered the Open-Label Post Virologic Failure (OLPVF) phase to receive raltegravir 400 mg BID.

In the double-blind phase, clinical adverse events occurred in 188 of 232 patients (81.0%) of the raltegravir 400 mg BID group and 98 of 118 patients (83.1%) of the placebo group. Adverse events occurring in ≥ 10% of patients in either treatment group are presented in the following table.

Adverse events occurring in ≥ 10% of subjects in either treatment group (Study 018, double-blind phase)

Adverse event (PT)	Raltegravir 400 mg BID (N=232)	Placebo (N=118)
	N (%)	N (%)
Diarrhoea	36 (15.5)	26 (22.0)
Nausea	16 (6.9)	12 (10.2)
Vomiting	13 (5.6)	12 (10.2)
Injection site reaction	16 (6.9)	14 (11.9)
Headache	14 (6.0)	18 (15.3)

Abnormal laboratory values were observed in 50 of 232 patients (21.6%) of the raltegravir 400 mg BID group and 20 of 118 patients (16.9%) of the placebo group. Abnormal laboratory values occurring in ≥ 10% of patients in either treatment group were neutrophil count decreased (1 of 6 patients [16.7%] of the raltegravir 400 mg BID group and 0 of 3 patients [0%] of the placebo group) and blood testosterone decreased (0 patient and 1 of 1 patient [100%], respectively).

Serious adverse events were reported by 25 of 232 patients (10.8%) of the raltegravir 400 mg BID group and 16 of 118 patients (13.6%) of the placebo group. Serious abnormal laboratory values were noted in the raltegravir 400 mg BID group only (2 of 232 patients [0.9%], 3 cases [ALT increased, AST increased, neutrophil count decreased]).

Deaths were reported in 3 of 232 patients (1.3%) of the raltegravir 400 mg BID group and 1 of 118 patients (0.8%) of the placebo group. Among which, a causal relationship to raltegravir potassium could not be denied for lymphoma (1 patient) [Note by PMDA: The details of this case are being asked to the prior assessment requestor]. Adverse events leading to treatment discontinuation occurred in 4 of 232 patients (1.7%) of the raltegravir 400 mg BID group and 2 of 118 patients (1.7%) of the placebo group. Among which, a causal relationship to study treatment could not be denied for 2 patients (hepatitis; hepatomegaly and hyperuricaemia) in the raltegravir 400 mg BID group and 1 patient (nausea) in the placebo group.

In the OLPVF phase, 24 of 54 patients (44.4%) experienced adverse events. Serious adverse events were reported in 5 of 54 patients (9.3%). There were no deaths or no

adverse events leading to treatment discontinuation.

According to the additionally submitted data up to [redacted], 20[redacted], 41 of 232 patients (17.7%) in the raltegravir 400 mg BID group and 65 of 118 patients (55.1%) in the placebo group experienced virologic failure. Deaths were reported in 3 of 232 patients (1.3%) of the raltegravir 400 mg BID group and 1 of 118 patients (0.8%) of the placebo group.

4.(ii).(2). 2) Study 019 (BENCHMRK-2)

An international, double-blind, randomized, comparative study in treatment-experienced, HIV-infected patients (HIV RNA > 1000 copies/mL) with documented resistance to at least 1 drug in each of the 3 classes of licensed anti-HIV agents (NRTI, NNRTI, PI) was conducted at 53 sites in 6 foreign countries from [redacted] 20[redacted] to [redacted] 20[redacted] (at 48-week data cutoff, the study is still ongoing) to evaluate the add-on effect of raltegravir 400 mg BID in combination with OBT (target number of subjects: 230 subjects in the raltegravir 400 mg BID group and 115 subjects in the placebo group).

Subjects were stratified by ENF use in OBT and degree of resistance to protease inhibitors (resistant to 1 PI or > 1 PI) at randomization (randomized in a 2:1 ratio to raltegravir or placebo).

Of the 512 enrolled patients, 351 patients (excluding the cases of inclusion criteria not met [142 patients], consent withdrawal [12 patients], protocol violations [2 patients], clinical adverse events [3 patients], and lost to follow-up [2 patients]) were randomized and excluding 2 patients who did not receive study drug, 349 patients (230 patients in the raltegravir 400 mg BID group, 119 patients in the placebo group) were included in the efficacy analysis population (modified-intention-to-treat [MITT]).

The primary efficacy endpoint, the proportion of patients with HIV RNA < 400 copies/mL at Week 16 was significantly higher in the raltegravir 400 mg BID group compared to the placebo group (see the table below). Also when NC = F approach and OF approach were used, similar outcomes were obtained.

Virologic response (Study 019, TRD = F approach[1)])

Proportion of patients with blood HIV RNA < 400 copies/mL								
	Week 16				Week 24			
Treatment group	n/N	% (95% CI)	Adjusted odds ratio [2)] (95% CI)	*P*-value [2)]	n/N	% (95% CI)	Adjusted odds ratio [2)] (95% CI)	*P*-value [2)]
Raltegravir 400 mg BID	177/226	78.3 (72.4, 83.5)	9.6 (5.0, 18.3)	< 0.001	97/128	75.8 (67.4, 82.9)	9.1 (4.0, 20.5)	< 0.001
Placebo	51/118	43.2 (34.1, 52.7)			27/69	39.1 (27.6, 51.6)		
Proportion of patients with blood HIV RNA < 50 copies/mL								
	Week 16				Week 24			
Treatment group	n/N	% (95% CI)	Adjusted odds ratio [2)] (95% CI)	*P*-value [2)]	n/N	% (95% CI)	Adjusted odds ratio [2)] (95% CI)	*P*-value [2)]
Raltegravir 400 mg BID	142/226	62.8 (56.2, 69.1)	4.5 (2.6, 8.0)	< 0.001	83/128	64.8 (55.9, 73.1)	5.7 (2.7, 12.2)	< 0.001
Placebo	43/118	36.4 (27.8, 45.8)			23/69	33.3 (22.4, 45.7)		
Proportion of patients with reduction from baseline in blood HIV RNA > 1.0 $\log_{10}$								
	Week 16				Week 24			
Treatment group	n/N	% (95% CI)	Adjusted odds ratio [2)] (95% CI)	*P*-value [2)]	n/N	% (95% CI)	Adjusted odds ratio [2)] (95% CI)	*P*-value [2)]
Raltegravir 400 mg BID	180/226	79.6 (73.8, 84.7)	6.8 (3.8, 12.2)	< 0.001	100/128	78.1 (70.0, 84.9)	9.0 (4.0, 20.2)	< 0.001
Placebo	56/118	47.5 (38.2, 56.9)			27/69	39.1 (27.6, 51.6)		
Proportion of patients with reduction from baseline in blood HIV RNA > 1.0 $\log_{10}$ or blood HIV RNA < 400 copies/mL								
	Week 16				Week 24			
Treatment group	n/N	% (95% CI)	Adjusted odds ratio [2)] (95% CI)	*P*-value [2)]	n/N	% (95% CI)	Adjusted odds ratio [2)] (95% CI)	*P*-value [2)]
Raltegravir 400 mg BID	190/226	84.1 (78.6, 88.6)	10.1 (5.2, 19.8)	< 0.001	103/128	80.5 (72.5, 86.9)	10.6 (4.5, 25.2)	< 0.001
Placebo	60/118	50.8 (41.5, 60.2)			30/69	43.5 (31.6, 56.0)		

1) Patients who prematurely discontinued the assigned treatment due to lack of efficacy or adverse experiences were considered as failures thereafter.
2) A logistic regression analysis adjusted for treatment group, the baseline HIV RNA level, enfuvirtide use in OBT in enfuvirtide -naïve patients, active PI in OBT determined by phenotypic resistance test, and darunavir use in OBT in darunavir-naïve patients.
n/N = (number of responders)/(number of patients)

The safety analyses included 349 patients treated with raltegravir 400 mg BID or placebo in the double-blind phase and 51 patients who were identified as virologic failures at Week 16 or beyond and entered the OLPVF phase to receive raltegravir 400 mg BID.

In the double-blind phase, adverse events occurred in 186 of 230 patients (80.9%) of

the raltegravir 400 mg BID group and 103 of 119 patients (86.6%) of the placebo group. Adverse events occurring in ≥ 10% of patients in either treatment group are presented in the following table.

Adverse events occurring in ≥ 10% of subjects in either treatment group (Study 019, double-blind phase)

Adverse event (PT)	Raltegravir 400 mg BID (N=230)	Placebo (N=119)
	N (%)	N (%)
Diarrhoea	39 (17.0)	20 (16.8)
Nausea	28 (12.2)	16 (13.4)
Fatigue	24 (10.4)	7 (5.9)
Injection site reaction	27 (11.7)	10 (8.4)
Pyrexia	11 (4.8)	18 (15.1)
Headache	26 (11.3)	10 (8.4)

Abnormal laboratory values were observed in 37 of 230 patients (16.1%) of the raltegravir 400 mg BID group and 20 of 119 patients (16.8%) of the placebo group. Abnoraml laboratory values occurring in ≥ 10% of patients in either treatment group were neutrophil count decreased (0 of 5 patients [0%] of the raltegravir 400 mg BID group and 1 of 3 patients [33.3%] of the placebo group).

Serious adverse events were reported by 22 of 230 patients (9.6%) of the raltegravir 400 mg BID group and 17 of 119 patients (14.3%) of the placebo group. No serious laboratory abnormalities were reported.

Deaths were reported in the raltegravir 400 mg BID group only (3 of 230 patients, 1.3%). Adverse events leading to treatment discontinuation occurred in 4 of 230 patients (1.7%) of the raltegravir 400 mg BID group and 1 of 119 patients (0.8%) of the placebo group. Among which, a causal relationship to study treatment could not be denied for 2 cases (renal failure, flatulence) in the raltegravir 400 mg BID group. Abnormal laboratory values leading to treatment discontinuation were noted in the raltegravir 400 mg BID group only (1 of 230 patients, 0.4%), of which a causal relationship could not be denied for 3 events of ALT increased, AST increased, and blood bilirubin increased.

In the OLPVF phase, 23 of 51 patients (45.1%) experienced adverse events. Serious adverse events were reported by 7 of 51 patients (13.7%). One patient died due to progressive multifocal leukoencephalopathy, but its causal relationship to raltegravir potassium was denied. There were no adverse events leading to treatment discontinuation.

According to the additionally submitted data (the data up to [redacted], 20[redacted]), 43 of 230 patients (18.7%) of the raltegravir 400 mg BID group and 62 of 119 patients (52.1%) of the placebo group experienced virologic failure. Deaths were reported in the raltegravir 400 mg BID group only (4 of 230 patients, 1.7%).

4.(ii).(3) Efficacy evaluation

4.(ii).(3).1) Primary endpoint

- In foreign phase II studies (Studies 004 and 005), the primary timepoint for analysis was "Week 24." On the other hand, in foreign phase III studies (Studies 018 and 019), the primary timepoint was initially defined as "Week 24" as in the phase II studies before initiating the studies, but was changed from "Week 24" to "Week 16" during the studies.

PMDA asked the prior assessment requestor to explain the following points: (a) The reason for choosing a primary timepoint of "Week 24" at the stage of planning the phase II studies, (b) The timing of changing the primary timepoint from "Week 24" to "Week 16" during the studies and the procedure for amending the study plan, and (c) The appropriateness of choosing a primary timepoint of "Week 16" in the end for the phase III studies.

The prior assessment requestor responded as follows:
(a) In Study 004, subjects in the raltegravir group achieved HIV RNA < 50 copies/mL more quickly than those in the EFV group and the efficacy results observed at "Week 16" were sustained through "Week 24." (b) In Study 005 including anti-HIV treatment-experienced patients, who are similar to the patient populations enrolled in Studies 018 and 019, raltegravir potassium in combination with OBT demonstrated more potent and superior anti-viral efficacy compared to placebo with OBT and the efficacy results seen at "Week 16" were sustained through "Week 24." Taking account of the analysis results of the phase II studies (the primary timepoint was Week 24), the protocols and associated statistical analysis plans for Studies 018 and 019 were amended prior to the unblinding and analysis of the database to change the primary timepoint for efficacy analysis from "Week 24" to "Week 16."

PMDA also asked the prior assessment requestor to explain the rationale for selecting "the proportion of patients with HIV RNA < 400 copies/mL" as the primary endpoint

for Studies 018 and 019 and its clinical significance.

The prior assessment requestor responded as follows:
Blood HIV RNA level and CD4 cell count are widely accepted surrogate markers for efficacy in clinical trials of HIV therapeutics. Since primary study endpoints in clinical trials change year by year with advances in treatment, although "change from baseline in blood HIV RNA" was selected as the primary endpoint for Study 005 (the study was planned at the end of 20[redacted]), it was considered appropriate to select "the proportion of patients with blood HIV RNA < 400 copies/mL" rather than a simple reduction in blood HIV RNA level for Studies 018 and 019 (the studies were planned at the end of 20[redacted]). For preparing the prior assessment data, to allow integration of efficacy data for treatment-experienced patients, the more stringent virologic endpoints of the proportion of patients with blood HIV RNA < 400 and < 50 copies/mL were used to show the efficacy of raltegravir.

As to the primary timepoint and the primary endpoint, PMDA considers as follows:
According to "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (October 2006)" by the Department of Health and Human Services (DHHS), (a) The treatment goal for HIV infection is to reduce HIV-related mortality and reductions in plasma viremia achieved with antiretroviral therapy account for substantial clinical benefits, (b) Analysis of 18 trials that included more than 5,000 participants with viral load monitoring showed a significant association between a decrease in plasma viremia and improved clinical outcome. Thus, viral load testing serves as a surrogate marker for treatment response, (c) Virologic failure on treatment can be defined as (i) HIV RNA level > 400 copies/mL (at Week 24), (ii) > 50 copies/mL (at Week 48), or (iii) a repeated detectable HIV RNA level (> 400 copies/mL) after prior suppression of viremia (< 400 copies/mL), (d) One key goal of therapy is suppression of viral load to below the limits of detection (< 50 copies/mL by Ampricor assay) and viral suppression is generally achieved in 16–24 weeks. Therefore, taking into account that the study populations for Studies 018 and 019 were treatment-experienced, HIV-infected patients with documented resistance to at least 1 drug in each of the 3 classes of anti-retroviral therapies, selecting "the proportion of patients with HIV RNA < 400 copies/mL at Week 16" as the primary endpoint of virologic response is acceptable.

On the other hand, as described in "Guidelines for the Use of Antiretroviral Agents in

HIV-1-Infected Adults and Adolescents (October 2006)," suppression of plasma viremia as much as possible for as long as possible is a critical goal of antiretroviral therapy. Thus, PMDA judged that it is important to check the virologic response not only at the primary timepoint of Week 16, but also at Week 24 as initially planned, and long-term results in the raltegravir 400 mg BID group in Study 005. PMDA also judged that it is important to check "the proportion of patients with blood HIV RNA < 50 copies/mL," "the proportion of patients with reduction from baseline in blood HIV RNA $\geq$ 1.0 $\log_{10}$," and "an increase in CD4+ cell count," as well as "the proportion of patients with blood HIV RNA < 400 copies/mL."

4.(ii).(3).2) Efficacy

- PMDA confirmed the following points:

  The primary endpoint for the pivotal, foreign phase III studies (Studies 018 and 019), "the proportion of patients with HIV RNA < 400 copies/ mL at Week 16" was significantly higher in the raltegravir group compared to the placebo group in both studies 018 and 019. The efficacy of raltegravir potassium (virologic response) was still maintained at Week 24 in both studies 018 and 019. Furthermore, pooled efficacy analysis of Studies 018 and 019 also showed favorable results with raltegravir potassium (table below).

Virologic response (pooled analysis of Studies 018/019, TRD = F approach [1])

Proportion of patients with blood HIV RNA < 400 copies/mL								
	Week 16				Week 24			
Treatment group	n/N	% (95% CI)	Adjusted odds ratio (95% CI) [2]	*P*-value [2]	n/N	% (95% CI)	Adjusted odds ratio (95% CI) [2]	*P*-value [2]
Raltegravir 400 mg BID	355/454	78.2 (74.1, 81.9)	9.7 (6.2, 15.2)	< 0.001	216/286	75.5 (70.1, 80.4)	8.2 (4.8, 3.9)	< 0.001
Placebo	99/235	42.1 (35.7, 48.7)			59/150	39.3 (31.5, 47.6)		
Proportion of patients with blood HIV RNA < 50 copies/mL								
	Week 16				Week 24			
Treatment group	n/N	% (95% CI)	Adjusted odds ratio (95% CI) [2]	*P*-value [2]	n/N	% (95% CI)	Adjusted odds ratio (95% CI) [2]	*P*-value [2]
Raltegravir 400 mg BID	283/454	62.3 (57.7, 66.8)	4.7 (3.2, 7.0)	< 0.001	179/286	62.6 (56.7, 68.2)	4.5 (2.8, 7.2)	< 0.001
Placebo	82/235	34.9 (28.8, 41.4)			50/150	33.3 (25.9, 41.5)		
Proportion of patients with reduction from baseline in blood HIV RNA > 1.0 $\log_{10}$								
	Week 16				Week 24			
Treatment group	n/N	% (95% CI)	Adjusted odds ratio (95% CI) [2]	*P*-value [2]	n/N	% (95% CI)	Adjusted odds ratio (95% CI) [2]	*P*-value [2]
Raltegravir 400 mg BID	362/454	79.7 (75.7, 83.3)	8.1 (5.4, 12.1)	< 0.001	218/286	76.2 (70.9, 81.0)	7.0 (4.3, 11.4)	< 0.001
Placebo	96/235	40.9 (34.5, 47.4)			56/150	37.3 (29.6, 45.6)		
Proportion of patients with reduction from baseline in blood HIV RNA > 1.0 $\log_{10}$ or blood HIV RNA < 400 copies/mL								
	Week 16				Week 24			
Treatment group	n/N	% (95% CI)	Adjusted odds ratio (95% CI) [2]	*P*-value [2]	n/N	% (95% CI)	Adjusted odds ratio (95% CI) [2]	*P*-value [2]
Raltegravir 400 mg BID	387/454	85.2 (81.6, 88.4)	12.8 (8.0, 20.4)	< 0.001	231/286	80.8 (75.7, 85.2)	9.0 (5.3, 15.4)	< 0.001
Placebo	109/235	46.4 (39.9, 53.0)			65/150	43.3 (35.3, 51.7)		

1) Patients who prematurely discontinued the assigned treatment due to lack of efficacy or adverse experiences were considered as failures thereafter.
2) A logistic regression analysis adjusted for treatment group, the baseline HIV RNA level, enfuvirtide use in OBT in enfuvirtide-naïve patients, active PI in OBT determined by phenotypic resistance test, darunavir use in OBT in darunavir-naïve patients, and study.
n/N = (number of responders)/(number of patients)

- PMDA confirmed that based on the results of a foreign phase II study conducted in treatment-experienced, HIV-infected patients (Study 005), durable virologic response through Week 48 can be expected with raltegravir 400 mg BID (see the table below).

Virologic response (Study 005 [NC = F approach][1])

(Subgroups A and B combined, entire study period)

Treatment group	Proportion of patients with HIV RNA < 400 copies/mL n/N [% (95% CI)]		
	Week 16	Week 24	Week 48
Raltegravir 400 mg BID	35/45 [77.8 (62.9, 88.8)]	32/45 [71.1 (55.7, 83.6)]	28/44 [63.6 (47.8, 77.6)]
Placebo	8/45 [17.8 (8.0, 32.1)]	7/45 [15.6 (6.5, 29.5)]	6/45 [13.3 (5.1, 26.8)]
Treatment group	Proportion of patients with HIV RNA < 50 copies/mL n/N [% (95% CI)]		
	Week 16	Week 24	Week 48
Raltegravir 400 mg BID	29/45 [64.4 (48.8, 78.1)]	25/45 [55.6 (40.0, 70.4)]	20/44 [45.5 (30.4, 61.2)]
Placebo	6/45 [13.3 (5.1, 26.8)]	6/45 [13.3 (5.1, 26.8)]	4/45 [8.9 (2.5, 21.2)]

1) Patients who prematurely discontinued the assigned treatment regardless of reasons were considered as failures thereafter.
n/N = (number of responders)/(number of patients)
[Note by PMDA: The proportion of patients with reduction from baseline in blood HIV RNA > 1.0 $\log_{10}$ is being asked to the prior assessment requestor]

- PMDA asked the prior assessment requestor to explain the change of CD4-positive T-lymphocyte counts over time and the prior assessment requestor responded as follows:

  Analysis of Week 24 data from all patients in Study 018, Study 019, and Studies 018/019 combined demonstrated significant increases in CD4 cell counts in the raltegravir 400 mg BID+OBT group compared to the placebo+OBT group.

Change from baseline in CD4 cell count over time (cells/mm^3)
(Studies 018/019 combined) (OF approach[1])

Key efficacy endpoint	Timepoint	Response						Difference in change (mean) from baseline [Group A - Group B] (95% CI)
		Raltegravir 400 mg BID group (Group A)			Placebo group (Group B)			
		N	Baseline (Mean)	Mean change from baseline (95% CI)	N	Baseline (Mean)	Mean change from baseline (95% CI)	
Change from baseline in CD4 cell count (cells/mm^3)	Week 2	432	148.8	34.7 (29.0, 40.4)	229	159.1	22.0 (14.9, 29.1)	12.7 (3.6, 21.7)
	Week 4	447	151.0	57.4 (49.1, 65.8)	225	160.5	29.9 (21.4, 38.5)	27.5 (15.6, 39.4)
	Week 8	446	152.3	68.7 (60.5, 76.8)	231	158.9	36.3 (27.0, 45.6)	32.3 (20.0, 44.7)
	Week 12	437	152.3	81.2 (72.4, 89.9)	226	160.7	38.0 (29.5, 46.6)	43.1 (30.9, 55.3)
	Week 16	446	152.6	84.4 (75.5, 93.3)	229	157.8	35.6 (26.0, 45.1)	48.8 (35.8, 61.9)
	Week 24	437	151.0	83.7 (74.9, 92.5)	229	158.8	36.5 (27.0, 46.0)	47.2 (34.3, 60.1)

1) Baseline value was carried forward for patients who prematurely discontinued the assigned treatment due to lack of efficacy.

- PMDA confirmed that raltegravir potassium is effective in 22 Asian patients [Note by PMDA: Based on the patients' declaration] (16 patients in the raltegravir group, 6 patients in the placebo group) in foreign phase III studies (Studies 018 and 019) (see the table below) and that there are no major differences in the efficacy of raltegravir potassium between Asian patients and other racial groups.

Efficacy results in Asian patients (pooled analysis of 018/019) (all randomized and treated patients)

	Week 16 n (%) [95% CI]		Week 24 n (%) [95% CI]	
	Raltegravir 400 mg BID (N=16)	Placebo (N=6)	Raltegravir 400 mg BID (N=9)	Placebo (N=5)
Patients with blood HIV RNA < 400 copies/mL	14 (87.5%) [61.7, 98.4]	2 (33.3%) [4.3, 77.7]	7 (77.8%) [40.0, 97.2]	2 (40.0%) [5.3, 85.3]
Patients with blood HIV RNA < 50 copies/mL	12 (75.0%) [47.6, 92.7]	2 (33.3%) [4.3, 77.7]	6 (66.7%) [29.9, 92.5]	2 (40.0%) [5.3, 85.3]
Patients with blood HIV RNA < 400 copies/mL or reduction in blood HIV RNA > 1.0 $\log_{10}$	14 (87.5%) [61.7, 98.4]	2 (33.3%) [4.3, 77.7]	7 (77.8%) [40.0, 97.2]	2 (40.0%) [5.3, 85.3]
Mean change from baseline in blood HIV RNA ($\log_{10}$ copies/mL)	-2.21 [-2.7, -1.7]	-0.24 [-0.9, 0.4]	-2.30 [-3.1, -1.5]	-0.47 [-1.4, 0.4]
Mean change from baseline in CD4 cell count (cells/mm^3)	87.9 [48.0, 127.8]	40.8 [-55.1, 136.7]	102.0 [43.1, 160.9]	36.2 [-96.2, 168.6]
Virologic failure†	1 (6.3%) [0.2, 30.2]	4 (66.7%) [22.3, 95.7]	1 (11.1%) [0.3, 48.2]	4 (80.0%) [28.4, 99.5]
Non-responder	0 (0.0%) [0.0, 20.6]	4 (66.7%) [22.3, 95.7]	0 (0.0%) [0.0, 33.6]	4 (80.0%) [28.4, 99.5]
Rebound	1 (6.3%) [0.2, 30.2]	0 (0.0%) [0.0, 45.9]	1 (11.1%) [0.3, 48.2]	0 (0.0%) [0.0, 52.2]

†Virologic failure: defined as non-responders who did not achieve reduction from baseline in blood HIV RNA > 1.0 $\log_{10}$ copies/mL or blood HIV RNA < 400 copies/mL by Week 16, or viral rebound, which was defined as: (a) Blood HIV-1 RNA > 400 copies/mL (on 2 consecutive measurements at least 1 week apart) after initial response with blood HIV RNA < 400 copies/mL, or (b) > 1.0 $\log_{10}$ copies/mL increase in blood HIV-1 RNA above nadir level (on 2 consecutive measurements at least 1 week apart).

n: number of responders, N: number of patients

- It has been reported (IASR 2004; 25: 175-177) that in Japan, most of HIV-infected individuals are infected with HIV-1 and about 75% of them are infected with subtype B, about 20% of them are infected with CRF01_AE (formerly called subtype E), and the remaining several percent of them are infected with subtype C, F, A, or D. In addition, HIV-1 subtypes were determined for the samples from 400 HIV-infected individuals sent to the Kanagawa Prefectural Institute of Public Health from 1987 to 2002 and analyzed by route of infection. As a result, 97.2% (106 of 109 cases) of the infections transmitted through homosexual activity among Japanese men were caused by subtype B and subtype B accounted for 48.3% (193 of 400 cases) of all the infections followed by subtype E which accounted for 43.8% (175 of 400 cases) (2000-2002 Anti-AIDS Research Project supported by Health and Labour Sciences Research Grants, Research on HIV subtype and the establishment of a framework for HIV testing 11-(1). HIV-1 subtype analysis in Japan). In view of these situations, PMDA reviewed the efficacy by viral subtype and confirmed that there are no major differences in the efficacy (virologic response) between different viral subtypes (table below). PMDA also confirmed that there are no major differences in the change from baseline in CD4+ cell count at Week 16 between the different viral subtypes for the raltegravir 400 mg BID and placebo groups.

Virologic response at Week 24 by viral subtype
(OF approach[1)], pooled analysis of 018/019)

Viral subtype	Proportion of patients with < 400 copies/mL		Proportion of patients with < 50 copies/mL	
	Raltegravir 400 mg BID group	Placebo	Raltegravir 400 mg BID group	Placebo
	n/N % [95% CI]	n/N % [95% CI]	n/N % [95% CI]	n/N % [95% CI]
Clade B	309/403 76.7% [72.2, 80.7]	85/213 39.9% [33.3, 46.8]	257/403 63.8% [58.9, 68.5]	71/213 33.3% [27.0, 40.1]
Non-Clade B	31/38 81.6% [65.7, 92.3]	7/15 46.7% [21.3, 73.4]	25/38 65.8% [48.6, 80.4]	7/15 46.7% [21.3, 73.4]

1) Patients who prematurely discontinued the assigned treatment due to lack of efficacy were considered as failures thereafter.
n/N = (number of responders)/(number of patients)

- PMDA asked the prior assessment requestor to explain the possible impact of unapproved drugs in Japan, e.g. ENF and tipranavir (TPV), on efficacy outcome.

  The prior assessment requestor responded as follows:
  It was concluded from the results of the foreign phase III studies (Studies 018 and 019) that at least 1 other active anti-HIV agent should be combined with raltegravir potassium in order to maximize the efficacy of raltegravir potassium. Also, there are no data supporting that raltegravir potassium must be used in combination with specific drugs. It has been suggested that the patient's treatment regimen should contain at least 2 drugs (i.e. raltegravir potassium and at least 1 other active anti-HIV drug) regardless of whether or not anti-HIV drugs to be combined with raltegravir potassium are approved in Japan. Therefore, also in Japan, raltegravir potassium can be an effective key drug in HIV therapy.

  Although the possibility that efficacy outcome may differ depending on drugs used in OBT can not be ruled out, the foreign phase III studies have demonstrated virologic response with any OBT regimens. Thus, PMDA accepted the prior assessment requestor's response.

4.(ii).(4) Safety

- Among the raltegravir 400 mg BID group in the double-blind phase of Studies 005/018/019 (507 subjects), the most commonly reported adverse event was diarrhoea (84 of 507 subjects, 16.6%). Other adverse events occurring in ≥ 10% of the subjects were injection site reaction (52 subjects, 10.3%).

- According to the pooled data from 3 studies (the raltegravir 400 mg BID group of Study 005, Study 018, and Study 019), adverse events occurring in ≥ 5% of the

subjects in either the raltegravir 400 mg BID + OBT group or the placebo + OBT group are shown in the following table.

Adverse events occurring in ≥ 5% of subjects in either raltegravir 400 mg BID+OBT group or placebo + OBT group
(400 mg BID group of Study 005, Study 018, and Study 019 combined)

		Raltegravir 400 mg BID + OBT (N=507)		Placebo + OBT (N=282)	
		n	%	n	%
No. of subjects with adverse events		426	84.0	243	86.2
Gastrointestinal disorders					
	Abdominal pain	26	5.1	11	3.9
	Diarrhoea	84	16.6	55	19.5
	Nausea	50	9.9	40	14.2
	Vomiting	35	6.9	23	8.2
General disorders and administration site conditions					
	Fatigue	40	7.9	13	4.6
	Injection site reaction	52	10.3	28	9.9
	Pyrexia	25	4.9	29	10.3
Infections and infestations					
	Nasopharyngitis	31	6.1	11	3.9
	Oral candidiasis	6	1.2	15	5.3
	Upper respiratory tract infection	27	5.3	16	5.7
Nervous system disorders					
	Headache	49	9.7	33	11.7
Skin and subcutaneous tissue disorders					
	Rash	27	5.3	7	2.5

- In Study 029 (a phase I study), 4 study discontinuations due to rash were reported. Among the raltegravir 400 mg BID group in the double-blind phase of Studies 005/018/019 (507 subjects), 27 subjects (5.3%) had rash.

- PMDA asked the prior assessment requestor to explain a dose response relationship for safety.

  The prior assessment requestor responded as follows:
  The results of the phase II studies (Studies 004 and 005) showed no dose response relationship for safety profile. The results of the phase III studies (Studies 018 and 019) indicated no clinically meaningful differences in the safety profile between the raltegravir and placebo groups. In the phase II studies, raltegravir at doses ranging from 100 mg BID to 600 mg BID was often administered in combination with drugs that increase plasma concentrations of raltegravir (e.g. atazanavir, tenofovir), but within the dose range administered, raltegravir was generally well-tolerated and there were no dose-dependent toxic findings or no dose-limiting toxicity.

PMDA considers as follows:

The incidences of rash and cardiovascular adverse events (cardiac and vascular disorders) tended to rise with increasing dose of raltegravir and these events occurred slightly more frequently in the raltegravir 400 mg BID group compared to the control group. Thus, caution is needed for the possible occurrence of these 2 events, especially when blood concentrations increase due to drug-drug interactions.

Incidence of rash (double-blind phase: Studies 004, 005, 018, and 019)

	Raltegravir group (% [n/N])					Control group
	100 mg BID	200 mg BID	400 mg BID	600 mg BID	All doses	
N	39	83	548	85	755	320
Study 004†	2.6 (1/39)	7.5 (3/40)	9.8 (4/41)	10.0 (4/40)	7.5 (12/160)	13.2 (5/38)
Study 005‡		4.7 (2/43)	2.2 (1/45)	13.3 (6/45)	6.8 (9/133)	4.4 (2/45)
Study 018‡			6.5 (15/232)		6.5 (15/232)	3.4 (4/118)
Study 019‡			10.4 (24/230)		10.4 (24/230)	5.0 (6/119)
Total	2.6 (1/39)	6.0 (5/83)	8.0 (44/548)	11.8 (10/85)	7.9 (60/755)	5.3 (17/320)

†Raltegravir+TDF+3TC group vs. EFV+TDF+3TD group
‡Raltegravir+OBT group vs. Placebo+OBT group

Incidence of cardiovascular adverse events (double-blind phase: Studies 004, 005, 018, and 019)

	Raltegravir group (% [n/N])					Control group
	100 mg BID	200 mg BID	400 mg BID	600 mg BID	All doses	
N	39	83	548	85	755	320
Study 004†	5.1 (2/39)	2.5 (1/40)	7.3 (3/41)	5.0 (2/40)	5.0 (8/160)	0.0 (0/38)
Study 005‡		11.6 (5/43)	15.6 (7/45)	15.6 (7/45)	14.3 (19/133)	8.9 (4/45)
Study 018‡			5.6 (13/232)		5.6 (13/232)	5.9 (7/118)
Study 019‡			5.7 (13/230)		5.7 (13/230)	6.7 (8/119)
Total	5.1 (2/39)	7.2 (6/83)	6.6 (36/548)	10.6 (9/85)	7.0 (53/755)	5.9 (19/320)

†Raltegravir+TDF+3TC group vs. EFV+TDF+3TD group
‡Raltegravir+OBT group vs. Placebo+OBT group

- In the double-blind phase of Studies 005/018/019, laboratory adverse events of increased blood creatine kinase (CK) occurred at a higher incidence in the raltegravir 400 mg BID group than in the placebo group [raltegravir 400 mg BID group: 3.7% (19 of 507 subjects), placebo group: 1.1% (3 of 282 subjects)].

PMDA asked the prior assessment requestor to explain about musculoskeletal adverse events associated with raltegravir potassium.

The prior assessment requestor responded as follows:

Adverse events of CK elevation occurred slightly more frequently in the raltegravir group than in the placebo group, but these CK elevations were usually transient and there were no serious adverse events or discontinuations due to elevated CK levels in the double-blind phase or OLPVF phase of Studies 005/018/019. Concerning rhabdomyolysis and myopathy, 1 case of rhabdomyolysis was reported in Study 019 and 2 cases of serious myopathy and 2 cases of rhabdomyolysis were reported in the

Expanded Access Program, i.e. a compassionate use study of raltegravir potassium.

PMDA considers as follows:
As a causal relationship to raltegravir potassium could not be denied for the 1 case of rhabdomyolysis reported in Study 019 and a causal relationship to raltegravir potassium or etravirine could not be denied for the 1 case of myopathy in the Expanded Access Program, the occurrence of musculoskeletal adverse events associated with raltegravir potassium, though rare, can not be ruled out. Therefore, it is necessary to perform clinical laboratory tests, e.g. CK, as appropriate and pay attention to the possible occurrence of clinical symptoms during treatment with raltegravir potassium.

- PMDA asked the prior assessment requestor to explain the occurrence of malignancies in anti-HIV treatment-experienced patients who received raltegravir potassium in combination with OBT, i.e. the types of malignancies and the time to onset from the start of treatment.

The prior assessment requestor responded as follows:
According to an updated analysis including the complete data from the double-blind phase of 4 studies (Studies 004, 005, 018, and 019) as of [redacted], 20[redacted], the malignancy rates adjusted for patient exposure years (patient-year) were 2.3/100 patient-years in the raltegravir group and 1.9/100 patient-years in the control group and the relative risk (95% CI) was 1.2 [0.4, 4.1]. When raltegravir-treated patients in the double-blind and open-label phases of Studies 004, 005, 018, and 019 as of [redacted], 20[redacted] were included in an analysis, 26 cases of malignancies were identified among 916 raltegravir-treated patients with 1,118 patient-years of exposure (rate, 2.3/100 patient-years) (see the table below).

Summary of malignancy events (Studies 004, 005, 018, and 019 combined)
(double-blind phase, pen-label phase, OLPVF phase, as of [redacted], 20[redacted])

		Raltegravir (N=916) 1118 Patient-Years
	n (%)[†]	Rate[‡]
Total number of patients with malignancy events	**26 (2.8)**	**2.3**
Kaposi's sarcoma	**5 (0.5)**	**0.4**
Non-Hodgkin's lymphoma	**4 (0.4)**	**0.4**
B-cell lymphoma	2 (0.2)	0.2
T-cell lymphoma	1 (0.1)	0.1
Lymphoma - other	0 (0.0)	0.0
Lymphoma - other (central nervous system)	1 (0.1)	0.1
Hodgkin's lymphoma	**2 (0.2)**	**0.2**
Squamous cell carcinoma - anogenital	**7 (0.8)**	**0.6**
Squamous cell carcinoma - anal	3 (0.3)	0.3
Squamous cell carcinoma - carcinoma in situ - anal	4 (0.4)	0.4
Squamous cell carcinoma - other	**1 (0.1)**	**0.1**
Rectal cancer	**1 (0.1)**	**0.1**
Metastatic neoplasm, NOS	**0 (0.0)**	**0.0**
Hepatocellular carcinoma	**1 (0.1)**	**0.1**
Non-melanoma skin cancer	**7 (0.8)**	**0.6**
Squamous cell carcinoma - skin	5 (0.5)	0.4
Basal cell carcinoma	3 (0.3)	0.3

Note: Subjects with multiple events may be counted more than once in different terms, but only once in one term.
[†] Crude incidence (100 × n/N)
[‡] Events per 100 PY (Patients-years at risk: PYR), PYR calculated based on overall events.

(a) There are no differences in the malignancy rate or relative risk between an analysis of data from Studies 004, 005, 018, and 019 and an analysis of data from Studies 005, 018, and 019 excluding Study 004 that included anti-HIV treatment-naïve patients. (b) The imbalance in the rate of malignancies between raltegravir arms and placebo/control arms during the double-blind phase of the 4 studies has not been sustained with a follow-up as of [redacted] 20[redacted]. (c) Even when the raltegravir data from the open-label phase were included, the malignancy rate did not change.

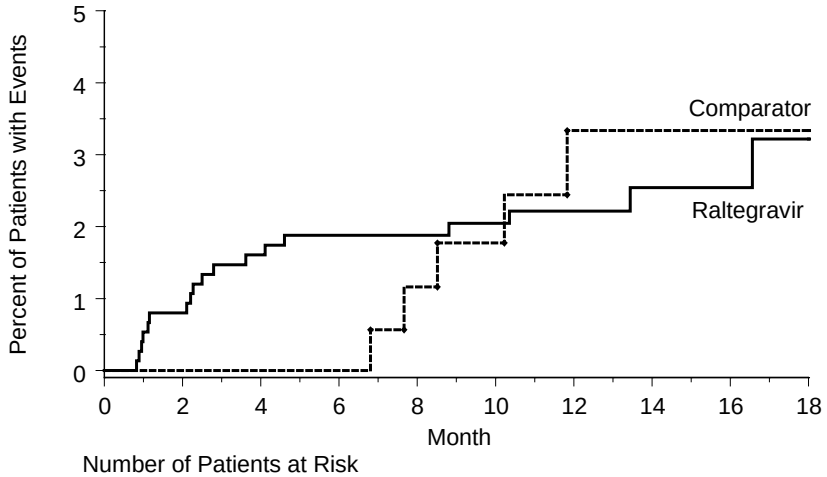
Therefore, raltegravir potassium is not considered associated with a specific risk of malignancies.

PMDA considers as follows:

The prior assessment requestor's response that raltegravir potassium is not associated with a specific risk of malignancies is acceptable. However, based on the pooled data from the double-blind phase of Studies 004, 005, 018, and 019, most of malignancies occurred within 6 months after the start of the study in the raltegravir group, while malignancies occurred beyond 6 months in the control group (see the figure below).

Taking account of this finding, the possibility of early onset of malignancies in the raltegravir group can not be ruled out and a post-marketing follow-up is needed.

Kaplan-Meier plot of time to malignancies
Pooled data from Studies 004, 005, 018, and 019 (double-blind phase, as of [redacted], 20[redacted])



Number of Patients at Risk

Raltegravir+OBT	758	739	727	666	612	573	406	238	145	141
Comparator+OBT	323	317	305	192	163	150	100	52	35	34

- As of [redacted], 20[redacted], 14 deaths have occurred in the raltegravir group and 1 death in the placebo group in Studies 005, 018, and 019. PMDA asked the prior assessment requestor to explain the reason for more deaths reported in the raltegravir group.

  The prior assessment requestor responded as follows:
  Safety analyses were based on the All-Patients-as-Treated (APaT) population consisting of all randomized patients who received at least 1 dose of study drug. The analysis demonstrates that the all-cause mortality rates per 100 patient-years were low in both the raltegravir and placebo groups during the double-blind phase and the entire study period (double-blind phase+open-label phase) of Studies 004, 005, 018, and 019 as of [redacted], 20[redacted] and the mortality rates during the double-blind phase were similar in the two groups (the following table). All deaths occurred in Studies 005, 018, or 019 that included anti-HIV treatment-experienced patients and no death was reported in Study 004 enrolling anti-HIV treatment-naïve patients, which should reflect the fact that the disease stage and immunodeficiency were considerably more advanced in patients from Studies 005, 018, and 019 compared to those from Study 004. All deaths were judged unrelated to study therapy by investigators.

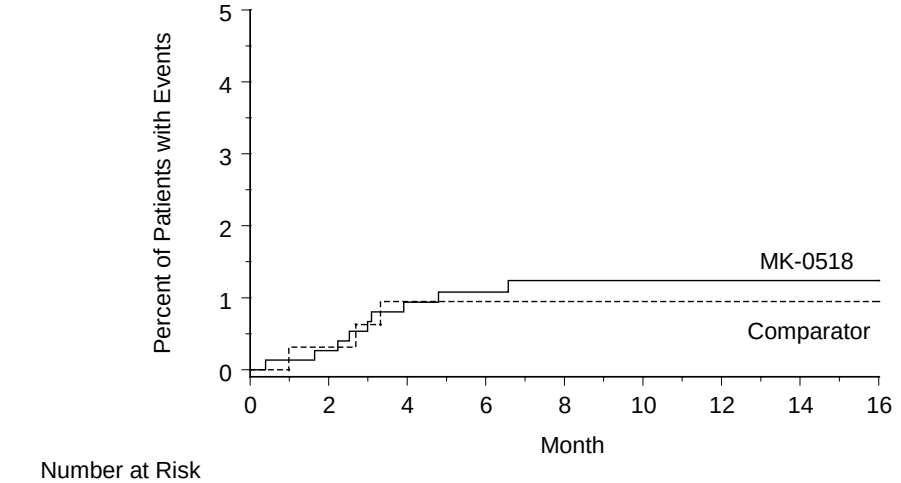
All-cause mortality – Relative risk and associated 95% CI
Studies 004, 005, 018, and 019 combined
(double-blind phase, frozen data, analysis as of [redacted], 20[redacted])

	Raltegravir group		Control group		Relative risk
	N	Cases/PYR[†] (Rate[‡])	N	Cases/PYR[†] (Rate[‡])	(95% CI)
Total	758	9/628 (1.433)	323	3/205 (1.465)	0.978 (0.244, 5.615)
Study 004	163	0/229 (0.000)	41	0/54 (0.000)	
Study 005	133	2/100 (2.004)	45	0/23 (0.000)	
Study 018	232	3/153 (1.963)	118	3/63 (4.741)	
Study 019	230	4/146 (2.733)	119	0/64 (0.000)	

[†] Patients-years at risk: Patient-years exposure.
[‡] Per 100 person-years.

Based on the pooled data from the double-blind phase of Studies 004, 005, 018, and 019, a majority of the deaths in both groups occurred prior to Week 16 (4 months) with no deaths in the raltegravir group after Week 28 (7 months) (see the figure below).

Kaplan-Meier plot of all-cause mortality
Studies 004, 005, 018, and 019 combined (double-blind phase, as of [redacted], 20[redacted])



Number at Risk

Raltegravir+OBT	758	745	735	676	463	243	154	145	142
Comparator+OBT	323	317	305	191	104	48	35	35	34

PMDA accepted the above response.

- A reduction of HIV viral load in blood to undetectable levels by HAART results in increased CD4 cell count and restoration of the immune system. During this process, flare-ups of opportunistic infections called immune reconstruction syndrome (IRS)

may occur.

PMDA asked the prior assessment requestor to explain IRS associated with raltegravir potassium.

The prior assessment requestor responded as follows:
In study 004 that included treatment-naïve patients and Studies 005 and 018 that included treatment-experienced patients, no cases of IRS have been reported. In Study 019, 4 cases of IRS (of which, 3 cases were in the raltegravir group and their primary diseases were hepatocellular carcinoma, cryptococcal meningitis, and unknown) have been reported.

PMDA considers as follows:
Since there is no consensus about how to manage IRS (Anti-HIV Treatment Guideline March 2007 [2006 Anti-AIDS Research Project supported by Health and Labour Sciences Research Grants, "Group for research on improvement and maintenance of drug adherence," Group leader: Takuma Shirasaka]), caution is needed when using raltegravir potassium like other anti-HIV agents.

・ PMDA asked the prior assessment requestor to explain the safety in the event of an overdosage.

The prior assessment requestor responded as follows:
In Study 018, overdosage with raltegravir was reported in 7 patients. Of whom, 5 patients took wrong doses (3 patients took 1200 mg for 1 day only; 1 patient took 1200 mg/day for 2 days; 1 patient took 1600 mg for 1 day only) and the other 2 patients took 1600 mg/day for 14 days and 1600 mg/days for 6 days, respectively. Patients who took 800 mg once daily were reported as having taken correct dose. None of these patients had adverse events associated with the wrong doses. In Study 019, 2 patients took over 800 mg/day for 1 day only. No adverse events associated with the wrong doses were reported in these patients. Up to June 7, 2007, in Study 019, 1 patient in the raltegravir group has mistakenly taken 1600 mg/day from Day 233 to Day 268, but has had no associated adverse events. According to clinical study data obtained to date, raltegravir should be well-tolerated at doses up to 800 mg BID and in combination with drugs that increase raltegravir exposure by 50% to 70% (e.g. TDF and ATV) and the possibility of toxicity from overdosage should be

low.

PMDA considers as follows:
Since the information on overdosage with raltegravir is limited and the extent to which raltegravir may be dialyzable is unknown, it is necessary to provide this information and continue to collect new information.

- The main mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation. PMDA asked for the prior assessment requestor's view on the association of UGT1A1 polymorphism with the pharmacokinetics and safety/efficacy of raltegravir in Japanese patients.

The prior assessment requestor responded as follows:
The results of preliminary analysis of UGT1A1 polymorphism study (Study 013) showed that the geometric mean ratios of $AUC_{0-\infty}$, C_{max}, and C_{12hr} ([UGT1A1*28/*28]/[UGT1A1*1/*1]) (90% CI) were 1.41 (0.96, 2.09), 1.40 (0.86, 2.28), and 1.91 (1.43, 2.55), respectively, suggesting that plasma concentrations of raltegravir were slightly higher in subjects with the variant UGT1A1 genotype (UGT1A1*28/*28) than in subjects with wild-type genotype (UGT1A1*1/*1). These results were consistent with the results of raltegravir drug interaction studies with ATV (UGT1A1 inhibitor) (Study 006, Study 010). Co-administration of raltegravir potassium with ATV in phase II and III studies demonstrated a favorable safety profile and the extent of increase in raltegravir plasma concentrations observed in subjects with UGT1A1*28/*28 in Study 013 was similar to that following the co-administration of raltegravir potassium and ATV. In Study 013, the upper limit of the 90% confidence interval for the geometric mean ratio of $AUC_{0-\infty}$ in patients with the UGT1A1*28/*28 genotype was slightly over the pre-specified clinically acceptable variation range (0.50, 2.00), but the overall effect was slight and no dose adjustment of raltegravir is required in patients with the UGT1A1*28/*28. Although it has been reported that the frequency of UGT1A1*28/*28 is lower among the Japanese population compared to the white and African populations (*Curr Drug Metab*. 2005; 6: 91-99, *Drug Metab Dispos*. 2005; 33: 458-465, *Drug Metab Rev.* 2005; 37: 327-378), there should be no essential differences in the pharmacokinetics, efficacy, and safety of raltegravir between Japanese and non-Japanese patients with UGT1A1 polymorphisms.

PMDA accepted the prior assessment requestor's response that no dose adjustment of raltegravir is required also in Japanese patients with the UGT1A1*28/*28 genotype, but considered that it is necessary at present to be fully aware that Japanese data are not available and to provide information appropriately, and instructed the prior assessment requestor accordingly.

- The prior assessment requestor explained as follows:
  Based on the results of Part I of Study 004, C_{trough} (C_{12hr}) is the most sensitive PK parameter to predict viral response. In this study, following coadministration with tenofovir and lamivudine, raltegravir AUC and C_{max} changes were within the clinically acceptable range and safety was unaffected, too. Although no drug interaction study with nevirapine has been conducted, there should be no clinically meaningful drug interactions. Inducers like EFV and nevirapine may be used concomitantly with the recommended dose of raltegravir. Although co-administration with ATV, which is known to be a strong UGT1A1 inhibitor, may increase raltegravir AUC by 30% to 70%, as the concomitant use of raltegravir 600 mg BID and ATV in Study 005 (13 subjects) was well tolerated, no dose adjustment of raltegravir is required.

  Taking into account that coadministration with EFV decreased raltegravir C_{trough} (C_{12hr}) by about 20% (geometric mean ratio [with EFV/without EFV], 0.79; 90% CI, 0.49-1.28), PMDA considers that the possibility of reduced efficacy of raltegravir when co-administered with UGT1A1 inducers such as EFV and nevirapine can not be ruled out.

4.(ii).(5) Clinical positioning

- PMDA asked the prior assessment requestor to explain the current criteria for determining an inadequate response to treatment.

  The prior assessment requestor responded as follows:
  Whether the response to anti-HIV therapy is adequate or not is determined based on the presence or absence of virologic failure, the presence or absence of immunologic failure, and the presence or absence of clinical failure, in both Japan and Europe/US. Since the primary goal of anti-HIV therapy is to keep blood HIV-RNA levels undetectable, the presence or absence of virologic failure as measured by blood HIV-RNA levels is very important for determining whether or not the response to

anti-HIV therapy is adequate.

PMDA furthermore asked the prior assessment requestor to explain the treatment of patients who are considered to have responded inadequately to their current therapies.

The prior assessment requestor responded as follows:
When drugs are changed, patients should be fully informed and they themselves need to examine the relevant information, and both the patients and healthcare professionals should be aware of the significance of changes of drugs and the importance of adherence and fewer treatment options in the future. The principles for changes of drugs are as follows: (a) Take into account that changes of drugs will lead to even fewer treatment options in the future, (b) Do not change drugs easily just because of short-term changes in blood HIV RNA levels or CD4+ lymphocyte counts, (c) Take different measures between a slightly/moderately treatment-experienced patient group (patients who have changed their anti-HIV therapy regimens once or twice and can be expected to benefit from changes of drugs to some extent) and a heavily treatment-experienced patient group (patients who have changed their anti-HIV therapy regimens at least several times and are unlikely to benefit from changes of drugs), (d) Even if therapeutic drugs are changed, efficacy can not be expected unless adherence is maintained, (e) When drugs are changed, choose preferentially drugs which are never used before and does not develop cross-resistance to drugs previously used, (f) Prior to changing drugs based on the results of drug resistance testing, seek specialist advice, (g) If drugs are discontinued due to adverse drug reactions etc., all drugs should be stopped simultaneously (except for EFV) in order to minimize the emergence of resistant virus.

In view of the above, PMDA asked the prior assessment requestor to explain the current clinical positioning of raltegravir potassium.

The prior assessment requestor responded as follows:
Since the choice of optimum combinations of anti-HIV drugs is generally limited for patients who have failed their current therapies, intra-class cross-resistance is a major issue. As raltegravir is an inhibitor of HIV integrase, which is 1 of 3 enzymes required for HIV-1 replication and catalyzes the stepwise process that results in the integration of the HIV-1 DNA into the genome of the host cell, and shows no

cross-resistance to anti-HIV agents from other classes, it would complement currently licensed anti-HIV agents.

PMDA considers as follows:
The prior assessment requestor's response is acceptable. At present, in the case where other drug options are available, e.g. in slightly or moderately treatment-experienced patients, the use of raltegravir potassium should be restricted unless it is necessary, with a view to avoiding the emergence of resistant virus against raltegravir wherever possible. In Japan, genotypic drug resistance testing to genotype the virus and identify amino acid mutations has been reimbursable under the National Health Insurance (NHI) system since April 2006. Therefore, anti-HIV therapy regimen should be changed based on the patient's anti-HIV treatment history and the results of drug resistance testing. This point will be finalized taking also account of the expert advisors' opinions.

- With respect to the prevalence of drug resistance mutations among newly infected individuals in Japan, the data from a research supported by Health and Labour Sciences Research Grants, "Research on the establishment of testing method and surveillance for drug-resistant HIV emergence (group leader: Wataru Sugiura)" have reported that 5% of the 576 treatment-naïve patients diagnosed between January 2003 and December 2004 had resistance mutations (Anti-HIV Treatment Guideline March 2006). According to the AIDS Annual Surveillance Report 2006 (from January 1 to December 31, 2006) (May 22, 2007, MHLW's AIDS Surveillance Committee), the annual number of new HIV infections peaked in 1992 and then declined, but kept increasing since 1996 and reached a record high (952 cases) in 2006. The number of new HIV (952 cases) and AIDS (406 cases) cases combined was 1358 in 2006, a record high and an increase of 159 cases from the previous year, and has exceeded 1000 for 3 consecutive years since 2004. Against this backdrop, there is a concern about an increase in drug resistance to currently available anti-HIV drugs as well, and a study on treatment-naïve patients with acute infections diagnosed between 1998 and 2004 in the US has reported that 19.7% of the cases had drug resistance mutations (12th Conference on Retroviruses and Opportunistic Infections abstract #673, 2005) and it has been reported that resistance mutations were detected in 13.5% of recently infected subjects and 8.7% of chronically infected subjects among treatment-naïve patients diagnosed between 1996 and 2001 in Europe (*J Infect Dis*. 2005;192: 958-66). As of December 2007, 22 active

ingredients have been approved for use in HIV infection, but since these drugs belong to NRTIs, NNRTIs, or PIs, PMDA considers that the clinical significance of raltegravir potassium with a different pharmacological mode of action from currently licensed drugs is very high. However, as the abuse of raltegravir potassium leads to the emergence of new resistant virus, raltegravir potassium should be used in treatment-experienced HIV patients with evidence of HIV replication despite ongoing anti-HIV therapy and resistance to at least 1 drug in each of the 3 classes of licensed anti-HIV agents (NRTI, NNRTI, PI), documented by drug resistance testing.

4.(ii).(6) Indication

- The indication presented for the prior assessment is "HIV-1 infection." The proposed "Precautions for Indications" section reads "Isentress should be used in combination with other anti-HIV medicines in HIV-1-infected patients with evidence of HIV-1 replication despite ongoing anti-HIV therapy."

- The US package insert includes the following indication: "Isentress in combination with other antiretroviral agents is indicated for the treatment of HIV-1 infection in treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral agents." Studies 018 and 019 included treatment-experienced, HIV-infected patients with documented resistance to at least 1 drug in each of the 3 classes of licensed oral anti-HIV agents (NRTI, NNRTI, PI).

- While the clinical studies have confirmed the efficacy of raltegravir potassium in HIV-1-infected patients only, a non-clinical study has demonstrated the activity against HIV-2 as well. Therefore, PMDA considers that the appropriate indication for raltegravir potassium should be "HIV infection" and it should be also stated that the activity against HIV-2 has been demonstrated in a non-clinical setting only. This point will be finalized, taking account of the expert advisors' opinions.

- "The current standard highly active antiretroviral therapy (HAART) is a combination of 2 NRTIs and 1 or 2 PIs (a total of 3-4 antiretroviral agents) or a combination of 2 NRTIs and 1 NNRTI (a total of 3 antiretroviral agents)" (Anti-HIV Treatment Guideline March 2007). For the treatment of patients who are considered to have responded inadequately to their current therapies, the following recommendation has been made: "Changes in therapy (salvage therapy) should be considered based on the

results of drug resistance testing for patients who are failing their current therapies due to drug resistance mutations, documented by drug resistance testing" (Anti-HIV Treatment Guideline March 2007 [2006 Anti-AIDS Research Project supported by Health and Labour Sciences Research Grants, "Group for Research on improvement and maintenance of drug adherence," group leader: Takuma Shirasaka]).

PMDA asked the prior assessment requestor to explain the choice of other anti-HIV agents to be combined with raltegravir potassium.

The prior assessment requestor responded as follows:
Based on the results of Studies 018 and 019, superior antiviral efficacy was observed with OBT regimens that included one or more active agents (e.g. Genotypic Sensitivity Score (GSS) ≥ 1), indicating that the treatment regimens that achieved adequate responses included two or more active anti-HIV agents (raltegravir potassium + one or more active agents). Japanese and foreign HIV treatment guidelines suggest that in order to resuppress the viral load maximally, at least 2 drugs in the virologically failing treatment regimen should be changed in treatment-experienced patients with documented drug resistance. Therefore, we, as the prior assessment requestor, consider that in the case of virologic failure in a treatment regimen, drug resistance testing should be performed to identify one or more active drugs to be combined with raltegravir potassium in a new regimen. We do not recommend the use of raltegravir potassium in place of any of the licensed drugs from the 3 classes and do not designate the total number of drugs to be used.

From an adherence standpoint, PMDA considers as follows:
Taking account of a report that the number of tablets (capsules) per day affects HAART treatment outcomes (Bartlett JA, et al. *AIDS*. 2001;15:1369), instead of simply increasing the number of tablets to be taken, drug resistance testing should be performed and then a raltegravir-containing regimen should be prescribed to appropriate patients in a way that ensures good adherence.

- It has been reported that in a study comparing drug resistance testing and conventional clinical experience without drug resistance testing for changes of drugs in patients who responded inadequately to anti-HIV therapy, the plasma HIV RNA level was reduced significantly in the former group (*AIDS Res Hum Retroviruses.* 2002; 18: 825-834, *AIDS.* 2002; 16:579-588).

PMDA asked the prior assessment requestor to explain the current status of the use of drug resistance testing in Japan.

The prior assessment requestor responded as follows:
The total number of new HIV-infected patients registered with the AIDS Surveillance Committee during the 2 years between January 2003 and December 2004 was 1,420 cases. According to a nationwide surveillance for drug-resistant HIV emergence among new HIV-infected patients conducted in the same period, drug resistance testing was performed for 575 new infection cases (267 cases in 2003 and 308 cases in 2004) (*Antiviral Res*. 2007; 75: 75-82).

PMDA asked the prior assessment requestor to explain about the measures to ensure that drug resistance testing is performed appropriately prior to the use of raltegravir potassium.

The prior assessment requestor responded as follows:
Through the distribution of "Guideline for HIV drug resistance testing (2006 Anti-AIDS Research Project supported by Health and Labour Sciences Research Grants, 'Research on preparation of medical service system for HIV infection,' chief researcher: Shinichi Oka, researcher: Wataru Sugiura)" and provision of information on raltegravir resistance based on foreign clinical studies, we will ask each medical institution to perform drug resistance testing at an appropriate timing.

PMDA accepted the above response.

- PMDA considers as follows:
  It is concerned that, in clinical practice, raltegravir potassium might be used also in patients for whom resistance to drugs in their current regimen has not been demonstrated, narrowing future therapeutic options due to easy changes of drugs. Therefore, raltegravir potassium should not be used in previously untreated patients or in the absence of drug resistance. The appropriate patient population should be "patients with an inadequate response to anti-HIV therapy and multi-drug resistance documented by drug resistance testing, in spite of good medication use behavior and adherence rates." However, as a foreign phase II clinical study in treatment-naïve patients (Study 004) has suggested the efficacy of raltegravir potassium (the table

below) and a foreign phase III study in treatment-naïve patients (Study 021) is currently ongoing (estimated completion date for 48-week CSR: [redacted], 20[redacted]), it is important to review the target population when new findings become available in future. Whether or not raltegravir potassium may be indicated for treatment-naïve patients will be determined, taking also account of the expert advisors' opinions.

Key virologic responses in treatment-naïve, HIV-infected patients

(Study 004 Part II Cohort II, NC = F approach[1)])

Study	Treatment group	Proportion of patients with HIV RNA < 400 copies/mL n/N (% [95% CI])			Proportion of patients with HIV RNA < 50 copies/mL n/N (% [95% CI])		
		Week 16	Week 24	Week 48	Week 16	Week 24	Week 48
004	Raltegravir 400 mg BID	34/35 (97.1% [85.1, 99.9])	35/35 (100.0% [90.0, 100.0])	35/35 (100.0% [90.0, 100.0])	34/35 (97.1% [85.1, 99.9])	33/35 (94.3% [80.8, 99.3])	31/35 (88.6% [73.3, 96.8])
	EFV 600 mg QD	32/34 (94.1% [(80.3, 99.3])	32/34 (94.1% [80.3, 99.3])	29/34 (85.3% [68.9, 95.0])	23/34 (67.6% [49.5, 82.6%])	31/34 (91.2% [76.3, 98.1])	29/34 (85.3% [68.9, 95.0])

1) Patients who prematurely discontinued the assigned treatment regardless of reasons were considered as failures thereafter.
n/N = (number of responders)/(number of patients)

4.(ii).(7) Dosage and administration

- "Dosage and administration" presented for the prior assessment is "The usual adult dosage is 400 mg as raltegravir administered orally, twice daily with or without food. Isentress must be used in combination with other anti-HIV medicines."

- PMDA asked the prior assessment requestor to explain the rationale for recommending raltegravir 400 mg BID.

The prior assessment requestor responded as follows:
Based on the results of phase I studies in healthy adult subjects, it was considered that the mean trough concentration of raltegravir would exceed the *in vitro* IC_{95} over the dose range of 100 to 600 mg. Thus, in a phase II study in treatment-naïve patients (Study 004), raltegravir was tested at the doses from 100 to 600 mg in combination with TDF and 3TC. In a phase II study in treatment-experienced patients (Study 005), raltegravir was tested at the doses from 200 to 600 mg in combination with OBT. Studies 004 and 005 showed that the use of raltegravir in combination therapy is very effective in reducing HIV RNA levels, but failed to demonstrate differences among the different doses of raltegravir for the efficacy endpoints. There were no dose-dependent or dose-limiting adverse events. According to PD analyses using the results of PK analysis of the rich sampling data from Study 004 and the results of PPK analysis of the sparse sampling data from

Studies 004, 005, 018, and 019, there were no clinically meaningful correlations between raltegravir concentrations and treatment responses. These data indicated that the range of blood concentrations obtained in the above 4 studies (Studies 004, 005, 018, and 019) falls near the top of the concentration-response curve (where treatment response may be only modestly concentration-dependent). Raltegravir 400 mg BID was chosen as the recommended dose for phase III studies based on the above efficacy and safety data and the general principle that the dose selection for anti-HIV therapy should focus on the maximum tolerated dose rather than the minimum effective dose.

PMDA considers that the prior assessment requestor's response has not fully explained the appropriateness of choosing raltegravir 400 mg BID from an efficacy and safety point of view. Therefore, the possibility that 400 mg BID may not be the optimal dosage of raltegravir can not be ruled out. But as the efficacy and safety of raltegravir 400 mg BID have been confirmed in the phase III studies, PMDA has determined that the dosage regimen of raltegravir 400 mg BID is acceptable.

・ PMDA asked the prior assessment requestor to explain the efficacy and safety of long-term treatment with raltegravir potassium in clinical studies.

The prior assessment requestor responded as follows:
Regarding efficacy, virologic response was sustained through 48 weeks of treatment with raltegravir potassium in Studies 004 and 005. As to safety, the mean duration of treatment with raltegravir potassium was 239.4 days (15-582 days) for the raltegravir 400 mg BID group in Study 004 and 297.8 days (1-612 days) for the raltegravir 400 mg BID group in Study 005 and the adverse event profile observed during a long-term follow-up was similar to the profile observed during the early phase of treatment.

PMDA considers that since the information on the efficacy and safety of long-term treatment with raltegravir potassium is limited at present, it is necessary to continue to collect information after the market launch.

・ PMDA asked the prior assessment requestor to compare the efficacy and safety data between fasted and fed administration and then explain the reason for determining that "raltegravir potassium can be taken with or without food."

The prior assessment requestor responded as follows:

In phase II (Studies 004 and 005) and phase III (Studies 018 and 019) studies where raltegravir potassium was administered, the timing of meals was not specified. Therefore, there are no data on whether raltegravir potassium was taken with or without food and it is difficult to compare the efficacy and safety of raltegravir potassium between fasted and fed administration. However, these studies have demonstrated excellent efficacy and good tolerability of raltegravir potassium regardless of food intake. The effect of food on the pharmacokinetics of raltegravir was evaluated and compared across Study 028 where a single dose of raltegravir was administered following a high-fat meal and Study 026 where multiple doses of raltegravir were administered following a moderate-fat meal, which suggested that food does not consistently increase individual C_{12hr} values. Then, in order to further evaluate the effect of food, a multiple-dose study to evaluate the effects of different types of food (a low-fat meal, a moderate-fat meal, a high-fat meal) (Study 035) was additionally conducted. The results of a preliminary analysis of the study are shown below.

Steady-state plasma pharmacokinetics in healthy adult subjects who received raltegravir potassium following a low-fat meal, a moderate-fat meal, and a high-fat meal or in the fasted state

PK parameter (Unit)	Type of food (Geometric mean)					Geometric mean ratio*			90% CI for geometric mean ratio		
	N	High	Moderate	Low	Fasted	High	Moderate	Low	High	Moderate	Low
C_{12hr} (nM)	19	453	182	93.9	110	4.13	1.66	0.86	(2.60, 6.57)	(1.04, 2.64)	(0.54, 1.36)
$AUC_{0\text{-}12h}$ (μM•hr)	19	21.2	11.3	5.38	10.0	2.11	1.13	0.54	(1.60, 2.80)	(0.85, 1.49)	(0.41, 0.71)
C_{max} (μM)	19	5.32	2.85	1.31	2.71	1.96	1.05	0.48	(1.41, 2.73)	(0.75, 1.46)	(0.35, 0.67)
T_{max} (hr)**	19	4.00	4.00	3.00	3.00				(1.05, 12.00)	(1.00, 10.00)	(0.50, 12.00)

*Geometric mean ratio vs. fasted administration **Median (Minimum, Maximum)

It was revealed that the effect of food on the pharmacokinetic profile of raltegravir differs depending on the types of food and its definite cause is unknown, but these differences may be attributable to differences in gastric or biliary secretions secondary to meal fat content or change in gastric pH. Considerable PK variability was also observed following fed administration and particularly the coefficients of variation for C_{12hr} were 201%, 123% and 221% for low-, moderate- and high-fat meals, respectively, compared to 47% for the fasted state. The geometric mean ratio of $AUC_{0\text{-}12hr}$ (a high-fat meal/fasting) was 2.11, which was slightly over the upper limit of changes that are not clinically meaningful (2.0), but no clinically relevant

safety findings were noted in subjects who took raltegravir potassium following a high-fat meal. Taking into account that the currently available data have shown no food effects that are consistent enough to strongly recommend taking raltegravir potassium after a meal, it has been determined that raltegravir potassium may be administered without regard to the timing of meals.

PMDA considers that the effect of food on the pharmacokinetics of raltegravir is apparent. However, there was no consistency in the changes of pharmacokinetic parameters across the different types of food and these changes do not seem to be significant enough to affect the efficacy or safety of raltegravir potassium, and the efficacy and safety of this drug product have been demonstrated in the phase II and III studies where raltegravir potassium was administered without regard to the timing of meals. Therefore, PMDA accepted the following dosing instruction also for Japanese patients: “Raltegravir potassium can be taken with or without food.”

- PMDA asked for the prior assessment requestor’s view on when to initiate treatment with raltegravir potassium.

The prior assessment requestor responded as follows:
If the response to ongoing anti-HIV therapy seems inadequate, the treatment regimen should be changed based on the principles for changes in anti-HIV therapy as recommended in the guidelines (HIV infection “Treatment Guide” Version 11 [Research Group for Therapy of HIV Infection]) and (Anti-HIV Treatment Guideline March 2007 [2006 Anti-AIDS Research Project supported by Health and Labour Sciences Research Grants, “Group for Research on improvement and maintenance of drug adherence”]).

PMDA considers as follows:
The use of raltegravir potassium should be restricted unless it is necessary, also with a view to avoiding the development of resistance. Meanwhile, as lower baseline HIV RNA levels are associated with better treatment outcomes (see the table below), patients considered appropriate to receive raltegravir potassium should promptly switch to a raltegravir-containing regimen based on their adherence and the results of drug resistance testing.

Efficacy analysis stratified by baseline HIV RNA level (at Week 48) (Study 004 Cohort I & II)

Treatment group	≤ 100000 copies/mL		> 100000 copies/mL		≤ 50000 copies/mL		> 50000 copies/mL	
	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)	N	% (95% CI)
Proportion of patients with HIV RNA < 400 copies/mL								
Raltegravir 400 mg BID	29	100.0% (88.1, 100.0)	12	91.7% (61.5, 99.8)	23	100.0% (85.2, 100.0)	18	94.4% (72.7, 99.9)
EFV 600 mg QD	24	95.8% (78.9, 99.9)	14	71.4% (41.9, 91.6)	13	92.3% (64.0, 99.8)	25	84.0% (63.9, 95.5)
Proportion of patients with HIV RNA < 50 copies/mL								
Raltegravir 400 mg BID	29	96.6% (82.2, 99.9)	12	66.7% (34.9, 90.1)	23	95.7% (78.1, 99.9)	18	77.8% (52.4, 93.6)
EFV 600 mg QD	24	95.8% (78.9, 99.9)	14	71.4% (41.9, 91.6)	13	92.3% (64.0, 99.8)	25	84.0% (63.9, 95.5)
Change from baseline in blood HIV RNA (log_{10} copies/mL)								
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)
Raltegravir 400 mg BID	29	-2.04 (-2.19, -1.89)	12	-2.77 (-3.34, -2.19)	23	-1.90 (-2.05, -1.76)	18	-2.69 (-3.06, -2.33)
EFV 600 mg QD	24	-2.12 (-2.36, -1.87)	12	-2.64 (-3.25, -2.02)	13	-1.78 (-2.15, -1.41)	23	-2.58 (-2.88, -2.28)

1) Patients who prematurely discontinued the assigned treatment regardless of reasons were considered as failures.
2) For patients who prematurely discontinued the assigned treatment due to lack of efficacy, baseline values were used.

Efficacy analysis by baseline HIV RNA level (at Week 24)
(Study 005 Substudies A&B, double-blind phase)

Treatment group	≤ 50000 copies/mL		> 50000 copies/mL	
	N	% (95% CI)	N	% (95% CI)
Proportion of patients with HIV RNA < 400 copies/mL [1)]				
Raltegravir 400 mg BID	21	90.48% (69.62, 98.83)	24	54.17% (32.82, 74.45)
Placebo	22	18.18% (5.19, 40.28)	23	13.04% (2.78, 33.59)
Proportion of patients with HIV RNA < 50 copies/mL [1)]				
Raltegravir 400 mg BID	21	61.90% (38.44, 81.89)	24	50.00% (29.12, 70.88)
Placebo	22	13.64% (2.91, 34.91)	23	13.04% (2.78, 33.59)
Change from baseline in blood HIV RNA (log_{10} copies/mL) [2)]				
	N	Mean (95% CI)	N	Mean (95% CI)
Raltegravir 400 mg BID	21	-1.87 (-2.09, -1.65)	24	-1.87 (-2.40, -1.34)
Placebo	22	-0.24 (-0.59, 0.10)	23	-0.45 (-0.85, -0.05)

1) Patients who prematurely discontinued the assigned treatment due to lack of efficacy were considered as failures.
2) For patients who prematurely discontinued the assigned treatment due to lack of efficacy, baseline values were used.

- PMDA considers as follows:

  Patients whose adherence rates are less than 95% do not have satisfactory treatment outcomes (*Ann Intern Med*. 2000; 133: 21-30) and the emergence of resistant HIV is closely associated with lowered adherence rates. Therefore, patients should not easily be switched to salvage therapy unless sure that nearly 100% adherence rates can be achieved. First of all, it is necessary to try to identify patient medication use behavior (adherence, dosing frequency, usage, e.g. after a meal/fasting) and adherence rates and to make the importance of improving the medication use behavior known.

  The prior assessment requestor described the following measures:

The information on appropriate use of raltegravir potassium will be communicated to each medical institution promptly and the development of a patient information leaflet (to be used by the medical institutions to explain to patients), which would help improve adherence, is under consideration.

PMDA accepted the above response.

4.(ii).(8) Drug resistance

- In Study 018, 34 of 232 subjects (14.7%) experienced virologic failure by Week 16, of whom 20 subjects were identified as virologic failures before the integrase genotyping cutoff date ([redacted], 20[redacted]) and 16 subjects had treatment-related integrase mutations. The virologic failure to raltegravir was primarily associated with Q148H/K/R or N155H mutation (observed in 12 subjects).

- In Study 019, 42 of 230 subjects (18.3%) experienced virologic failure by Week 16, of whom 19 subjects were identified as virologic failures before the integrase genotyping cutoff date ([redacted], 20[redacted]) and 11 subjects had treatment-related integrase mutations. The virologic failure to raltegravir was primarily associated with Q148H/K/R or N155H mutation (observed in 11 subjects).

Number (%) of patients on raltegravir 400 mg BID with virologic failures by Week 16 with integrase mutations at amino acids Q148/N155 (Study 018/Study 019)

Number (%) with mutation at amino acid Q148/N155	Study 018 (N=232)		Study 019 (N=230)	
	Non-Response* (N=1)	Viral Rebound** (N=19)	Non-Response* (N=7)	Viral Rebound** (N=12)
	N (%)	N (%)	N (%)	N (%)
With mutation at amino acid Q148/N155	0 (0)	12 (63.2)	3 (42.9)	8 (66.7)
With mutation at amino acid Q148	0 (0)	4 (21.1)	1 (14.3)	4 (33.3)
Q148H	0 (0)	1 (5.3)	1 (14.3)	1 (8.3)
Q148K	0 (0)	1 (5.3)	0 (0)	1 (8.3)
Q148R	0 (0)	2 (10.5)	0 (0)	2 (16.7)
With the N155H mutation	0 (0)	9 (47.4)	2 (28.6)	6 (50.0)
No mutation at amino acid Q148/N155	1 (100.0)	7 (36.8)	4 (57.1)	4 (33.3)

*: Patients who did not achieve > 1.0 $\log_{10}$ HIV RNA reduction or < 400 copies/mL by Week 16
**: Viral rebound (HIV RNA > 400 copies/mL on 2 consecutive measurements at least 1 week apart after initial response with HIV RNA < 400 copies/mL or > 1.0 $\log_{10}$ increase in HIV RNA above nadir level on 2 consecutive measurements at least 1 week apart).

- PMDA asked the prior assessment requestor to explain the currently available information on the reports of raltegravir resistance and its mechanism.

The prior assessment requestor responded as follows:

Phenotypic analysis of viruses with specific integrase mutations demonstrated that the key integrase mutations against raltegravir (N155H, Q148H/K/R, Y143R) conferred approximately 13- to 45-fold resistance to raltegravir [Note by PMDA: see 3. (i) Pharmacology]. Addition of L74M, E92Q, T97A, E138A/K or G140A/S to these single mutations substantially augmented resistance. As the co-crystal structure of raltegravir bound to integrase is not available, a biochemical study to understand the development of resistance to raltegravir associated with the aforementioned mutations was considered necessary and the study is currently ongoing.

PMDA considers as follows:

After the market launch, raltegravir potassium is expected to be used in many patients and resistant viruses may emerge and a currently unknown mechanism of acquiring resistance may be identified. Therefore, it is necessary to proactively collect information on raltegravir resistance not only from the biochemical study being conducted by the prior assessment requestor but also from the literature.

- PMDA asked the prior assessment requestor to explain any causes of virologic failures identified in Studies 004, 005, 018, and 019, other than integrase mutations, and the prior assessment requestor submitted the following table.

Summary of virologic failures without raltegravir resistance mutations (raltegravir group)

Study No.	Virologic failures (double-blind phase)†	Virologic failures with integrase genotypic data	Virologic failures without raltegravir resistance mutations (N, %)
Study 004	5	5	3 (60)
Study 005	38	38	3 (8)
Study 018	34	20‡	4 (20)
Study 019	42	19‡	7 (37)

† Virologic failure was analyzed at Week 48 in Study 004/005 and at Week 16 in Study 018/019.
‡ The genotypic data that became available at the time of preparing this document.

PMDA considers as follows:

Apart from resistance acquisition, medication non-compliance may be associated with virologic failure. Thus, attention needs to be paid to raltegravir resistance also from an adherence standpoint. Since integrase mutations associated with resistance to raltegravir were detected relatively early in the raltegravir 400 mg BID group (see the table below), it is necessary to carefully monitor resistance development and continue to collect information on virologic failure (rebound) and its causes.

Cumulative number of patients receiving raltegravir 400 mg BID with mutations at amino acids Q148/N155

	Study 005 *	Study 018	Study 019
N	45	232	230
	N (%)	N (%)	N (%)
Week 0	0 (0)	0 (0)	0 (0)
Week 2	0 (0)	0 (0)	0 (0)
Week 4	0 (0)	3 (1.3)	1 (0.4)
Week 8	0 (0)	7 (3.0)	7 (3.0)
Week 12	0 (0)	10 (4.3)	8 (3.5)
Week 16	8 (17.8)	12 (5.2)	12 (5.2)
Week 24	11(24.4)	12 (5.2)	12 (5.2)

*: Substudies A and B combined; double-blind phase

4.(ii).(9) Special patient population

4.(ii).(9).1) Children (low birth weight infants, neonates, nursing infants, infants, children)

- PMDA asked the prior assessment requestor to explain a pediatric development plan for raltegravir potassium (low birth weight infants, neonate**s**, nursing infants, infants, and children).

  The prior assessment requestor responded as follows:
  At present, there have been no data on the use of raltegravir potassium in children aged < 16 years. A multi-center, open-label, uncontrolled, phase I/II study in HIV-infected children aged between 2 and 18 years (target number of subjects: 120-140) is currently ongoing [Note by PMDA: NCT00485264, http://clinicaltrials.gov/ct2/show/NCT00485264?term=IMPAACT+P1066&rank=1 (January 2008)]. This study is intended to determine the pharmacokinetics, safety, tolerability, and efficacy of raltegravir potassium in this age group. In addition, the conduct of a clinical study in babies aged 4 weeks and [redacted] will be considered.

  PMDA considers that as the ongoing pediatric clinical study is expected to be completed in 2011, as soon as the study results become available, the information should be provided appropriately and promptly.

4.(ii).(10) Outline and progress status of ongoing or planned clinical studies

- PMDA asked the prior assessment requestor to explain the outline and progress status of ongoing or planned studies and the prior assessment requestor responded as follows.

List of ongoing or planned clinical studies of raltegravir potassium and estimated completion dates for clinical study reports

Study Description	Estimated completion date for CSR
Phase III (Studies 018 and 019): Week 48 safety and efficacy data (ongoing) [The both studies are multi-center, randomized, double-blind, placebo-controlled studies to evaluate the safety and anti-HIV activity of raltegravir potassium in combination with an optimized background therapy (OBT) versus OBT alone in HIV-infected patients with documented resistance to at least 1 drug in each of the 3 classes of licensed oral anti-HIV agents (NRTI, NNRTI, PI)]	May 31, 2008
Clinical studies:	
Study 004: A multi-center, double-blind, randomized, dose-ranging study to compare the safety and anti-HIV activity of raltegravir potassium plus TDF and 3TC versus EFV plus TDF and 3TC in anti-HIV treatment-naïve patients	June 30, 2009 (Final report) *
Study 005: A multi-center, randomized, double-blind, placebo-controlled, dose-ranging study to evaluate the safety, pharmacokinetics, and anti-HIV activity of raltegravir potassium in combination with an optimized background therapy (OBT) versus OBT alone in HIV-infected patients with documented resistance to at least 1 drug in each of the 3 classes of licensed oral anti-HIV agents (NRTI, NNRTI, PI)	June 30, 2009 (Final report) *
Study 018: A multi-center, randomized, double-blind, placebo-controlled study to evaluate the safety and anti-HIV activity of raltegravir potassium in combination with an optimized background therapy (OBT) versus OBT alone in HIV-infected patients with documented resistance to at least 1 drug in each of the 3 classes of licensed oral anti-HIV agents (NRTI, NNRTI, PI)	March 31, 2010 (Final report) *
Study 019: A multi-center, randomized, double-blind, placebo-controlled study to evaluate the safety and anti-HIV activity of raltegravir potassium in combination with an optimized background therapy (OBT) versus OBT alone in HIV-infected patients with documented resistance to at least 1 drug in each of the 3 classes of licensed oral anti-HIV agents (NRTI, NNRTI, PI)	March 31, 2010 (Final report) *
Study 021: A multi-center, randomized, double-blind, active-controlled study to evaluate the safety and anti-HIV activity of raltegravir potassium plus Truvada™ versus EFV plus Truvada™ in anti-HIV treatment-naïve patients	March 31, 2009 (Week 48) March 31, 2010 (Week 96) *
Study 023: Early access program with raltegravir potassium in combination with an optimized background therapy for highly treatment-experienced HIV-1 patients with no treatment options	June 30, 2009 (Final report) *
Study 032: A multi-center, randomized, double-blind, active-controlled study to evaluate the safety and anti-HIV activity of raltegravir potassium versus Kaletra™ in HIV-infected patients switched from a stable and effective Kaletra™-based regimen (Study A)	June 30, 2010 (Final report) *
Study 033: A multi-center, randomized, double-blind, active-controlled study to evaluate the safety and anti-HIV activity of raltegravir potassium versus Kaletra™ in HIV-infected patients switched from a stable and effective Kaletra™-based regimen (Study B)	June 30, 2010 (Final report) *
Drug interaction studies:	
Study 027: [redacted]	[redacted]
Study 029: [redacted]	[redacted]
Study 030: [redacted]	[redacted]
Study 034: [redacted]	[redacted]
Study 035: [redacted]	[redacted]
Study 036: [redacted]	[redacted]

* These studies may be extended beyond their originally planned duration. In such case, the submission date for clinical study report will be reviewed.

PMDA instructed the prior assessment requestor to report the results of these studies as soon as they become available and consider the necessity of providing information etc. and the prior assessment requestor accepted it.

Overall Evaluation

As a result of the above review based on the submitted prior assessment data, PMDA has concluded that the efficacy and safety of raltegravir potassium in "HIV-1-infected patients with evidence of HIV-1 replication despite ongoing anti-HIV therapy" have been demonstrated. Although there are no study data on the use of raltegravir potassium in Japanese subjects at present, since no ethnic differences among Hispanic, black, and white subjects have been noted, the pharmacokinetics of raltegravir in Japanese subjects may be determined after the market launch. The following points will be finalized taking also account of the expert advisors' opinions.

- How patients should switch to a raltegravir-containing regimen based on prior anti-HIV treatment history and the results of drug resistance testing.
- Whether or not raltegravir potassium may be indicated for anti-HIV treatment-naïve patients and HIV-2 infected patients.
- Due to very limited Asian pharmacokinetic data, the pharmacokinetics of raltegravir in Japanese subjects should be determined promptly after approval.

Review Report (1)

April 14, 2008

I. Product Submitted for Registration

[Brand name] Isentress Tablets 400 mg

[Non-proprietary name] Raltegravir Potassium

[Applicant] Banyu Pharmaceutical Co., Ltd.

[Date of application] March 12, 2008

[Dosage form/Strength]

Each film-coated tablet contains 434.4 mg of raltegravir potassium (400 mg as raltegravir).

[Proposed indication] HIV-1 infection

[Proposed dosage and administration]

The usual adult dosage is 400 mg as raltegravir administered orally, twice daily with or without food. Isentress must be used in combination with other anti-HIV medicines.

II. Content of the Review

The Pharmaceuticals and Medical Devices Agency (PMDA) sought the expert advisors' opinions based on the Prior Assessment Report (1). Discussions with the expert advisors are outlined below.

The expert advisors attending the Expert Discussion have declared that they did not come under the Section 1 or 2 (1) of "Measures against the problem of conflict of interests involving the outside experts of the PMDA", dated May 8, 2007, regarding the product submitted for registration.

1) Pharmacokinetics

PMDA considers that as raltegravir pharmacokinetic data from only 1 Asian subject are available at present, it is necessary to fully provide information about Asian pharmacokinetic data being very limited and then determine the pharmacokinetics in Japanese subjects promptly after approval. The expert advisors' opinions on this point were sought.

The following comments were raised from the expert advisors:

Since there are no major differences in AUC between subjects with the variant UGT1A1 genotype (UGT1A1*28/*28) and subjects with wild-type genotype (UGT1A1*1/*1), it is

predicted that the effects of race on the pharmacokinetics of raltegravir are insignificant. However, as there are little Asian data, it is necessary to determine the pharmacokinetics in Japanese subjects promptly while fully providing information about a lack of Asian pharmacokinetic data. It is also necessary to continue to collect data and investigate the factors producing inter-individual variability in raltegravir blood concentrations.

Taking account of the above comments from the expert advisors, PMDA instructed the applicant to determine the pharmacokinetics in Japanese subjects promptly after approval and consider collecting information on the factors including those producing inter-individual variability in blood concentrations.

The applicant accepted it.

2) Efficacy

Concerning the efficacy of raltegravir potassium, PMDA considered that taking into account that the study populations for foreign phase III studies were treatment-experienced, HIV-infected patients with documented resistance to at least 1 drug in each of the 3 classes of anti-retroviral therapies (NRTI, NNRTI, PI), selecting “the proportion of patients with HIV RNA < 400 copies/mL at Week 16” as the primary endpoint of virologic response was acceptable.

However, PMDA considered that it was important to also check the virologic response at the initially planned primary timepoint of “Week 24,” long-term results in the raltegravir 400 mg BID group in Study 005, and “the proportion of patients with blood HIV RNA < 50 copies/mL,” “the proportion of patients with reduction from baseline in blood HIV RNA $\geq$ 1.0 $\log_{10}$,” and “an increase in CD4+ cell count” and reviewed the data from a phase II study (Study 005) and phase III studies (Studies 018 and 019) conducted in foreign countries. As a result, PMDA judged that (a) Durable virologic response through Week 48 can be expected with raltegravir 400 mg BID, (b) There are significant increases in CD4 cell counts in the raltegravir 400 mg BID+OBT group compared to the placebo+OBT group at Week 24, and (c) There are no major differences in the efficacy of raltegravir potassium between Asian patients and other racial groups.

The above judgments by PMDA on the efficacy of raltegravir potassium were supported by the expert advisors.

3) Safety

Concerning the safety of raltegravir potassium, PMDA considered that there are no particular tolerability problems based on the results from foreign phase III studies, but asked for the expert advisors' opinions on the items requiring particular caution and its method.

The following comments were raised from the expert advisors:

Concerning the safety of raltegravir potassium, PMDA's judgment that there are no particular tolerability problems seems appropriate. But raltegravir has a novel mode of action and thorough information collection, e.g. the conduct of a post-marketing survey over a certain period of time, covering all patients treated with raltegravir potassium, in order also to identify the occurrence of unexpected adverse drug reactions, is needed. Adequate attention needs to be paid to the possible occurrence of musculoskeletal adverse events and changes in blood creatine kinase (CK). Caution is needed for the possible occurrence of rash and cardiovascular adverse events (Cardiac and vascular disorders) when blood concentrations increase due to drug-drug interactions. Furthermore, as there is no information on the safety of long-term treatment with raltegravir potassium, it is necessary to adequately collect post-marketing information on the safety of long-term use, including the occurrence of malignancies.

Taking account of the above comments from the expert advisors, PMDA instructed the applicant to collect post-marketing safety information (including safety information concerning long-term use).

The applicant accepted it.

4) The patient population for which raltegravir potassium is indicated

While the clinical studies have confirmed the efficacy of raltegravir potassium in HIV-1 infection only, a non-clinical study has demonstrated the activity against HIV-2 as well. Therefore, PMDA judged that the indication "HIV infection" is acceptable as long as it is clearly stated that the activity against HIV-2 has been demonstrated in a non-clinical setting only. This judgment by PMDA was supported by the expert advisors.

PMDA also considered as follows:

Since the choice of optimum combinations of anti-HIV drugs is generally limited for patients who have failed their current therapies, intra-class cross-resistance is a major issue. As raltegravir is an inhibitor of HIV integrase and shows no cross-resistance to anti-HIV agents from other classes, it would complement currently licensed anti-HIV agents. However, at

present, in the case where other drug options are available, e.g. in slightly or moderately treatment-experienced patients, the use of raltegravir potassium should be restricted unless it is necessary also with a view to avoiding the emergence of resistant virus against raltegravir wherever possible. As a rule, raltegravir potassium should be used in treatment-experienced HIV patients with an inadequate response to anti-HIV therapy in spite of good medication use behavior and adherence rates and resistance to at least 1 drug in each of the 3 classes of licensed anti-HIV agents (NRTI, NNRTI, PI), documented by drug resistance testing.

The expert advisors' opinions on this point were sought and the following comments were raised from the expert advisors:
Based on the currently available data, raltegravir potassium should be used in anti-HIV treatment-experienced patients infected with resistant virus documented by drug resistance testing and raltegravir potassium should not be used in previously untreated patients or in the absence of drug resistance. However, since not a few cases of drug resistance have been reported even among previously untreated patients, drug resistance testing should be performed also for treatment-naïve patients and if the test results indicate resistance to at least 1 drug in each of the 3 classes of licensed anti-HIV agents (NRTI, NNRTI, PI), the use of raltegravir potassium should preferably be allowed. It is also preferable to allow the use of raltegravir potassium not only in the case of drug resistance but also in the case of intolerability, e.g. patients who can not use licensed anti-HIV drugs because of adverse events for which a causal relationship to these drugs can not be denied. Furthermore, as a foreign clinical study in treatment-naïve patients is ongoing, it is important to review the target population when new findings become available in future.

Taking account of the above comments from the expert advisors, PMDA determined that the appropriate indication should be "HIV infection" and the preferred patient population should be described in the "Precautions for Indications" section. PMDA also instructed the applicant to take measures to promote the proper use of raltegravir potassium after the market launch.

The applicant accepted it.

5) The items to be investigated via post-marketing surveillance
PMDA sought the expert advisors' opinions on the high priority items to be investigated via post-marketing surveillance and the following comments were raised from the expert advisors:
Prior to the use of raltegravir potassium, drug resistance testing should be performed and the information on the results of drug resistance testing should be collected. Regarding safety, the

information on the association between UGT1A1 polymorphism and adverse events, etc. should be collected. Furthermore, as resistance development to raltegravir has been reported from foreign post-marketing experience, considering that raltegravir pottasium will be used in many patients after the market launch also in Japan, it seems necessary to collect information on the development of resistance associated with the use of this drug. As soon as the results of ongoing clinical studies including a pediatric study and a study in treatment-naïve patients become available, the relevant information needs to be provided promptly.

Taking account of the above comments from the expert advisors, PMDA considered that in addition to the above information, the information on the occurrence of musculoskeletal adverse events such as changes in blood creatine kinase (CK), rash, cardiovascular adverse events (Cardiac and vascular disorders), and malignancies should continue to be collected and instructed the applicant accordingly.

The applicant accepted it.

6) Others

(1) The points that were being asked at the time of preparing the Prior Assessment Report

With respect to the points that were being asked to the applicant at the time of preparing the Prior Assessment Report, the applicant submitted the responses and PMDA reviewed the following information.

1) The details of the results of a toxicity study to qualify Related Substance A

Although a toxicity study on a metabolite of raltegravir (Related Substance A) has not been conducted, it was excreted in rat urine as a minor metabolite (M3) and has been identified as a metabolite in blood. Based on the NOAEL for a rat 5-week toxicity study (TT066055), i.e. 600 mg/kg/day (0.840 mg/kg/day as Related Substance A) and the NOAEL for a dog 53-week toxicity study (TT049001), i.e. 360 mg/kg/day (0.864 mg/kg/day as Related Substance A), the safety margins for Related Substance A contained in raltegravir at the upper specification limit level ([redacted]%) have been determined to be 14.7-fold and 15.1-fold, respectively. This response does not affect PMDA's view.

2) Virologic response in Study 005

The following table presenting virologic response in Study 005 was submitted and PMDA has confirmed that durable virologic response through Week 48 can be expected with raltegravir 400 mg BID from the data of the proportion of patients with reduction from baseline in blood HIV

RNA > 1.0 $\log_{10}$ (NC = F approach), the proportion of patients with blood HIV RNA < 400 copies/mL, and the proportion of patients with blood HIV RNA < 50 copies/mL. This response does not affect PMDA's view.

Virologic response [Study 005 (NC = F approach[1)])]
(Subgroups A and B combined, entire study period)

Treatment group	Proportion of patients with blood HIV RNA < 400 copies /mL n/N [% (95% CI)]		
	Week 16	Week 24	Week 48
Raltegravir 400 mg BID	35/45 [77.8 (62.9, 88.8)]	32/45 [71.1 (55.7, 83.6)]	28/44 [63.6 (47.8, 77.6)]
Placebo	8/45 [17.8 (8.0, 32.1)]	7/45 [15.6 (6.5, 29.5)]	6/45 [13.3 (5.1, 26.8)]
Treatment group	Proportion of patients with blood HIV RNA < 50 copies/mL n/N [% (95% CI)]		
	Week 16	Week 24	Week 48
Raltegravir 400 mg BID	29/45 [64.4 (48.8, 78.1)]	25/45 [55.6 (40.0, 70.4)]	20/44 [45.5 (30.4, 61.2)]
Placebo	6/45 [13.3 (5.1, 26.8)]	6/45 [13.3 (5.1, 26.8)]	4/45 [8.9 (2.5, 21.2)]
Treatment group	Proportion of patients with reduction from baseline in blood HIV RNA > 1.0 $\log_{10}$ n/N [% (95% CI)]		
	Week 16	Week 24	Week 48
Raltegravir 400 mg BID	40/45 [88.9 (75.9, 96.3)]	36/45 [80.0 (65.4, 90.4)]	29/44 [65.9 (50.1, 79.5)]
Placebo	10/45 [22.2 (11.2, 37.1)]	8/45 [17.8 (8.0, 32.1)]	5/45 [11.1 (3.7, 24.1)]

1) Patients who prematurely discontinued the assigned treatment regardless of reasons were considered as failures thereafter.

III. Results of Compliance Review Concerning the Submitted Data and Conclusion by PMDA

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

Document-based inspections and data reliability assessment was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in support of the new drug application. As a result, there were no particular problems. Also for clinical studies conducted in foreign countries, a document-based inspection was conducted and no problems were found. Therefore, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted documents.

IV. Overall Evaluation

As a result of the above review, PMDA has determined that the submitted data have demonstrated the efficacy and safety of raltegravir potassium. It is an anti-HIV drug with a novel mode of action and is expected to be effective in patients refractory to currently licensed

anti-HIV agents. On the other hand, due to its different mode of action, adverse drug reactions that are different from those associated with currently licensed anti-HIV agents may occur and careful monitoring is required. According to the submitted data, there have been no particular tolerability problems. However, as it is not long even in foreign countries since the product was approved, the available safety information is limited and thorough information collection is needed. Especially, the pharmacokinetics and safety/efficacy of the product in Japanese patients need to be investigated early after the market launch as no Japanese data are available.

Based on the above, it has been concluded that the product may be approved for the indication and dosage and administration as described below, with the following instructions and conditions. Since the product is an orphan drug, the appropriate re-examination period should be 10 years. The drug substance and the drug product are both classified as powerful drugs and the product is not classified as a biological product or a specified biological product.

[Indication] HIV infection

[Dosage and administration]

The usual adult dosage is 400 mg as raltegravir administered orally, twice daily with or without food. Isentress must be used in combination with other anti-HIV medicines.

[Instructions]

• Collect the following information after the market launch.

- Pharmacokinetics in Japanese subjects
- Results of drug resistance testing
- Emergence of resistant virus associated with the use of the product
- Association between UGT1A1 polymorphism and adverse events
- Safety in terms of musculoskeletal adverse events such as changes in blood creatine kinase (CK), rash, and cardiovascular adverse events
- Safety of long-term treatment with the product, including the occurrence of malignancies
- Factors producing inter-individual variability in blood concentrations, etc.

[Conditions for approval]

1. Since a pharmacokinetic study will be conducted in Japan, 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. Report the progress status of a Japanese pharmacokinetic study on a regular basis and submit the study data and analysis results promptly after the study completion. Also, as for ongoing or planned foreign clinical studies, submit the study data and analysis results promptly after the study completion.
3. Conduct a post-marketing survey 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 information on actual use of the product (patient background, 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.