Report on the Deliberation Results

March 3, 2014
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Efient 3.75 mg Tablets, Efient 5 mg Tablets
[Non-proprietary name]	Prasugrel Hydrochloride (JAN*)
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	June 18, 2013

[Results of deliberation]
In the meeting held on February 24, 2014, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug. The product is not classified as a biological product or a specified biological product.

**Japanese Accepted Name (modified INN)*

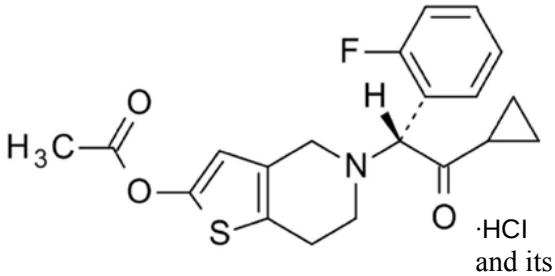
Review Report

February 3, 2014
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Efient 3.75 mg Tablets, Efient 5 mg Tablets
[Non-proprietary name]	Prasugrel Hydrochloride
[Name of applicant]	Daiichi Sankyo Company, Limited
[Date of application]	June 18, 2013
[Dosage form/Strength]	Film-coated tablets: Each tablet contains 3.75 mg or 5 mg of prasugrel which is present in the form of the hydrochloride salt.
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



and its enantiomer

Molecular formula: $C_{20}H_{20}FNO_3S \cdot HCl$
Molecular weight: 409.90
Chemical name:
5-[(1-*RS*)-2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate monohydrochloride

[Items warranting special mention]	Drug subjected to prior assessment consultations
[Reviewing office]	Office of New Drug II

Review Results

February 3, 2014

[Brand name] Efient 3.75 mg/5 mg Tablets
[Non-proprietary name] Prasugrel Hydrochloride
[Name of applicant] Daiichi Sankyo Company, Limited
[Date of application] June 18, 2013
[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in patients with ischemic heart disease (acute coronary syndrome [unstable angina, non ST segment elevation myocardial infarction, ST segment elevation myocardial infarction], stable angina pectoris, or old myocardial infarction) to be managed with percutaneous coronary intervention (PCI) has been demonstrated and its safety is acceptable in view of its observed benefits. The safety in patients with severe heart disease, in patients with hepatic impairment, in patients with a history of intracranial haemorrhage, cerebral infarction, or transient ischemic attack, and in patients with renal impairment needs to be further investigated via post-marketing surveillance.

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

[Indication]
The following ischemic heart diseases in patients who are to be managed with percutaneous coronary intervention (PCI):

- Acute coronary syndrome (unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction)
- Stable angina pectoris or old myocardial infarction

[Dosage and administration]
The usual adult dosage of prasugrel is 20 mg administered orally as a single loading dose on Day 1, and then 3.75 mg once daily orally as the maintenance dose from Day 2 onward.

Review Report (1)

December 9, 2013

I. Product Submitted for Registration

[Brand name]	Efient 3.75 mg Tablets, Efient 5 mg Tablets
[Non-proprietary name]	Prasugrel Hydrochloride
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	June 18, 2013
[Dosage form/Strength]	Film-coated tablet: Each tablet contains 3.75 mg or 5 mg of prasugrel which is present in the form of the hydrochloride salt.
[Proposed indication]	Reduction of thrombotic events in patients with the following ischemic heart diseases who are to be managed with percutaneous coronary intervention (PCI): • Acute coronary syndrome (unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction) • Stable angina pectoris or old myocardial infarction

[Proposed dosage and administration]

The usual adult dosage of prasugrel is 20 mg administered orally as a single loading dose on Day 1, and then 3.75 mg once daily orally as the maintenance dose from Day 2 onward.

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant in the application and the outline of a review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

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

Prasugrel Hydrochloride (hereinafter referred to as "prasugrel hydrochloride" or "prasugrel" as its free base) is an adenosine diphosphate (ADP) receptor antagonist with a thienopyridine skeleton discovered by Ube Industries, Ltd. and Sankyo Co., Ltd. (currently Daiichi Sankyo Company, Limited), and its drug product is administered orally. Prasugrel is metabolized to its active metabolite, which specifically and irreversibly inhibits $P2Y_{12}$, an ADP receptor on the platelet membrane, thereby reducing platelet aggregation.

In foreign countries, prasugrel hydrochloride was developed jointly by Eli Lilly and Company (US) and Daiichi Sankyo Company, Limited. Prasugrel hydrochloride was approved in Europe in February 2009 for the indication of "prevention of atherothrombotic events in patients with acute coronary syndrome (unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction) undergoing PCI," and in the US in July 2009 for the indication of "reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome (unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction) who are to be managed with PCI." As of June 2013, prasugrel hydrochloride has been approved in at least 70 countries or regions.

In Japan, the clinical development of prasugrel hydrochloride was initiated by Daiichi Sankyo in 20[redacted]. A marketing application has now been filed based mainly on the results of Japanese clinical studies which were conducted with a dosage regimen different from those approved in foreign countries.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance is white to brownish white crystals or crystalline powder. The general properties of the drug substance, including description, solubility, hygroscopicity, melting point, thermal analysis, dissociation constant, distribution coefficient, optical rotation, and crystalline polymorphism, have been determined. [redacted].

The chemical structure of the drug substance has been elucidated by elemental analysis, ultraviolet spectroscopy (UV), infrared spectrophotometry (IR), nuclear magnetic resonance spectra (^{1}H, ^{13}C NMR), mass spectrometry, and X-ray crystallography.

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

[redacted].

Step [redacted] is defined as the critical process. In-process controls and their acceptance criteria are defined in Steps [redacted], [redacted], and [redacted]. [redacted].

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

The proposed specifications for the drug substance include content, description (visual inspection), identification (IR, chloride [precipitation reaction]), purity (heavy metals [colorimetry]), related substances (liquid chromatography [HPLC]), residual solvents (gas chromatography), water content (Karl-Fisher), residue on ignition, and assay (HPLC).

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

Table 1 shows the main stability studies conducted on the drug substance. A photostability test showed that the drug substance was photostable.

Table 1. Stability studies of drug substance

Study	Primary batch	Temperature	Relative humidity	Storage form	Storage period
Long-term	3 commercial-scale batches	25°C	60%RH	[redacted][a]	36 months
Accelerated		40°C	75%RH		6 months

a, LDPE i.e., low density polyethylene

[redacted].

2.A.(2) Drug product

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

Efient 3.75 mg Tablets are slightly reddish white, oval film-coated tablets, each containing 4.12 mg of the drug substance (3.75 mg as prasugrel), and Efient 5 mg Tablets are slightly yellowish red, oval film-coated tablets, each containing 5.49 mg of the drug substance (5 mg as prasugrel). Each of 5-mg tablets has a score on one side (these proposed products are hereinafter collectively referred to as “Efient”). The drug product contains, as excipients, lactose hydrate, microcrystalline cellulose, low substituted hydroxypropylcellulose, hydroxypropylcellulose, magnesium stearate, hypromellose, titanium oxide, talc, red ferric oxide, and yellow ferric oxide (yellow ferric oxide is contained in 5-mg tablets only).

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

The manufacturing process of the drug product consists of milling, mixing, tableting, coating, and packaging/labeling steps.

[redacted]

The following studies were performed using a quality-by-design approach.

- Setting of the quality attributes of the target product and of the critical quality attributes (CQAs)
- Identification of process parameters and material attributes that affect the CQAs of the drug product based on quality risk assessment and on design of experiments

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

The proposed specifications for the drug product include content, description (visual inspection), identification (HPLC-UV), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), dissolution (paddle method, HPLC), and assay (HPLC).

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

Table 2 shows the main stability studies performed on the drug product. A photostability test showed that the drug product was photostable.

Table 2. Stability studies of drug product

Study	Primary batch	Temperature	Relative humidity	Storage form	Storage period
Long-term	3 pilot-scale batches	25°C	60%RH	PTP package[a]	24 months
Accelerated		40°C	75%RH	Bottle package[b]	6 months

a. Press-through package (PTP, made of polypropylene and aluminum foil) sheets placed in a laminated aluminum bag together with the desiccant (synthetic zeolite)
b. Glass bottles (made of soda-lime glass and metal [caps]) containing the desiccant (synthetic zeolite)

Based on the above results, a shelf life of 36 months has been proposed for the drug product when stored at room temperature in PTP sheets or bottles (3.75-mg tablets only), according to the "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003). The long-term study will be continued up to 36 months.

2.B Outline of the review by PMDA

Based on the review of the submitted data and the responses to the inquiries, PMDA has concluded that the quality of the drug product is controlled in an appropriate manner.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

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

3.(i).A.(1).1) *Ex vivo* and *in vivo* studies

(a) *Ex vivo* studies of inhibitory effect on platelet aggregation

i) Inhibitory effect on platelet aggregation in rats, monkeys, and dogs (Attached documents 4.2.1.1-1, 4.2.1.1-7, 4.2.1.1-9)

Prasugrel hydrochloride, prasugrel, clopidogrel sulfate, or vehicle was administered orally in a single dose, or once daily for 3 days, to 8-week-old male Sprague-Dawley (SD) rats (n = 5). All the compounds tested inhibited platelet aggregation induced by 20 μM adenosine diphosphate (ADP). The 50% effective dose (ED_{50}) in single-dose administration and repeat-dose administration was 2.3 mg/kg and 0.62 mg/kg/day, respectively, with prasugrel hydrochloride; 1.8 mg/kg and 0.65 mg/kg/day, respectively, with prasugrel; and 19 mg/kg and 6.0 mg/kg/day, respectively, with clopidogrel sulfate. A similar inhibitory effect was observed against platelet aggregation induced by 5 μM ADP.

Prasugrel hydrochloride or the control (vehicle, gelatin capsule) was administered orally once daily for 14 days to male cynomolgus monkeys (4-6 years old; n = 5) and to male beagle dogs (19-22 months old; n = 5). Prasugrel hydrochloride inhibited platelet aggregation induced by 20 μM ADP in a dose-dependent manner. The platelet aggregation-inhibitory effect of prasugrel hydrochloride was significantly potent in all prasugrel hydrochloride groups compared with the control group on Day 3 and Day 5, and remained almost stable up to Day 14 of administration. On Day 14 of administration, platelet-aggregating activity did not show any significant variability among at pre-dose, 4 hours post-dose, and 24 hours post-dose in any of the prasugrel hydrochloride groups. After the end of the repeated administration of prasugrel hydrochloride, platelet-aggregating activity recovered gradually and, on 7 and 14 days after the last dose, showed no significant difference between the prasugrel hydrochloride groups and the control group. On Day 7 of administration, prasugrel hydrochloride at all doses tested significantly inhibited ADP- or collagen-induced platelet aggregation.

ii) Change over time in inhibitory effect against platelet aggregation in rats (Attached document 4.2.1.1-4)

Prasugrel hydrochloride (1, 3 mg/kg [prasugrel equivalent]), clopidogrel sulfate (10, 30 mg/kg [clopidogrel equivalent]), or vehicle was administered orally in a single dose to male SD rats (8 weeks old; n = 5), and platelet-aggregating activity was measured over time. Prasugrel hydrochloride inhibited platelet aggregation induced by 20 μM ADP in a dose-dependent manner. In the 3 mg/kg group, the inhibitory effect reached the near maximum level at 1 hour post-dose and persisted up to 12 hours post-dose. Clopidogrel sulfate also showed a dose-dependent inhibitory effect against ADP-induced platelet aggregation, but the effect tended to develop more slowly compared with prasugrel hydrochloride. With both drugs, the platelet aggregation-inhibitory effect gradually decreased after 12 hours post-dose, and platelet-aggregating activity recovered at 96 hours post-dose.

iii) Platelet aggregation-inhibitory effect of enantiomer (Attached documents 4.2.1.1-14, 4.2.1.1-15)

R-isomer of prasugrel hydrochloride (R-96875), S-isomer of prasugrel hydrochloride (R-96876), or vehicle was administered orally in a single dose to male SD rats (262-359 g; n = 4-7) or to male beagle dogs (9.7-14.0 kg; n = 5-6). Both optical isomers inhibited ADP-induced platelet aggregation to a similar extent in a dose-dependent manner.

R-96875 or R-96876 was administered orally for 3 days to male cynomolgus monkeys (5.45-8.35 kg; n = 5). As a result, both optical isomers inhibited ADP-induced platelet aggregation to a similar extent.

(b) *In vivo* studies of antithrombotic effect and on haemorrhagic effect

i) Arteriovenous shunt thrombosis model (Attached document 4.2.1.1-16)

Prasugrel hydrochloride (0.3, 1, 3 mg/kg [prasugrel equivalent]), clopidogrel sulfate (3, 10, 30 mg/kg [clopidogrel equivalent]), or vehicle was administered orally in a single dose to male SD rats (7-9 weeks old; n = 10). A shunt was placed between the carotid artery and the jugular vein, and blood was allowed to circulate through the shunt for 30 minutes at 4 hours post-dose, after which the weight of thrombus that adhered to silk fibers that had been placed within the shunt was measured. Prasugrel hydrochloride at all doses significantly suppressed thrombus formation compared with the vehicle, with the thrombus suppressive rate (mean ± standard error [SE]) being 21% ± 9%, 32% ± 4%, and 69% ± 3%, respectively, in the prasugrel hydrochloride 0.3, 1, and 3 mg/kg groups (ED_{50}, 1.7 mg/kg). Clopidogrel sulfate at 10 and 30 mg/kg significantly suppressed thrombus formation compared with the vehicle, with the thrombus suppressive rate being 13% ± 4%, 48% ± 8%, and 72% ± 3%, respectively, in the clopidogrel sulfate 3, 10, and 30 mg/kg groups (ED_{50}, 11 mg/kg).

ii) Arterial thrombosis model (electric stimulation method) (Attached documents 4.2.1.1-18, 4.2.1.1-19)

Prasugrel (0.3, 1, 3 mg/kg), clopidogrel sulfate (3, 10, 30 mg/kg), ticlopidine hydrochloride (30, 100, 300 mg/kg), or vehicle was administered orally in a single dose to male SD rats (8-9 weeks old; n = 8). At 4 hours post-dose, an electric stimulus (3 mA for 5 minutes) was applied to the carotid artery to generate endothelial injury thereby promoting progressive thrombus formation and, during the 60-minute period after the electric stimulus, blood flow within the carotid artery was measured by a Doppler blood-flowmeter. Time to vascular obstruction and the percentage of time during which blood flowed in

the artery (patency rate) was calculated. Prasugrel, clopidogrel sulfate, and ticlopidine hydrochloride prolonged the time to vascular obstruction in a dose-dependent manner, and increased the patency rate, compared with the vehicle.

Prasugrel (0.1, 0.3, 1 mg/kg,), clopidogrel sulfate (1, 3, 10 mg/kg), ticlopidine hydrochloride (30, 100, 300 mg/kg), or vehicle was administered orally once daily for 3 days to male SD rats (8-10 weeks old; n = 8) and, at 4 hours after the last dose, blood flow in the carotid artery was measured in a similar manner as in the single dose study. Both the time to vascular obstruction and the patency rate increased significantly in the prasugrel ≥0.3 mg/kg groups, the clopidogrel sulfate ≥3 mg/kg groups, and the ticlopidine hydrochloride ≥100 mg/kg groups compared with the vehicle group.

iii) Haemorrhage model (caudal vein puncture) (Attached document 4.2.1.1-20)
Prasugrel hydrochloride (0.3, 1, 3, 10 mg/kg [prasugrel equivalent]), clopidogrel sulfate (3, 10, 30, 100 mg/kg [clopidogrel equivalent]), or vehicle was administered orally in a single dose to male SD rats (7-8 weeks old; n = 10). At 4 hours post-dose, an injection needle was inserted into the caudal vein, and time to hemostasis was measured. Prasugrel hydrochloride and clopidogrel sulfate prolonged the bleeding time in a dose-dependent manner, with the dose that caused a 2-fold increase in the bleeding time (ED_{200}) being 4.3 mg/kg for prasugrel hydrochloride and 40 mg/kg for clopidogrel sulfate.

iv) Haemorrhage model (tail cut model) (Attached document 4.2.1.1-21)
Prasugrel, clopidogrel sulfate, ticlopidine hydrochloride, or vehicle was administered orally in a single dose, or once daily for 3 days, to male SD rats (251-279 g; n = 7). The doses of prasugrel were 0.1 mg/kg (repeat-dose administration only), and 0.3, 1, and 3 mg/kg (single-dose administration only); the doses of clopidogrel sulfate were 1 mg/kg (repeat-dose administration only), and 3, 10, and 30 mg/kg (single-dose administration only); and the doses of ticlopidine hydrochloride were 30, 100, and 300 mg/kg. At 4 hours after the last dose of each drug, the tip of the rat's tail was cut and the time to hemostasis was measured. Prasugrel, clopidogrel sulfate, and ticlopidine hydrochloride prolonged the bleeding time in a dose-dependent manner, with ED_{200} in single-dose administration being 0.50, 4.6, and 130 mg/kg, respectively, and ED_{200} in repeat-dose administration being 0.14, 1.8, and 75 mg/kg, respectively.

v) Myocardial infarction model (Attached document 4.2.1.1-22)
Prasugrel hydrochloride (1, 3, 10 mg/kg [prasugrel equivalent]) or vehicle was administered orally in a single dose to male SD rats (n = 7). At 2 hours post-dose, rose bengal (20 mg/kg) was administered intravenously while the bifurcation between the left circumflex coronary artery and the anterior descending branch was irradiated with green light to photochemically cause injuries within the vascular endothelium thereby to induce thrombosis formation. The heart was isolated at 24 hours after the end of photoirradiation. In all prasugrel hydrochloride groups, the myocardial infarct size (necrotic region/total left ventricular region) was significantly smaller compared with the vehicle group.

3.(i).A.(1).2) *In vitro* studies

(a) *In vitro* studies of prasugrel hydrochloride and its active metabolites

i) *In vitro* studies of prasugrel hydrochloride and its metabolites (Attached documents 4.2.1.1-27, 4.2.1.1-35, 4.2.1.1-42)
Prasugrel, the major and active metabolite (R-138727), or other metabolites (R-95913, R-100932, R-104434, R-106583, R-118443, R-119251) of prasugrel hydrochloride were added to human platelet rich plasma (PRP). Neither prasugrel nor other metabolites affected ADP-induced platelet aggregation, whereas R-138727 significantly inhibited platelet aggregation. In a separate experiment, R-138727 was added to human PRP and the mixture was incubated for 1.5 to 30 minutes. R-138727 inhibited ADP-induced platelet aggregation in a concentration- and an incubation time-dependent manner. IC_{50} at an incubation time of 1.5 and 30 minutes was 28 and 1.8 μM, respectively.

Similarly, prasugrel did not affect, whereas R-138727 significantly inhibited, ADP-induced platelet aggregation in PRP of male SD rats.

ii) Inhibitory effect of 4 stereoisomers of R-138727 on platelet aggregation (Attached document 4.2.1.1-29)

Four stereoisomers of R-138727 (R-125687 [3-300 μM], R-125688 [3-300 μM], R-125689 [0.3-30 μM], R-125690 [0.03-3 μM]) were added to washed human platelets. All stereoisomers significantly and dose-dependently inhibited platelet aggregation induced by 5 and 20 μM ADP. IC_{50} of R-125687, R-125688, R-125689, and R-125690 against 20 μM ADP-induced platelet aggregation was 120, 300, 2.4, and 0.42 μM, respectively.

(b) Comparison between R-138727 and the active metabolite of clopidogrel sulfate (Attached document 4.2.1.1-36)

R-138727 or the active metabolite of clopidogrel sulfate was added to human PRP. Both compounds over a similar concentration range (3.0-30 μM) inhibited 1.25 to 80 μM ADP-induced platelet aggregation in a concentration-dependent manner. The IC_{50} of R-138727 or the active metabolite of clopidogrel sulfate against ADP-induced platelet aggregation was 3.9 to 7.5 μM or 5.2 to 9.7 μM, respectively. Also, both metabolites potently inhibited platelet aggregation induced by low concentration (0.625 and 2.5 μg/mL) of collagen, but their inhibition rate against platelet aggregation induced by high concentration (10 and 40 μg/mL) of collagen and by 1.25 to 80 μM thrombin receptor activating peptide (TRAP) was ≤50%.

3.(i).A.(1).3) Studies on the mechanism of action

(a) *Ex vivo* studies on the mechanism of action

i) Receptor selectivity (Attached document 4.2.1.1-43)

Prasugrel (0.3, 1, 3, 10 mg/kg), clopidogrel sulfate (3, 10, 30, 100 mg/kg), or vehicle was administered orally in a single dose to male SD rats (7-10 weeks old; n = 6). Prasugrel and clopidogrel sulfate dose-dependently inhibited the binding to platelets of ^{3}H-labeled 2-methylthio adenosine diphosphate ([^{3}H]-2-MeS-ADP), a ligand of ADP receptor on platelets. However, even at the maximum dose, both drugs showed approximately 60% of the binding relative to the vehicle group. Scatchard analysis showed that both drugs increased the dissociation constant, resulting in decrease in the maximum level of [^{3}H]-2-MeS-ADP binding.

ii) Study on inhibition of platelet aggregation, inhibition of binding, and PK (Attached documents 4.2.1.1-11, 4.2.1.1-48)

Prasugrel was administered orally in a single dose to male SD rats (8 weeks old; n = 6). A significant positive correlation was observed between the inhibitory effect of prasugrel against the binding of [^{3}H]-2-MeS-ADP to $P2Y_{12}$ receptor and the inhibitory effect against ADP-induced platelet aggregation. Also, a significant positive correlation was observed between the area under the plasma concentration-time curve of the active metabolite in plasma from 0 up to t hours post-dose (AUC_{0-t}) and the rate of inhibition of ADP-induced platelet aggregation (n = 5).

(b) *In vitro* studies on the mechanism of action

i) Receptor selectivity (Attached document 4.2.1.1-51)

Active metabolites of prasugrel hydrochloride (R-138727, R-99224, R-100364) or $P2Y_1$ receptor antagonist MRS2179 were added to CHO K-1 cells engineered to express recombinant human $P2Y_1$ or $P2Y_{12}$ receptor. As a result, R-138727, R-99224, and R-100364 inhibited the binding of [^{3}H]-2-MeS-ADP to $P2Y_{12}$ receptor in a concentration-dependent manner, with IC_{50} of 2.5, 1.3, and 45 μM, respectively, whereas MRS2179 did not inhibit the binding of [^{3}H]-2-MeS-ADP to $P2Y_{12}$ receptor. In contrast, MRS2179 inhibited the binding of [^{3}H]-2-MeS-ADP to $P2Y_1$ receptor in a concentration-dependent manner, whereas R-138727, R-99224, and R-100364 did not inhibit the binding of [^{3}H]-2-MeS-ADP to $P2Y_1$ receptor.

ii) Correlation between effect on vasodilator-stimulated phosphoprotein phosphorylation and inhibition of ADP-induced platelet aggregation (Attached document 4.2.1.1-54)

After R-138727 (0.30-10 μM) or MRS2179 (100 μM) was added to human blood samples, vasodilator-stimulated phosphoprotein (VASP) was measured by enzyme-linked immunosorbent assay (ELISA), and platelet reactivity index (PRI) was calculated using VASP phosphorylation as the index. Also, PRP was prepared from the above blood samples added with R-138727 or MRS2179, and 5 and 20 μM ADP-induced platelet aggregation was measured. Both R-138727 and MRS2179 significantly inhibited ADP-

induced platelet aggregation, whereas R-138727 decreased PRI in a concentration-dependent manner but MRS2179 did not decrease PRI. In the presence of R-138727, a significant positive correlation was observed between the rate of ADP-induced platelet aggregation and PRI at all ADP concentrations tested.

iii) Other *in vitro* studies on the mechanism of action (Attached documents 4.2.1.1-55, 4.2.1.1-56, 4.2.1.1-58 to 4.2.1.1-60)

In washed human platelet samples, R-99224 affected neither ADP-induced increase in Ca^{2+} concentration in human platelets nor morphological changes of human platelets induced by ADP and 2-MeS-ADP. Instead, R-99224 inhibited ADP-induced decrease in cAMP concentration in platelets and the binding of ^{125}I-labeled fibrinogen in a concentration-dependent manner.

In human PRP, R-99224 inhibited ADP-induced release of platelet-derived growth factor and β-thromboglobulin in a concentration-dependent manner.

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

No secondary pharmacodynamic data were submitted.

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

Among safety pharmacology studies, 2 studies (Attached document 4.2.1.3-1, 4.2.1.3-5) conducted before the enforcement of the guideline "Safety Pharmacology Studies for Human Pharmaceuticals" (PMSB/ELD Notification No.902 dated June 21, 2001) were conducted under non-GLP conditions; instead, they followed the Guidelines for General Pharmacology Studies (Attachment to PAB/NDD Notification No. 4 dated January 29, 1991).

3.(i).A.(3).1) Effect on smooth muscles, autonomic nervous system, and somatic nervous system (Attached document 4.2.1.3-1 [non-GLP])

In ileal preparations isolated from male Hartley guinea pigs, prasugrel hydrochloride (1×10^{-5} g/mL) inhibited contraction induced by acetylcholine, histamine, serotonine, and barium chloride.

Prasugrel hydrochloride (1×10^{-4} g/mL) significantly inhibited spontaneous motility in ileal preparations isolated from male Japanese white rabbits, significantly decreased the amplitude of spontaneous motility and increased the frequency of periodical contraction in uterine preparations isolated from non-pregnant female SD rats, mildly decreased the amplitude of the spontaneous motility and increased the frequency of periodical contraction in uterine preparations isolated from pregnant female SD rats, and enhanced nerve-stimulated twitch contractions in diaphragm preparations isolated from male SD rats.

In male ddY mice (3-4 weeks old; n = 10), a single oral administration of prasugrel (10, 30, 100 mg/kg) did not have muscle-relaxant activity.

In male Hartley guinea pigs (3 weeks old; n = 5), ocular application of 0.1 mL solution containing 1% or 5% prasugrel had no effect on corneal reflexes.

3.(i).A.(3).2) Effect on cardiovascular system and respiratory system (Attached documents 4.2.1.3-1 [non-GLP], 4.2.1.3-2 to 4.2.1.3-4, 4.2.3.2-12, 4.2.3.2-13 [GLP])

In CHO-K1 cells transfected with human ether-a-go-go related gene (hERG), R-138727, R-106583, and R-95913 up to the maximum concentration tested (R-138727 and R-106583, 30 μM; R-95913, 15 μM) had no effect on potassium channel current.

In atrial preparations isolated from male Hartley guinea pigs, prasugrel hydrochloride affected neither the intensity nor the frequency of spontaneous contraction up to the maximum concentration tested (1×10^{-4} g/mL).

In pentobarbital-anesthetized male beagle dogs (10-12 kg; n = 5), a single intraduodenal administration of prasugrel (30, 100 mg/kg) did not affect respiratory rate, blood pressure, heart rate, carotid artery blood flow, electrocardiogram (ECG), or blood pressure response to intravenous injection of norepinephrine or acetylcholine and to bilateral carotid occlusion.

3.(i).A.(3).3) Effect on central nervous system (Attached document 4.2.1.3-1 [non-GLP])
Prasugrel (10, 30, 100 mg/kg) or vehicle was administered orally in a single dose to male Wistar rats (12 weeks old; n = 5). Prasugrel did not affect total sleep time, whereas paradoxical sleep time was significantly decreased in the 100 mg/kg group compared with the vehicle group.

Prasugrel (10, 30, 100, 300 mg/kg) or vehicle was administered orally in a single dose to male ddY mice (3-4 weeks old) and male SD rats (5-6 weeks old). Prasugrel did not affect the behavior of mice (n = 5), whereas a tendency of increased response to tactile stimulus was observed in rats of the 300 mg/kg group (n = 5).

In male ddY mice (3-4 weeks old; n = 10-12), a single oral administration of prasugrel (10, 30, 100 mg/kg) did not affect locomotor activity, duration of thiopental-induced anesthesia or its antalgic effect, or maximum electric shock-induced or pentylenetetrazole-induced convulsions.

In male SD rats (5-6 weeks old; n = 10), a single oral administration of prasugrel (10, 30, 100 mg/kg) did not affect body temperature.

3.(i).A.(3).4) Effect on renal function (Attached document 4.2.1.3-1 [non-GLP])
A single oral administration of prasugrel (0 [vehicle], 10, 30, 100 mg/kg) to male SD rats (5-6 weeks old; n = 9-12) did not affect urine volume, electrolyte excretion, or urine osmotic pressure.

3.(i).A.(3).5) Effect on digestive system (Attached documents 4.2.1.3-1, 4.2.1.3-5 [non-GLP])
Prasugrel (10, 30, 100 mg/kg) or vehicle was administered orally in a single dose to male SD rats (5-6 weeks old; n = 11). Decreased gastric acid and decreased gastric juice secretion were observed in the prasugrel 100 mg/kg group.

Prasugrel (30, 100, 300 mg/kg) or vehicle was administered orally in a single dose, or once daily for 3 days, to male ddY mice (4 weeks old; n = 11-12). At 4 hours after the last dose of study drug, 10% charcoal powder suspension was administered orally and, 30 minutes later, the entire small intestine was isolated and the distance travelled from the pyloric end by the charcoal powder was measured. Neither single-dose nor repeat-dose administration of prasugrel affected gastrointestinal propulsion.

Prasugrel (30, 100, 300 mg/kg) or vehicle was administered orally in a single dose, or once daily for 3 days, to male ddY mice (4 weeks old; n = 10). At 4 hours after the last dose of study drug, 60% barium sulfate suspension was administered orally and, 30 minutes later, the stomach was isolated and the amount of residual barium sulfate in the stomach was measured. A single-dose administration of prasugrel did not affect the gastrointestinal emptying, whereas a significant decrease in the speed of gastric emptying was observed in the 300 mg/kg repeat-dose group.

In male ddY mice (4 weeks old; n = 10), a single oral administration or 3-day once daily repeated oral administration of prasugrel (30, 100, 300 mg/kg) did not affect defecation time.

In male SD rats (6 weeks old; n = 8-10), a single oral administration or 3-day once daily repeated oral administration of prasugrel (30, 100, 300 mg/kg) did not affect the volume or acidity of gastric juice or presence/absence of ecchymotic haemorrhage.

3.(i).A.(3).6) Other effects (Attached document 4.2.1.3-1 [non-GLP])
In male SD rats (5-6 weeks old; n = 10), a single oral administration of prasugrel (10, 30, 100 mg/kg) did not affect blood glucose level.

In blood samples of male Japanese white rabbits, prasugrel hydrochloride (1×10^{-6} to 1×10^{-4} g/mL) did not show any hemolytic effect.

In male SD rats (5-6 weeks old; n = 5), a single oral administration of prasugrel (10, 30, 100 mg/kg) did not affect the blood coagulation system.

In the safety pharmacology studies, prasugrel hydrochloride or prasugrel affected smooth muscles, the autonomic nervous system, and the somatic nervous system (*in vitro* studies), paradoxical sleep time, response to tactile stimulus, gastric acid, gastric juice secretion, and the speed of gastric emptying (*in vivo* studies). However, the applicant determined that no further investigations on these findings were necessary because they were related to the exposure to a high concentration of prasugrel hydrochloride or prasugrel and there is a sufficiently wide safety margin.

3.(i).A.(4) Pharmacodynamic drug interactions

3.(i).A.(4).1) *Ex vivo* and *in vivo* studies on concomitant use of prasugrel hydrochloride with aspirin

(a) Effect of concomitant use of prasugrel hydrochloride with aspirin on *ex vivo* platelet aggregation in rats and dogs (Attached documents 4.2.1.4-1, 4.2.1.4-4)

Prasugrel hydrochloride (0.6, 1 mg/kg [prasugrel equivalent]) and aspirin (10 mg/kg) either alone or in combination, or vehicle was administered orally in a single dose to male SD rats (8-9 weeks old; n = 10). In all prasugrel hydrochloride groups, 5 or 20 μM ADP-induced or 5, 7, or 10 μg/mL collagen-induced platelet aggregation was significantly and potently inhibited than in the vehicle group. In the aspirin group, in contrast, little or no effect was observed on ADP-induced platelet aggregation, and only 5 μg/mL collagen-induced platelet aggregation was significantly and potently inhibited than in the vehicle group. In the prasugrel hydrochloride + aspirin group, the inhibitory effect on ADP-induced platelet aggregation was similar to that observed in the prasugrel hydrochloride group, whereas the inhibitory effect on collagen-induced platelet aggregation was significantly stronger than in the prasugrel hydrochloride alone group and the aspirin alone group.

Aspirin was administered once daily for 8 days to male beagle dogs (3-9 years old) from Day 1 of the study, and prasugrel was administered once daily for 5 days from Day 4. As a result, ADP-induced platelet aggregation was more strongly inhibited by prasugrel alone than aspirin alone. When both drugs were administered in combination, the inhibitory effect was more potent than either prasugrel or aspirin alone. Platelet aggregation induced by collagen + epinephrine was not inhibited to any significant extent by prasugrel alone, but was weakly inhibited by aspirin alone, whereas the aggregation was more strongly inhibited by the co-administration compared with either drug alone.

(b) Comparison of prasugrel and clopidogrel sulfate in *ex vivo* synergistic inhibitory effect with aspirin on platelet aggregation in rats (Attached document 4.2.1.4-3)

Male SD rats (8 weeks old; n = 6) received prasugrel (3, 6 mg/kg), clopidogrel sulfate (100 mg/kg), or aspirin (10 mg/kg) alone, prasugrel or clopidogrel sulfate in combination with aspirin, or vehicle, all orally in a single dose. The prasugrel 3 mg/kg group showed little or no inhibition of 20 μg/mL collagen-induced platelet aggregation (inhibition rate, 8.2%), while the 6 mg/kg group showed a significant inhibition (inhibition rate, 22.8%) compared with the vehicle group. The aspirin group showed little or no inhibition of collagen-induced platelet aggregation (inhibition rate, 6.8%). All prasugrel + aspirin groups showed an add-on inhibitory effect on platelet aggregation (prasugrel 3 mg/kg + aspirin group, inhibition rate of 61.8%; prasugrel 6 mg/kg + aspirin group, 73.7%). In contrast, the clopidogrel sulfate groups showed a significantly potent inhibition of collagen-induced platelet aggregation compared with the vehicle group (inhibition rate, 15.1%), whereas the aspirin alone group showed little inhibitory effect (inhibition rate, 7.4%). The add-on effect of clopidogrel sulfate + aspirin (inhibition rate, 22.2%) was smaller than that of prasugrel + aspirin.

(c) Concomitant use of prasugrel with aspirin in rat thrombosis model and haemorrhage model (Attached document 4.2.1.4-5)

Prasugrel (0.3, 0.6 mg/kg) and aspirin (10 mg/kg) were administered alone or in combination to male SD rats of the arteriovenous shunt thrombosis model and haemorrhage (tail cut) model. In rats of the arteriovenous shunt thrombosis model (n = 6), the weight of thrombus adhering to silk fibers was significantly lower in the combination therapy group than in the prasugrel alone group and the aspirin alone group. In rats of the haemorrhage (tail cut) model (n = 8), bleeding time tended to be longer in the combination therapy group than in the prasugrel alone group and the aspirin alone group.

3.(i).A.(4).2) *In vitro* studies on the concomitant use of R-138727 with aspirin (Attached document 4.2.1.4-6)

To human PRP, 3-30 μM R-138727 and 0.3 mM aspirin were added alone or in combination. Platelet aggregation induced by 1 mM arachidonic acid was not completely inhibited by R-138727 alone, but completely inhibited by simultaneous addition of R-138727 and aspirin. Platelet aggregation induced by 5, 20 μM ADP was inhibited to a similar extent by R-138727 alone and by simultaneous addition of R-138727 and aspirin. Platelet aggregation induced by 2, 4, 10 μg/mL collagen was partially inhibited by R-138727 alone and by aspirin alone, and an add-on inhibitory effect against platelet aggregation was observed by simultaneous addition of both drugs. Also, simultaneous addition of R-138727 and aspirin showed an add-on inhibitory effect against platelet aggregation induced by 11.5 μM protease-activated receptor 1 (PAR-1) agonist peptide.

3.(i).B Outline of the review by PMDA

PMDA considers as follows:

Primary pharmacodynamic studies clearly demonstrated that prasugrel hydrochloride has an antiplatelet effect comparable to or more potent than similar drugs. Therefore, prasugrel hydrochloride is expected to exhibit an inhibitory effect against thrombotic events in the target patients of the present application, i.e., patients with ischemic heart disease (e.g., non-ST segment elevation myocardial infarction, ST segment elevation myocardial infarction, unstable angina, stable angina pectoris) to be managed with percutaneous coronary intervention (PCI). On the other hand, since aspirin is assumed to be concomitantly administered with prasugrel hydrochloride in these patients, resulting in possible enhancement of bleeding, it is necessary to carefully determine the clinical dose so that the benefits outweigh the risks.

3.(ii) Summary of pharmacokinetic studies

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

In mice, rats, and dogs, orally administered prasugrel hydrochloride or prasugrel is rapidly metabolized to R-95913 by carboxylesterase present within cells of the gastrointestinal tract, and transferred to the portal vein. R-95913 is then metabolized to the active metabolite R-138727 and the inactive metabolite R-104434, and the former is further metabolized to R-119251 or R-106583, and the latter to R-118443 or R-100932. Plasma R-138727 concentration was measured by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS); the lower limit of quantification was 20 ng/mL in mice, 20 or 40 ng/mL in rats, and 5.0, 10, or 20 ng/mL in dogs. Pharmacokinetic parameters are expressed in mean values unless otherwise specified.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose administration

(a) Single dose studies (Attached documents 4.2.2.2-3, 4.2.2.2-4, 4.2.2.2-5, 4.2.2.2-7, 4.2.3.1-3)

Among the submitted pharmacokinetic data obtained following single-dose administration of prasugrel or prasugrel hydrochloride, data on R-138727 following the administration of prasugrel or prasugrel hydrochloride to rats and dogs are described below.

Following a single oral administration of prasugrel (2 mg/kg) to male rats (n = 4), the area under the plasma concentration-time curve from 0 to 6 hours post-dose ($AUC_{0\text{-}6h}$) of R-138727 was 1140 ng·h/mL. Following an intravenous administration of the equimolar amount of R-138727 as prasugrel 2 mg/kg to male rats (n = 4), $AUC_{0\text{-}6h}$ of R-138727 was 4530 ng·h/mL. The percentage of $AUC_{0\text{-}6h}$ of R-138727 following oral administration of prasugrel to that following intravenous administration of R-138727 was 25.2% in rats.

Following a single intravenous administration of prasugrel 0.3, 1, and 3 mg/kg to male rats (n = 4 or 5), t_{max} of R-138727 was 0.32, 0.22, and 0.25 hours, respectively; C_{max} was 94.65, 398.57, and 1083.56 ng/mL, respectively; and $AUC_{0\text{-}6h}$ was 159.01, 712.37, and 1772.42 ng·h/mL, respectively.

Following a single oral administration of prasugrel hydrochloride (5 mg/kg) to male rats (n = 6), t_{max} of R-138727 was 1.00 hour, C_{max} was 1550 ng/mL, and the area under the plasma concentration-time curve from 0 to 8 hours post-dose ($AUC_{0\text{-}8h}$) was 3390 ng·h/mL. C_{max} and $AUC_{0\text{-}8h}$ of R-138727 following a single oral administration of prasugrel (5 mg/kg) to male rats (n = 4) were not significantly different

from those observed following the administration of prasugrel hydrochloride.

Following a single oral administration of prasugrel or prasugrel hydrochloride (500, 1000, 2000 mg/kg) to male and female rats (n = 5 each), C_{max} and $AUC_{0-\infty}$ of R-138727 were as shown in Table 3.

Table 3. Pharmacokinetics of R-138727 following a single oral administration of prasugrel or prasugrel hydrochloride in rats

Dose (mg/kg)	Prasugrel				Prasugrel hydrochloride			
	C_{max} (μg/mL)		$AUC_{0-\infty}$ (μg·h/mL)		C_{max} (μg/mL)		$AUC_{0-\infty}$ (μg·h/mL)	
	Male	Female	Male	Female	Male	Female	Male	Female
500	59.4	41.8	374	321	71.0	54.2	513	565
1000	69.1	59.2	709	985	71.7	62.5	859	798
2000	70.1	57.9	1005	769	78.7	59.0	1401	1786

Following a single oral administration of prasugrel hydrochloride (2 mg/kg) to male dogs (n = 6), t_{max}, C_{max}, and AUC_{0-8h} of R-138727 was 0.500 hours, 1020 ng/mL, and 1050 ng·h/mL, respectively. C_{max} and AUC_{0-8h} of R-138727 following a single oral administration of prasugrel (2 mg/kg) to male dogs (n = 6) were not significantly different from those observed following the administration of prasugrel hydrochloride.

(b) Effect of intragastric pH (Attached document 4.2.2.2-8)

Prasugrel (10 mg), prasugrel hydrochloride (10 mg), or prasugrel maleate (10 mg) was orally administered in three-treatment, three-period crossover manner (washout period, 1-week) to male dogs (n = 6) treated with tetragastrin. Blood concentration of each metabolite (R-95913, R-100932, R-106583, R-118443, R-119251) was similar among treatment groups. When a similar experiment was performed in male dogs (n = 6) treated with ranitidine, blood concentration of each metabolite following prasugrel administration was lower than that observed following the administration of prasugrel hydrochloride or prasugrel maleate.

3.(ii).A.(1).2) Repeat-dose administration (Attached documents 4.2.3.2-3, 4.2.3.2-8, 4.2.3.2-14)

As pharmacokinetic data of repeated oral administration of prasugrel or prasugrel hydrochloride, toxicokinetics data obtained in repeat-dose toxicity studies in mice, rats, rabbits, and dogs were submitted. As pharmacokinetic data of R-138727 after administration of prasugrel hydrochloride, Table 4 shows C_{max} and the area under the plasma concentration-time curve from 0 to 24 hours post-dose (AUC_{0-24h}) of R-138727 in 14-day repeated oral administration of prasugrel hydrochloride in male and female mice (n = 10 each), in 28-day repeated oral administration of prasugrel hydrochloride in male and female rats (n = 10 each), and in 28-day repeated oral administration of prasugrel hydrochloride in male and female dogs (n = 3 each).

Table 4. Pharmacokinetic parameters of R-138727 in repeated oral administration of prasugrel hydrochloride

	Dose (mg/kg)	After initial dose				Day 14[a] or 28[b]			
		C_{max} (μg/mL)		AUC_{0-24h} (μg·h/mL)		C_{max} (μg/mL)		AUC_{0-24h} (μg·h/mL)	
		Male	Female	Male	Female	Male	Female	Male	Female
Mice	100	7.47	5.90	14.2	11.8	4.52	7.03	7.16	13.5
	300	19.4	14.6	49.8	49.4	18.9	12.0	38.4	39.5
	1000	22.7	21.1	134	178	41.2	34.3	107	100
Rats	30	3.21	7.46	6.72	15.0	2.85	5.42	5.02	9.55
	100	13.1	12.2	44.3	49.2	8.80	17.3	22.3	39.1
	300	32.8	21.1	175	181	22.6	37.4	60.6	93.2
Dogs	4	1.12	0.98	1.66	1.78	0.74	1.02	1.01	1.42
	20	3.20	5.92	7.44	10.7	3.02	3.07	6.57	5.74
	100	6.05	15.6	24.1	46.0	5.14	6.04	21.4	27.7

a, Mice; b, Rats and dogs

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution following single-dose administration (Attached document 4.2.2.3-1)

^{14}C-labeled prasugrel (5 mg/kg) was administered orally in a single dose to albino and pigmented male rats that had been fasted for ≥16 hours, and radioactivity concentration at 1, 2, 4, 8, 12, 24, 48, and 72 hours post-dose was measured by quantitative whole-body autoradioluminography (n = 1/time point). In a majority of tissues, radioactivity concentration reached the maximum level at 1 hour post-dose; a significantly higher radioactivity concentration compared with that in blood (2411 ng·eq/g in albino rats, 2336 ng·eq/g in pigmented rats) was observed in the urinary bladder (374,623 ng·eq/g, 93,915 ng·eq/g), small intestine (16,511, 16,463 ng·eq/g), liver (17,308, 11,225 ng·eq/g), and kidneys (6648, 6331 ng·eq/g). Radioactivity concentration at 72 hours post-dose was significantly higher in the urinary bladder (1053, 1989 ng·eq/g), cecum (1206, 1172 ng·eq/g), liver (744, 698 ng·eq/g), kidneys (497, 250 ng·eq/g), thyroid gland (244, 367 ng·eq/g), and aorta (491, 307 ng·eq/g) compared with that in blood (165, 164 ng·eq/g). Radioactivity distribution in most tissues was similar between albino rats and pigmented rats, whereas distribution in the eyes was higher in pigmented rats. $t_{1/2}$ of radioactivity in the eyes and skin of pigmented rats was 649.6 and 263.1 hours, respectively, which was longer than that in albino rats (9.6 and 106.4 hours).

3.(ii).A.(2).2) Tissue distribution following repeated administration (Attached document 4.2.2.3-2)

^{14}C-labeled prasugrel (5 mg/kg) was administered orally once daily for 21 days to male pigmented rats under fed conditions, and tissue radioactivity concentration at 24 hours after the first, seventh, and 14th dose and up to 168 hours after the 21st dose was measured by quantitative whole-body autoradioluminography (n = 1/time point). Also, plasma radioactivity concentration up to 168 hours after a single dose or after the 21st dose was measured (n = 3). AUC of plasma radioactivity after a single dose and after the 21st dose was 19.1 and 19.8 μg eq·h/mL, respectively ($AUC_{0-\infty}$ and AUC_{0-24h}, respectively), and $t_{1/2}$ was 1.6 and 2.3 days, respectively.

In a majority of tissues, radioactivity concentration at 24 hours post-dose tended to increase with the increase in the number of times of dose. In a majority of tissues, radioactivity concentration at 24 hours post-dose almost reached a steady level at or before the 14th dose. Radioactivity concentration at 24 hours after the 21st dose was highest in the cecum (9922 ng·eq/g), followed in decreasing order by the urinary bladder (9201 ng·eq/g), liver (5242 ng·eq/g), small intestine (5216 ng·eq/g), thyroid gland (4597 ng·eq/g), kidneys (3063 ng·eq/g), aorta (2753 ng·eq/g), and eyes (2236 ng·eq/g), with the level in these tissues being higher than the level in blood (1892 ng·eq/g). At 168 hours after the 21st dose, radioactivity concentration decreased to 71% and 41%, respectively, of the maximum level in the eyes and thyroid gland, and to ≤28% of the maximum level in other tissues.

3.(ii).A.(2).3) Plasma protein binding and distribution in blood cells (Attached documents 4.2.2.3-3, 4.2.2.2-2, 4.2.2.2-6)

Following the addition of R-95913, R-100932, R-106583, and R-119251 to rat and dog plasma samples to a final concentration of 50 to 500 ng/mL, plasma protein binding in rats was 85.12% to 87.61%, 92.05% to 92.86%, 82.69% to 83.17%, and 71.02% to 77.17%, respectively, and that in dogs was 88.45% to 89.76%, 79.88% to 85.13%, 80.72% to 84.68%, and 26.36% to 35.54%, respectively. A study on plasma protein binding of R-138727 was not conducted because of the instability of the compound in the plasma.

Following a single oral or intravenous administration of ^{14}C-labeled prasugrel (5 mg/kg) to male rats (n = 3), the percentage of radioactivity distribution in blood cells at 0.5 to 24 hours post-dose was 9.7% to 24.0% and 22.1% to 29.5%, respectively. Following a single oral administration of ^{14}C-labeled prasugrel (2 mg/kg) to male dogs (n = 3), the percentage of radioactivity distribution in blood cells at 0.25 to 72 hours post-dose was 0.5% to 25.9%.

3.(ii).A.(2).4) Concentration of metabolites in platelets (Attached document 4.2.2.3-4)

Following a single oral administration of prasugrel (3 mg/kg) to male rats, the concentration of metabolites in plasma and in platelets was measured at 0.5, 1, 2, 4, and 6 hours post-dose (n = 6/timepoint). R-100932 showed the highest plasma concentration at all time points tested, followed by

R-106583 and R-138727; R-95913 was not detectable. The major metabolite detected in platelets was R-138727. R-138727 concentration in platelets rapidly increased after administration. R-138727 concentration in plasma decreased more rapidly than the concentration in platelets. R-95913 was barely detectable in platelets only at 2 hours post-dose, while neither R-106583 nor R-100932 was detectable.

3.(ii).A.(2).5) Placental transfer (Attached document 4.2.2.3-5)

Following a single oral administration of ^{14}C-labeled prasugrel (5 mg/kg) to rats at gestation day 13, radioactivity concentration in tissues of maternal animals and in fetuses was measured at 1, 24, and 48 hours post-dose (n = 1/time point). Radioactivity concentration in fetuses at 1 hour post-dose was 0.27 times the blood concentration of maternal animals and, at 48 hours post-dose, decreased to 3% of the level observed at 1 hour post-dose.

In a similar manner, radioactivity concentration in tissues of maternal animals at gestation day 18 and in fetal tissues was measured. Radioactivity concentration in the fetal blood, brain, heart, kidneys, lungs, and liver at 1 hour post-dose was 0.20 to 0.33 times the blood concentration of maternal animals and, at 48 hours post-dose, decreased below the detection limit or to ≤4% of the level observed at 1 hour post-dose (n = 1/time point).

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

3.(ii).A.(3).1) Ratio of stereoisomers of R-138727 in *in vivo* systems (Attached documents 4.2.2.4-1, 4.2.2.4-2, 4.2.2.4-4, 4.2.2.4-5)

Prasugrel or prasugrel hydrochloride (5, 50 mg/kg) was administered orally in a single dose to male and female rats (n = 3 each), prasugrel or prasugrel hydrochloride (2, 20 mg/kg) was administered orally in a single dose to male and female dogs (n = 3 each), and prasugrel hydrochloride (30 mg/kg) was administered orally in a single dose to male and female mice (n = 4 each/time point) or to pregnant rabbits (n = 3/time point). In all animal species tested, the sum of R-125689 and R-125690, 2 more active metabolites among 4 stereoisomers of R-138727 present in plasma, accounted for about 60% to 100% of the isomers regardless of the administered drug substance (prasugrel or prasugrel hydrochloride), dose, or sex.

3.(ii).A.(3).2) Metabolic profile (Attached documents 4.2.2.2-1, 4.2.2.2-2, 4.2.2.4-7, 4.2.2.4-8)

^{14}C-labeled prasugrel was administered orally in a single dose, and metabolites in plasma, urine, feces, or bile were investigated as follows: in male mice, ^{14}C-labeled prasugrel 30 mg/kg was administered, metabolites were investigated in plasma (n = 3/time point) and in urine and feces (n = 4); in male rats, ^{14}C-labeled prasugrel 30 mg/kg, in plasma (n = 1/time point) and in urine and feces (n = 4); in female rats, ^{14}C-labeled prasugrel 5 mg/kg, in in bile (n = 3); in male dogs, ^{14}C-labeled prasugrel 10 mg/kg, in plasma, urine, feces, and bile (n = 3 or 4).

(a) Metabolites in plasma

Major metabolites observed in the plasma of mice, rats, and dogs up to 12 hours post-dose were R-106583 and R-100932 (S-methylated forms of inactive metabolite R-104434 generated via an R-95913 isomer), which accounted for 9.7% to 36.9% and 3.2% to 6.7% in mice, 5.3% to 13.1% and 11.0% to 19.8% in rats, 0% to 17% and 3.7% to 25.4% in dogs, respectively, of the plasma radioactivity at each time point. Other metabolites generally accounted for ≤10% of total radioactivity in plasma at all time points tested. When blood samples were treated with a derivatization reagent 3'-methoxyphenacyl bromide, the percentage of R-138727 and R-104434 relative to the plasma radioactivity was 4.3% to 16.5% and 0% to 2.3%, respectively, in mice; 3.3% to 8.9% and 0% to 1.3%, respectively, in rats; and 0% to 33.0% and 0% to 3.6%, respectively, in dogs.

(b) Metabolites in urine

The percentage of radioactivity excreted in urine relative to the radioactivity administered was 51.8% in mice up to 24 hours post-dose, 17.6% in rats up to 72 hours post-dose, and 29.95% in dogs up to 96 hours post-dose. Major metabolites recovered in urine were M11 (R-106583 sulfoxide) both in mice (23.6% of the radioactivity administered) and rats (7.9%) and M1 (4.1%; a downstream metabolite of R-104434) and M12 (3.2%; a downstream metabolite of R-95913 generated by a pathway different from that of R-138727) in dogs. The other metabolites accounted for ≤2.8%, ≤1.2%, and ≤1.9% of the radioactivity administered to the respective animals. Metabolites commonly observed in urine samples

of all animal species were M1, R-106583, R-100932, M10 (a metabolite of R-100932), M11, and M12. M13, M14, M15, and M19, which are glucuronide conjugates of R-95913, R-106583, R-100932, and M18 (M12 hydroxide), respectively, were detected in the urine of dogs, and M13 and M14 were detected in the urine of mice. Glucuronide conjugates were not excreted in the urine of rats.

(c) Metabolites in feces

The percentage of radioactivity excreted in feces relative to the radioactivity administered was 37.3% in mice up to 24 hours post-dose, 68.4% in rats up to 72 hours post-dose, and 46.7% in dogs up to 96 hours post-dose. In all animal species tested, the major metabolite recovered from feces was R-106583, which accounted for 5.7%, 15.3%, and 17.0%, respectively, of the radioactivity administered, and the other metabolites accounted for ≤2.8%, ≤5.9%, and ≤4.4% of the radioactivity administered to the respective animals. The other metabolites commonly observed in feces of all animal species tested were M1, R-95913, R-100932, M10, and M21. M18 was observed only in the feces of dogs.

(d) Metabolites in bile

Of the radioactivity administered to rats, 87.5% was excreted in bile within 6 hours post-dose. Major metabolites recovered from the bile were R-100932 and unidentified metabolites RB8 and RB9, which accounted for 10.2%, 11.0%, and 11.8%, respectively, of the radioactivity administered. The other metabolites detected in bile were R-95913, R-118443, R-119251, and unidentified metabolites RB1 to 7, RB10 to 11, all of which combined accounted for ≤8.3% of the radioactivity administered.

3.(ii).A.(3).3 Hydrolysis to R-95913 after absorption from the gastrointestinal tract (Attached document 4.2.2.4-9)

Following intraduodenal administration of prasugrel (50 mg/kg) to male rats (n = 5), C_{max} of R-95913 in the plasma of the portal vein was 15.8 μM and t_{max} was 0.20 hours, and the area under the plasma concentration-time curve from 0 to 1 hour post-dose ($AUC_{0\text{-}1h}$) was 10.7 μM·h. Prasugrel was not detected in the plasma of the portal vein.

3.(ii).A.(3).4 *In vivo* studies on the induction of metabolic enzymes (Attached documents 4.2.2.4-10, 4.2.2.4-11)

Prasugrel (1, 10, 100, 300 mg/kg), phenobarbital sodium (80 mg/kg), or vehicle was administered orally once daily for 7 days to male rats (n = 5), and the activity and the amount of drug-metabolizing enzymes in the liver were investigated at 1 day after the last dose (all doses) and at 7 days after the last dose (300 mg/kg/day only).

In the 1 mg/kg group, the activity of each drug-metabolizing enzyme was not significantly different from that in the vehicle group. In the ≥10 mg/kg groups, increases in the amount of cytochrome b_5 and the activity of glutathione-S-transferase (GST) compared with the vehicle group were observed at 1 day after the last dose. In the 100 and 300 mg/kg groups, increased CYP content, increased activities of aminopyrine N-demethylase, aniline hydroxylase, 7-ethoxycoumarin O-deethylase, testosterone 6β hydroxylase, UDP-glucuronosyl transferase (UGT), and GST were observed compared with the vehicle group at 1 day after the last dose. The activity of each drug-metabolizing enzyme was approximately 50% to 150% of that in the phenobarbital sodium group. At 7 days after the last dose, no parameters increased more than in the vehicle group except for UGT and GST activities in the 300 mg/kg group, and the increased levels of UGT and GST activities tended to return toward the baseline level compared with the level at 1 day after the last dose. At 1 day after the last dose, the content of CYP2B and 3A2 in liver microsomes of the 100 and 300 mg/kg groups and of the phenobarbital sodium group was higher than in the vehicle group.

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

3.(ii).A.(4).1 Excretion in urine and feces (Attached documents 4.2.2.2-1, 4.2.2.2-2, 4.2.2.2-6)

Following a single oral administration of ^{14}C-labeled prasugrel (30 mg/kg) to male mice (n = 4), 52.84% and 39.35% of the radioactivity administered were excreted in urine and feces, respectively, within 120 hours post-dose.

Following a single oral or intravenous administration of ^{14}C-labeled prasugrel (5 mg/kg) to male rats (n = 3), approximately 20% and 79% of the radioactivity administered were excreted in urine and feces, respectively, within 168 hours post-dose, regardless of the route of the administration.

Following a single oral administration of ^{14}C-labeled prasugrel (2 mg/kg) to male dogs (n = 3), 24.5% and 72.8% of the radioactivity administered were excreted in urine and feces, respectively, within 168 hours post-dose.

3.(ii).A.(4).2) Excretion in bile (Attached document 4.2.2.2-2)
Following a single oral or intravenous administration of ^{14}C-labeled prasugrel (5 mg/kg) to bile duct-cannulated male rats (n = 3), 90.1% and 88.1%, respectively, of the radioactivity administered were excreted in bile within 48 hours post-dose.

3.(ii).A.(4).3) Excretion in milk (Attached document 4.2.2.5-1)
Following a single oral administration of ^{14}C-labeled prasugrel (5 mg/kg) to lactating rats (n = 3), the ratio of radioactivity concentration in milk to that in plasma was 1.72 to 4.78 at each time point up to 24 hours post-dose, and 0.58 at 48 hours post-dose. In milk and plasma, $t_{1/2}$ of radioactivity was 9.5 and 18 hours, respectively.

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Enzyme induction
Among drug-metabolizing enzymes shown to be induced by prasugrel hydrochloride in rats, CYPs were investigated for induction by prasugrel hydrochloride in *in vitro* studies using human biomaterials, whereas inducibility of UGT and GST was not investigated using human biomaterials. Therefore, it is necessary to discuss the inducibility of these enzymes by prasugrel hydrochloride in humans, based on the results of studies in rats. PMDA asked the applicant to explain the possible effects of UGT and GST on the pharmacokinetics of the metabolites of prasugrel hydrochloride and concomitant drugs in humans, if either of them were to be induced in humans like in rats.

The applicant responded as follows:
In rats, UGT and GST were induced when high doses (100, 300 mg/kg) of prasugrel hydrochloride were administered, and C_{max} of R-95913, R-106583, and R-138727 after dosing of 100 mg/kg to rats was approximately 250, 4170, and 12,700 ng/mL, respectively. In a study in healthy elderly subjects (Study CS0747S-B-J110), when prasugrel hydrochloride was administered at 20 mg loading dose and then at 3.75 mg maintenance dose for 6 days, C_{max} of R-95913, R-106583, and R-138727 after the last dose was approximately 14, 33, and 25 ng/mL, respectively, which was approximately one eighteenth, one one-hundred-twentieth, and one five-hundredth times the level observed in rats. The above results suggest that induction of UGT and GST, which was observed in rats, is unlikely to pose any problem in humans.

In humans, R-95913, R-106583, and R-100932 are supposed to undergo glucuronide conjugation. If UGT were to be induced in humans, the exposures to R-95913, R-106583, and R-100932 would decrease after multiple doses. However, no such decreases in these metabolites were observed in phase I multiple dose studies, which suggests that UGT was not induced in humans. In addition, no particular problems have been reported regarding drug-drug interactions caused by UGT induction after market launch in foreign countries. Based on the above, prasugrel hydrochloride is unlikely to induce UGT to such an extent as to have any significant effect on the pharmacokinetics of the prasugrel hydrochloride metabolites or concomitant drugs.

GST is an enzyme that catalyzes glutathione conjugation reaction. The enzyme is abundantly present in various organs including the liver, accounting for approximately 10% of soluble proteins in hepatocytes. Since GST is not involved in the metabolism of prasugrel hydrochloride, GST would not likely affect the pharmacokinetics of prasugrel hydrochloride, even if GST were induced by prasugrel hydrochloride. On the other hand, if it were induced by prasugrel hydrochloride, GST, could affect the metabolism of concomitant drugs that undergo glutathione conjugation. However, since GST is a highly active metabolizing enzyme present throughout the body, the induced enzyme, if any, would not likely to significantly affect the pharmacokinetics of concomitant drugs.

PMDA considers as follows:
From the above explanation of the applicant, administration of prasugrel hydrochloride at the proposed clinical dose in humans is unlikely to pose any clinical problems due to GST or UGT induction by prasugrel hydrochloride, even if such induction occurs as observed in rats.

3.(ii).B.(2) Melanin affinity
In a study on tissue distribution in rats, the distribution of radioactivity in the eyes was higher, and the elimination half-life was longer, in pigmented rats than in albino rats. Therefore, PMDA asked the applicant to explain whether or not adverse events related to melanin-containing tissues such as the eyes tend to occur with a higher frequency in Japanese subjects than in foreign subjects, based on the safety information in Japanese and foreign clinical studies.

The applicant responded as follows:
The incidences of adverse events involving the eyes and skin (nonhaemorrhagic adverse events with an incidence of ≥0.4% in the prasugrel hydrochloride groups in Japanese phase III studies) were investigated in Japanese phase III studies (pooled analysis of the Japanese phase III study in patients with ACS-PCI and the Japanese phase III study in patients with elective PCI) and the foreign ACS phase III study. In the Japanese phase III studies, the incidence of nonhaemorrhagic adverse events involving the eyes (system organ class, eye disorders) in the prasugrel hydrochloride group and in the clopidogrel sulfate group was 0.7% (7 of 1055 patients) and 0.3% (3 of 1050 patients), respectively, for cataract, 0.5% (5 of 1055 patients) and 0.3% (3 of 1050 patients) for diabetic retinopathy, and 0.4% (4 of 1055 patients) and 0.2% (2 of 1050 patients) for conjunctivitis, showing no significant difference between the prasugrel hydrochloride group and the clopidogrel sulfate group. Similarly, in the foreign ACS phase III study, the incidences of the above adverse events in the prasugrel hydrochloride group were not significantly different compared with the clopidogrel sulfate group. As for nonhaemorrhagic adverse events involving the skin (system organ class, skin and subcutaneous tissue disorders), the incidence in the prasugrel hydrochloride group and in the clopidogrel sulfate group in the Japanese phase III studies was 3.1% (33 of 1055 patients) and 3.0% (31 of 1050 patients), respectively, for rash; 2.9% (31 of 1055 patients) and 2.5% (26 of 1050 patients) for eczema; 1.5% (16 of 1055 patients) and 2.4% (25 of 1050 patients) for dermatitis contact; 1.7% (18 of 1055 patients) and 1.4% (15 of 1050 patients) for drug eruption; 1.5% (16 of 1055 patients) and 1.0% (11 of 1050 patients) for pruritus; 1.2% (13 of 1055 patients) and 1.0% (10 of 1050 patients) for erythema; 0.7% (7 of 1055 patients) and 1.3 (14 of 1050 patients) for urticaria; 0.8% (8 of 1055 patients) and 0.8% (8 of 1050 patients) for blister; 0.7% (7 of 1055 patients) and 0.7% (7 of 1050 patients) for dermatitis; 0.6% (6 of 1055 patients) and 0.3% (3 of 1050 patients) for dermal cyst; 0.5% (5 of 1055 patients) and 0.8% (8 of 1050 patients) for eczema asteatotic; 0.4% (4 of 1055 patients) and 0.5% (5 of 1050 patients) for seborrhoeic dermatitis; and 0.4% (4 of 1055 patients) and 0% (0 of 1050 patients) for heat rash, showing no significant difference between the prasugrel hydrochloride group and the clopidogrel sulfate group. Similarly, in the foreign ACS phase III study, the incidences of the above adverse events in the prasugrel hydrochloride group were not significantly different from those in the clopidogrel sulfate group. Thus, although there is a certain limitation to the discussion on the incidence of adverse events between different studies, there was no significant difference in the incidence of adverse events related to melanin-containing tissue between the clopidogrel sulfate group and the prasugrel hydrochloride group in Japanese and foreign clinical studies, nor increasing incidence in Japanese patients compared with foreign patients following the administration of prasugrel hydrochloride.

Based on the above explanation of the applicant and on the results of nonclinical toxicity studies, PMDA concluded that distribution of prasugrel hydrochloride-derived compounds in melanin-containing tissues is unlikely to be clinically significant.

3.(iii) Summary of toxicology studies
3.(iii).A Summary of the submitted data
Toxicology studies of prasugrel hydrochloride conducted include single-dose toxicity studies, repeat-dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other toxicity studies (antigenicity studies, toxicity studies on impurities, photosafety studies). During the initial phase of the development, toxicity studies were conducted using prasugrel, the free base form of prasugrel hydrochloride. Therefore, in order to compare

the toxicity between prasugrel hydrochloride and prasugrel, a single dose administration study (rats) and repeat-dose administration studies (mice, rats, dogs) were conducted and, based on the results, the applicant determined that it is feasible to include the results of the toxicity studies conducted using prasugrel, the free base form of prasugrel hydrochloride, in the evaluation of the toxicity of prasugrel hydrochloride.

3.(iii).A.(1) Single-dose toxicity

As single dose toxicity studies, studies of oral administration of prasugrel to mice, rats, and dogs, and a study of oral administration of prasugrel hydrochloride and prasugrel to rats were conducted.

3.(iii).A.(1).1) Single oral toxicity study in mice (Attached document 4.2.3.1-1)

Prasugrel (2000 mg/kg) was administered orally in a single dose to male and female RFVL mice. No death occurred, and the applicant determined the approximate lethal dose to be >2000 mg/kg. As the only change in general signs, yellow-brown urine was observed.

3.(iii).A.(1).2) Single oral toxicity study in rats (Attached document 4.2.3.1-2)

Prasugrel (1000, 2000 mg/kg) was administered orally in a single dose to male and female F344 rats. No death occurred, and the applicant determined the approximate lethal dose to be >2000 mg/kg. As changes in general signs, yellow-brown urine, mydriasis, respiratory irregularity, decreased activity, eyelid ptosis, lacrimation, staggering gait, and transient reduction in body weight gain were observed.

3.(iii).A.(1).3) Single oral toxicity study in rats, comparison between prasugrel hydrochloride and prasugrel (Attached document 4.2.3.1-3)

Prasugrel hydrochloride or prasugrel (0 [vehicle], 500, 1000, 2000 mg/kg) was administered orally in a single dose to male and female F344 rats. Death occurred in 3 of 5 males and in 4 of 5 females in the prasugrel hydrochloride 2000 mg/kg group, whereas no death occurred in the prasugrel group. Comparison of $AUC_{0\text{-}24h}$ of 6 metabolites (R-95913, R-100932, R-106583, R-118443, R-119251, R-138727) between the prasugrel hydrochloride 2000 mg/kg group and the prasugrel 2000 mg/kg group showed that, for all metabolites tested, $AUC_{0\text{-}24h}$ was 1.2 to 3.5 times higher in the prasugrel hydrochloride group than in the prasugrel group, and the applicant discussed that the difference in the time-course of plasma concentration resulted in the difference in the lethal dose. Changes in general signs observed were yellow-brown urine in animals treated with either prasugrel hydrochloride or prasugrel at ≥500 mg/kg, and decreased activity, mydriasis, and reduction in body weight gain at ≥1000 mg/kg.

3.(iii).A.(1).4) A single-dose titration oral toxicity study in dogs (Attached document 4.2.3.1-4 [non-GLP])

Prasugrel (10, 30, 100, 300, 1000, 2000 mg/kg) was administered orally everyday (except between 300 mg/kg and 1000 mg/kg doses where a 3-day washout period existed) in a dose-escalating manner to male and female beagle dogs. No death occurred, and the applicant determined the approximate lethal dose to be >2000 mg/kg. Changes observed after administration were vomiting, suppressed platelet aggregation, increased alkaline phosphatase (ALP), and atrophy of hepatocytes.

3.(iii).A.(2) Repeat-dose toxicity

As repeat-dose toxicity studies, oral toxicity studies of prasugrel in mice (3 months), rats (3 and 6 months), and dogs (3 and 9 months) and oral toxicity studies of prasugrel hydrochloride and prasugrel in mice (14 days), rats (28 days), and dogs (28 days) were conducted. The main target organ for the toxicity of prasugrel hydrochloride and prasugrel was the liver. Changes observed in relation to the administration were yellow-brown urine presumably caused by metabolites of prasugrel (mice, rats); reduction in body weight gain (mice, rats); decreased erythrocytic parameter values suggesting anemia (mice, rats); increased reticulocyte count (RET), increased platelet count, prolonged prothrombin time (PT), and prolonged activated partial thromboplastin time (APTT) (rats); decreased platelet aggregation and increased ALP (dogs); and increased liver weight and hepatocyte hypertrophy associated with the induction of hepatic drug-metabolizing enzymes (mice, rats, dogs).

3.(iii).A.(2).1) Three-month repeated oral dose toxicity study in mice (Attached document 4.2.3.2-2)

As a dose-finding study for carcinogenicity studies, prasugrel (0, 100, 300, 1000 mg/kg/day) was administered orally for 3 months to male and female $B6C3F_1$ mice (n = 10/sex/group). One male in the 1000 mg/kg group died on Day 84 of administration. The cause of death was unknown, with the animal showing no abnormality except for hepatocyte hypertrophy. Males and females in the ≥100 mg/kg groups showed yellow-brown urine and increased liver weight, and females in the same groups showed decreased ALP and increased total cholesterol (T-Cho). Males and females in the ≥300 mg/kg groups showed reduction in body weight gain and centrilobular hypertrophy of hepatocytes, and males in the same groups showed increased alanine aminotransferase (ALT). Males and females in the 1000 mg/kg group showed decreased red blood cell count (RBC), decreased hemoglobin (Hb), decreased hematocrit (Ht), increased RET, decreased albumin, decreased blood urea nitrogen (BUN), hypertrophy of duodenal mucosal epithelium, decreased frequency of spindle cell hyperplasia in adrenals, and decreased adrenal X-zone. Males in the 1000 mg/kg group showed decreased ALP and decreased albumin/globulin (A/G) ratio, and females in the same group showed increased ALT, decreased total protein, ovarian atrophy, and thymic atrophy. The mean maximum plasma concentration (C_{max}) and $AUC_{0\text{-}24h}$ of metabolites increased with an increase in the dose of prasugrel. The mean C_{max} and $AUC_{0\text{-}24h}$ of metabolites were highest for R-106583, followed in descending order by R-119251, R-100932, R-95913, and R-118443. $AUC_{0\text{-}24h}$ of R-106583 was approximately 50 to 110 times that of R-118443. No marked sex difference was observed in the plasma concentration of metabolites, while decrease in the exposure level was observed following repeated administration. The maximum tolerated dose (MTD) in this study was determined to be 300 mg/kg.

3.(iii).A.(2).2) Fourteen-day repeated oral dose toxicity study in mice, comparison between prasugrel hydrochloride and prasugrel (Attached document 4.2.3.2-3)

Prasugrel hydrochloride (0, 100, 300, 1000 mg/kg [prasugrel equivalent]) or prasugrel (1000 mg/kg) was administered orally for 14 days to male and female $B6C3F_1$ mice (n = 10/sex/group). No death occurred. In the prasugrel hydrochloride groups, males and females in the ≥100 mg/kg groups showed hyperplasia of duodenal mucosal epithelium, and males in the same groups showed increased liver weight and decreased ALP; in the ≥300 mg/kg groups, males and females showed hepatocyte hypertrophy, females showed yellow-brown urine, increased liver weight, and decreased A/G ratio and males showed hyperplasia of squamous epithelium of the forestomach, decreased Hb, and increased platelet count. In the 1000 mg/kg group of both compounds, males and females showed yellow-brown urine, reduction in body weight gain, decreased RBC, decreased Ht, decreased Hb, increased ALT, increased T-Cho, decreased ALP, decreased A/G ratio, increased liver weight, hepatocyte hypertrophy, hyperplasia of squamous epithelium of the forestomach, and hypertrophy of the duodenal mucosal epithelium; males showed increased RET and increased platelet count; and females showed increased total protein and hypertrophy of adrenal fasciculata cells. Decreased erythrocyte parameter values and histopathological changes of the liver, adrenal, and forestomach were more prominent in the prasugrel hydrochloride group. There was no difference in changes over time of plasma concentrations of 6 metabolites after administration of prasugrel hydrochloride or prasugrel at 1000 mg/kg.

Based on the comprehensive evaluation of the above results, the applicant determined that there was no qualitative difference in the toxicological profile between prasugrel hydrochloride and prasugrel.

3.(iii).A.(2).3) Three-month repeated oral dose toxicity study in rats (Attached document 4.2.3.2-6)

Prasugrel (0, 10, 30, 100, 300 mg/kg/day) was administered orally for 3 months to male and female F344 rats (n = 10/sex/group). No death occurred. Males in the ≥30 mg/kg groups showed prolonged PT, and females in the same groups showed increased liver weight; males and females in the ≥100 mg/kg groups showed prolonged APTT, and males in the same groups showed increased liver weight, hypertrophy and eosinophilic change of hepatocytes, and increased platelet count. Males and females in the 300 mg/kg group showed yellow-brown urine and reduction in body weight gain, and females in the same group showed hypertrophy and eosinophilic change of hepatocytes and increased platelet count. Based on the above, the applicant determined the no observed adverse effect level (NOAEL) to be 100 mg/kg/day in both males and females using the reduction in body weight gain as the index.

3.(iii).A.(2).4) Six-month repeated oral dose toxicity study in rats (Attached document 4.2.3.2-7)

Prasugrel (0, 10, 30, 100, 300 mg/kg/day) was administered orally for 6 months to male and female F344 rats (n = 15/sex/group). Death occurred in 1 male in the 30 mg/kg group on Day 85 of administration and in 1 female in the 100 mg/kg group on Day 132. Food retention was observed in the mouth and the esophagus of the dead animals, but no findings indicative of the cause of death were noted. In addition, no death occurred in animals in the 300 mg/kg group. Based on the above, the death was considered to be accidental. Males in the ≥10 mg/kg groups showed increased liver weight. In the ≥30 mg/kg groups, males and females showed yellow-brown urine, and females showed increased liver weight and hepatocyte hypertrophy. In the ≥100 mg/kg groups, males and females showed reduction in body weight gain, decreased food intake, decreased Hb, decreased mean red blood cell Hb concentration, increased platelet count, increased calcium concentration; males showed hepatocyte hypertrophy, prolonged APTT, decreased TG, increased total protein, increased β-globulin; and females showed increased α2-globulin. In the 300 mg/kg group, males and females showed decreased absolute neutrophil count and decreased γ-globulin; males showed increased albumin, decreased α1-globulin, increased α2-globulin, decreased T-Cho, prolonged PT, and increased fibrinogen; and females showed increased RET, increased total bilirubin, and prolonged APTT. The applicant explained that the changes observed in the liver in the 10 and 30 mg/kg groups were related to the induction of drug-metabolizing enzymes and determined the NOAEL to be 30 mg/kg using the reduction in body weight gain and decreased food intake as the indices.

At Week 26 of prasugrel administration at the NOAEL,the mean area under the plasma concentration-time curve of R-95913, R-100932, and R-106583 from 1 to 24 hours post-dose ($AUC_{1\text{-}24h}$) was 0.052, 5.989, and 6.454 μg·h/mL, respectively, in males, and 0.126, 4.977, and 8.259 μg·h/mL, respectively, in females.

3.(iii).A.(2).5) Twenty-eight-day repeated oral dose toxicity study in rats, comparison between prasugrel hydrochloride and prasugrel (Attached document 4.2.3.2-8)

Prasugrel hydrochloride (0, 30, 100, 300 mg/kg/day [prasugrel equivalent]) or prasugrel (300 mg/kg/day) was administered orally for 28 days to male and female F344 rats (n = 10/sex/group). In the prasugrel hydrochloride ≥30 mg/kg groups, males and females showed yellow-brown urine, increased liver weight, and hepatocyte hypertrophy, and males showed increased total protein and increased β-globulin. In the prasugrel hydrochloride ≥100 mg/kg groups, males and females showed increased α2-globulin and increased calcium; females showed reduction in body weight gain, decreased food intake, increased RET, increased total protein, increased β-globulin, and decreased A/G ratio; and males showed increased albumin and decreased potassium. In the prasugrel hydrochloride 300 mg/kg group, males and females showed decreased red blood cell parameter values, prolonged APTT, increased fibrinogen, increased platelet count, and decreased chlorine; males showed reduction in body weight gain, decreased food intake, decreased TG, and decreased glucose; and females showed decreased potassium and decreasing tendency of urine pH.

In the prasugrel 300 mg/kg group, males and females showed yellow-brown urine, reduction in body weight gain, decreased food intake, increased liver weight, hepatocyte hypertrophy, decreased red blood cell parameter values, prolonged APTT, increased fibrinogen, increased platelet count; and females showed decreasing tendency of urine pH and increased RET. There was no difference in the extent of the reduction in body weight gain, increased liver weight, or hepatocyte hypertrophy between the 2 compounds. There was no difference in changes over time of plasma concentrations of 6 metabolites after administration of prasugrel hydrochloride or prasugrel. The applicant determined the NOAEL of prasugrel hydrochloride to be 30 mg/kg/day using the reduction in body weight gain and decreased food intake as indices.

Toxicological findings were similar between the prasugrel hydrochloride 300 mg/kg group and the prasugrel 300 mg/kg group. Also, toxicological findings in the prasugrel hydrochloride groups were similar to those observed in the 14-day (Attached document 4.2.3.2-4 [Reference data]), 3-month, and 6-month repeated oral dose toxicity studies of prasugrel. Based on the above, the applicant considered that there is no qualitative difference in the toxicological profile between prasugrel hydrochloride and prasugrel.

3.(iii).A.(2).6) Three-month repeated oral dose toxicity study in dogs (Attached document 4.2.3.2-12)

Prasugrel hydrochloride (0 [empty capsule], 0.8, 4, 20 mg/kg/day) was administered orally for 3 months to male and female beagle dogs (n = 3/sex/group). Males and females in the ≥0.8 mg/kg groups showed suppressed platelet aggregation. Males and females in the ≥4 mg/kg groups showed hepatocyte hypertrophy accompanied by ground glass-like changes. Males and females in the 20 mg/kg group showed increased ALP, mild hyperplasia of smooth endoplasmic reticulum in the liver, and females in the same group showed decreased T-Cho and increased liver weight. Based on the above, the applicant determined the NOAEL to be 4 mg/kg/day using increased ALP as the index.

3.(iii).A.(2).7) Nine-month repeated oral dose toxicity study in dogs (Attached document 4.2.3.2-13)

Prasugrel (0, 0.8, 4, 20 mg/kg/day) was administered orally for 9 months to male and female beagle dogs (n = 4/sex/group). In the 20 mg/kg group, males and females showed increased ALP, and males showed hepatocyte hypertrophy accompanied by ground glass-like changes. The increased ALP and changes in the liver disappeared after a 1-month withdrawal period. Based on the above, the applicant determined the NOAEL to be 4 mg/kg/day using increased ALP as the index.

Following the 9-month repeated administration at the NOAEL (4 mg/kg/day), the mean $AUC_{0\text{-}24h}$ of R-95913, R-100932, and R-106583 at Week 39 of administration was 0.7622, 0.5156, and 0.6513 μg·h/mL, respectively, in males, and 0.3042, 0.3370, and 0.4169 μg·h/mL, respectively, in females.

3.(iii).A.(2).8) Twenty-eight-day repeated oral dose toxicity study in dogs, comparison between prasugrel hydrochloride and prasugrel (Attached document 4.2.3.2-14)

Prasugrel hydrochloride (0, 4, 20, 100 mg/kg/day [prasugrel equivalent]) or prasugrel (100 mg/kg/day) was administered orally for 28 days to male and female beagle dogs (n = 3/sex/group). Hepatocyte hypertrophy and increased ALP were observed in females of the prasugrel hydrochloride ≥20 mg/kg groups, in males of the prasugrel hydrochloride 100 mg/kg group, and in males and females of the prasugrel 100 mg/kg group. Increased liver weight and lamellar inclusions in the hepatocyte were observed in males and females of the prasugrel hydrochloride 100 mg/kg group and in males of the prasugrel 100 mg/kg group. Hypertrophy of follicular epithelial cells in the thyroid gland, supposed to be a change secondary to the enhanced metabolism of thyroid hormone caused by increased hepatic drug-metabolizing enzymes, was observed in males and females of the prasugrel hydrochloride 100 mg/kg group and in males of the prasugrel 100 mg/kg group. There was no difference in the extent of the increase in liver weight or the hypertrophy of hepatocytes between prasugrel hydrochloride and prasugrel. Plasma concentrations of 6 metabolites in the prasugrel hydrochloride 100 mg/kg group tended to be slightly higher than in the prasugrel 100 mg/kg group.

Toxicological findings were similar between the prasugrel hydrochloride 100 mg/kg group and the prasugrel 100 mg/kg group. Also, toxicological findings in the prasugrel hydrochloride groups were similar to those observed in the 14-day (Attached document 4.2.3.2-9 [Reference data]), 3-month, and 9-month repeated oral dose toxicity studies of prasugrel. Based on the above, the applicant considered that there is no qualitative difference in the toxicological profile between prasugrel hydrochloride and prasugrel.

Based on the comparison of the exposures[1] to active metabolite R-138727 and inactive metabolite R-106583 following the administration of prasugrel hydrochloride at the NOAEL (4 mg/kg/day) and at the recommended clinical maintenance dose (3.75 mg; Study CS0747S-B-J110), the applicant discussed that there is a safety margin of 30 to 41 fold and 4.1 to 5.4 fold, respectively, for C_{max} and 40 to 57 fold and 2 to 3 fold, respectively, for AUC.

3.(iii).A.(3) Genotoxicity (Attached documents 4.2.3.3.1-1, 4.2.3.3.1-2, 4.2.3.3.2-1)

Genotoxicity of prasugrel was evaluated by bacterial reverse mutation assay, chromosomal aberration assay using cultured mammalian cells (female Chinese hamster lung-derived [CHL] fibroblasts), and

[1] C_{max} (μg/mL) of R-138727 and R-106583 was 0.74 and 1.02, respectively, in males; 0.135 and 0.177, respectively, in females; and 0.025 and 0.033, respectively, in humans. $AUC_{0\text{-}24h}$ (μg·h/mL) was 1.01 and 0.445, respectively, in males; 1.42 and 0.651, respectively, in females; and 0.025 and 0.217, respectively, in humans (AUC_{last} in humans).

micronucleus assay using mouse bone marrow cells. The results were all negative and the applicant considered that prasugrel is not genotoxic.

3.(iii).A.(4) Carcinogenicity

Carcinogenicity of prasugrel hydrochloride was evaluated by 2-year carcinogenicity studies in mice and rats. Neither of the studies showed any increase in neoplastic lesions associated with the administration of prasugrel hydrochloride and thus, the applicant considered that prasugrel hydrochloride is not carcinogenic.

3.(iii).A.(4).1) Two-year carcinogenicity study in mice (Attached document 4.2.3.4.1-1)

Prasugrel hydrochloride (0, 30, 100, 300 mg/kg/day) was administered orally for 2 years to male and female $B6C3F_1$ mice (n = 55/sex/group). A tendency toward an increase in the frequency of hepatocellular carcinoma was observed in animals receiving prasugrel hydrochloride, and a significant increase in the frequency of hepatocellular adenoma was observed in females of the ≥100 mg/kg groups and in males of the 300 mg/kg group. Hepatoblastoma was observed in 1 female of the 100 mg/kg group and in 1 male of the 300 mg/kg group. Also, hepatocyte hypertrophy suggestive of induction of hepatic drug-metabolizing enzymes was observed. Therefore, the applicant discussed that these changes were associated with the phenobarbital-type induction of hepatic drug-metabolizing enzymes.

Non-neoplastic lesions observed were increased eosinophil degeneration loci in the liver in males and females of the ≥100 mg/kg groups, centrilobular hypertrophy of hepatocytes in males of the ≥100 mg/kg groups, and pigmentation and hypertrophy of follicular epithelial cells in the thyroid gland in males and females of the 300 mg/kg group. The applicant considered that all were changes associated with the induction of drug-metabolizing enzymes.

Gastrointestinal tumor (duodenal adenocarcinoma, jejunal adenocarcinoma, ileal adenocarcinoma, rectal adenocarcinoma, jejunal adenoma, cecal leiomyosarcoma) was observed in 8 animals treated with prasugrel hydrochloride.

3.(iii).A.(4).2) Two-year carcinogenicity study in rats (Attached document 4.2.3.4.1-2)

Prasugrel hydrochloride (0, 10, 30, 100 mg/kg/day) was administered orally for 2 years to male and female F344 rats (n = 55/sex/group). The frequency of neoplastic lesions was not increased by the administration of prasugrel hydrochloride and the applicant determined that prasugrel hydrochloride was not carcinogenic. Non-neoplastic lesions observed were tendency of increase in discolored region in the lung and in accumulation of foam cells in males and females of the ≥30 mg/kg groups, tendency of increase in globule leucocytes in the tracheal epithelium in females of the ≥30 mg/kg groups, diffuse hepatocyte hypertrophy in males and females of the 100 mg/kg group, and increased eosinophil foci in the liver and tendency of increase in globule leucocytes in the tracheal epithelium in males of the 100 mg/kg group. The applicant considered that the hepatic lesions were changes associated with the induction of drug-metabolizing enzymes.

3.(iii).A.(5) Reproductive and developmental toxicity

Reproductive and developmental toxicity was evaluated by a study of prasugrel on fertility and early embryonic development to implantation in rats, studies of prasugrel for effects on embryo-fetal development in rats and rabbits, and a study of prasugrel hydrochloride for effects on pre- and postnatal development, including maternal function in rats. The results showed decreased body weight in maternal animals, decreased food intake (rats, rabbits), decreased fetal body weight (rats, rabbits), decreased body weight of pups before weaning (rats), whereas no teratogenicity was observed. Prasugrel was shown to be transferred to fetuses in rats (Attached document 4.2.2.3-5).

3.(iii).A.(5).1) Study of fertility and early embryonic development to implantation in rats (Attached document 4.2.3.5.1-1)

Prasugrel (0, 30, 100, 300 mg/kg/day) was administered orally to SD rats (n = 24/sex/group) from 4 weeks before mating until the end of the mating for males, and from 2 weeks before mating until gestation day 7 for females. One male in the 300 mg/kg group died, but the applicant considered that the death was accidental because death occurred in only 1 animal. Females of the ≥30 mg/kg groups showed yellow-brown urine. In the ≥100 mg/kg groups, males and females showed a transient salivation

and reduction in body weight gain; males showed yellow-brown urine; and females showed mydriasis. In the 300 mg/kg group, males and females showed decreased food intake, males showed decreased adrenal weight, decreased seminal vesicle weight, decreased prostate weight, and decreased epididymal weight, but the applicant considered that these observations were of low toxicological significance. No prasugrel-related changes were observed in fertility or early embryonic development to implantation. Based on the above, the applicant determined the NOAEL to be 30 mg/kg/day regarding general toxicity in parental animals and 300 mg/kg/day regarding the fertility of parental animals and the development of the offspring.

3.(iii).A.(5).2) Study of effects on embryo-fetal development in rats (Attached document 4.2.3.5.2-1)

Prasugrel (0, 30, 100, 300 mg/kg/day) was administered orally to pregnant SD rats (n = 24/group) from gestation day 7 to gestation day 17. One female in the 100 mg/kg group died of haemorrhage, but no other deaths or similar findings were observed either in the same group or in the 300 mg group, from which the applicant considered that the death was accidental. Maternal animals in the ≥100 mg/kg groups showed mydriasis, reduction in body weight gain, and decreased food intake. Fetuses in the 300 mg/kg group showed decreased body weight, but no other prasugrel-related changes were observed. Based on the above, the applicant determined the NOAEL to be 30 mg/kg/day for general toxicity in maternal animals, 300 mg/kg/day for the reproductive function of parental animals, and 100 mg/kg/day for the development of the offspring.

3.(iii).A.(5).3) Study of effects on embryo-fetal development in rabbits (Attached document 4.2.3.5.2-3)

Prasugrel (0, 30, 100, 300 mg/kg/day) was administered orally to pregnant New Zealand White (NZW) rabbits (n = 19-20/group) from gestation day 6 to gestation day 18. One female in the 100 mg/kg group died, but no other deaths or similar findings were observed either in the same group or in the 300 mg group, from which the applicant considered that the death was accidental. Maternal animals in the ≥100 mg/kg groups showed mild decrease in food intake, and those in the 300 mg/kg group showed yellow-brown urine and reduction in body weight gain during mid-pregnancy. Fetuses in the 300 mg/kg group showed decreased body weight. Based on the above, the applicant determined the NOAEL to be 30 mg/kg/day for general toxicity in maternal animals, 300 mg/kg/day for the reproductive function of parental animals, and 100 mg/kg/day for the development of the offspring.

3.(iii).A.(5).4) Study of effects on pre- and postnatal development, including maternal function in rats (Attached document 4.2.3.5.3-2)

Prasugrel hydrochloride (0, 30, 100, 300 mg/kg/day) was administered orally to pregnant SD rats (n = 22/group) from gestation day 6 to postpartum day 20. No death occurred. Maternal animals showed salivation at ≥30 mg/kg, yellow-brown urine at ≥100 mg/kg, and reduction in body weight gain and decreased food intake at 300 mg/kg. Pups at 300 mg/kg showed decreased pre-weaning body weight, while no study drug-related changes were observed in the test for behavioral development, necropsy observation, or study of mating of the offspring. Based on the above, the applicant determined the NOAEL to be 100 mg/kg/day for general toxicity in maternal animals and for the development of the offspring, and 300 mg/kg/day for the fertility of maternal animals.

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

3.(iii).A.(6).1) Antigenicity (Attached documents 4.2.3.7.1-1, 4.2.3.7.1-2)

In a study in which prasugrel was administered concurrently with an adjuvant to mice and guinea pigs, no passive cutaneous anaphylaxis (PCA) antibody was detected in the serum, from which the applicant determined that prasugrel was not antigenic.

3.(iii).A.(6).2) Toxicity studies of impurities (Attached documents 4.2.3.7.6-1 to 4.2.3.7.6-3)

[redacted]. As a result, there was no qualitative difference in the toxicity profile between prasugrel hydrochloride that contains these impurities at high concentrations and

prasugrel hydrochloride that does not, suggesting that these impurities would not cause any specific toxicity in clinical use.

3.(iii).A.(6).3) Photosafety testing (Attached documents 4.2.3.7.7-2, 4.2.3.7.7-3)
The ultraviolet-visible spectra from the active metabolite (R-138727) and other major metabolites of prasugrel in humans exhibit photoabsorption (maximum absorption wavelength, <310 nm). Also, prasugrel disappeared only slowly from the skin and eyeballs of pigmented rats. Therefore, *in vitro* phototoxicity testing was conducted on R-138727 and R-106583 using 3T3 NRU as the testing reagent. Based on the test results, the applicant considered that R-106583 was not phototoxic. The applicant once considered that R-138727 was non-phototoxic from the results of a preliminary test but, based on the results of this test, determined that the metabolite may possibly be phototoxic.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Concomitant use with aspirin
It is expected that prasugrel hydrochloride is concomitantly administered with aspirin in routine clinical practice. Therefore, PMDA asked the applicant to explain whether there is no concern that the concomitant use may cause increased toxicity or new toxicity of prasugrel hydrochloride or aspirin.

The applicant responded as follows:
Specific target organ toxicity of aspirin is probably haemorrhage caused by its antiplatelet effect and gastrointestinal tract disturbance and renal disturbance due to inhibition of cyclooxygenase. The liver is the main target of the toxicity of prasugrel hydrochloride, and no gastrointestinal or renal disorder was observed in long-term repeat-dose toxicity studies, demonstrating a safety margin of ≥10 fold. Also, an *in vitro* study has shown that neither prasugrel nor aspirin affects the formation of metabolites of each other (Attached document 4.2.2.7-1). In addition, a clinical study of concomitant use of prasugrel hydrochloride with aspirin showed that the concomitant use did not affect the plasma concentrations of the metabolites of prasugrel hydrochloride. Data from a clinical pharmacology study in healthy subjects and a clinical study in patients undergoing elective PCI suggested that concomitant use of prasugrel hydrochloride with aspirin may increase the frequencies of subcutaneous haemorrhage and subcutaneous haematoma, but all were assessed as mild or moderate, with none of them leading to treatment discontinuation. Thus, although it cannot be ruled out that concomitant use of prasugrel hydrochloride with aspirin at the usual dose in clinical settings may possibly enhance haemorrhage, the concomitant use is unlikely to enhance the toxicity of aspirin other than haemorrhage or cause new toxicity.

PMDA accepted the applicant's response.

3.(iii).B.(2) Carcinogenicity
Regarding hepatocellular adenoma, hepatocellular carcinoma, and hepatoblastoma observed in the carcinogenicity study in mice, PMDA asked the applicant to explain the reason for considering that they are changes associated with phenobarbital-type induction of hepatic drug-metabolizing enzymes, and to explain the relevance of the study results to humans and the safety margin in humans, also by taking account of the similarity in the types of metabolic enzymes induced by prasugrel and those induced by non-genotoxic compounds of phenobarbital-type.

The applicant responded as follows:
Prasugrel or phenobarbital was administered for 7 days to male and female $B6C3F_1$ mice and induction of drug-metabolizing enzymes in the liver was investigated. The results showed, in both the prasugrel group and the phenobarbital group, a marked induction of CYP2B and induction of CYP1A2, CYP2C, CYP3A, etc., with a similar pattern of hepatic drug-metabolizing enzyme induction in the 2 groups. Also, the prasugrel group showed pathological characteristics similar to those observed in the phenobarbital group, such as increased liver weight and centrilobular hypertrophy of hepatocytes. In addition, in the carcinogenicity study in mice, the prasugrel group showed hepatocyte hypertrophy suggestive of induction of hepatic drug-metabolizing enzymes. Phenobarbital is known to induce CYP1A2, 2B6, 2C9, and 3A4 in humans. In a study on CYP induction using the primary culture of human hepatocytes (Attached document 5.3.2.2-9), R-95913, a metabolite of prasugrel, did not induce CYP1A2, but seemed to induce CYP3A4. However, the apparent induction occurred only at a high

concentration (10 μM), indicating that the metabolite does not induce the enzyme under clinical conditions. As regards CYP2B6, prasugrel was considered unlikely to induce the enzyme for the following reasons: (i) in a phase I multiple dose study (Study CS0747S-A-J102), time-course change in plasma concentration of the active metabolite R-138727 (which is generated by CYP2B6 as well) was not affected by multiple administrations, and (ii) in a foreign clinical study (Study H7T-EW-TAAS) which investigated the interactions of rifampicin or bupropion with prasugrel hydrochloride, concomitant use of prasugrel hydrochloride with bupropion slightly inhibited the formation of hydroxybupropion which is generated by CYP2B6. Based on the above, the applicant considers that prasugrel hydrochloride is unlikely to cause clinically significant enzyme induction.

In light of the fact that $B6C3F_1$ mouse strain is apt to develop neoplastic lesions in the liver, together with the finding that hepatocyte hypertrophy associated with the induction of hepatic drug-metabolizing enzyme occurred following the administration of prasugrel, it was inferred that the increased frequency of neoplastic lesions in the liver observed in the carcinogenicity study in mice was a change related to the phenobarbital-type induction of hepatic drug-metabolizing enzymes (Attached document 4.2.2.4-10, 4.2.2.4-11). It is known that non-genotoxic compounds of phenobarbital-type induce liver tumor specifically in rodents (particularly mice). An epidemiological survey in humans has revealed that neither phenobarbital nor other anticonvulsants have carcinogenicity (Holsapple MP et al. *Toxicol Sci.* 2006;89:51-6.). Furthermore, prasugrel hydrochloride was tested negative in genotoxicity studies and was shown not to have tumor-promoting activity either in *in vitro* or *in vivo* studies. Based on the above, the increased frequency of neoplastic lesions observed in mice is unlikely to be relevant to humans. The NOAEL of prasugrel hydrochloride in mice for tumorigenic action in the liver was 30 mg/kg/day in females and 100 mg/kg/day in males. Comparison of the exposures to R-138727 and R-106583 following the administration of prasugrel hydrochloride at the NOAEL in rats and the exposures to these metabolites after administration of the proposed clinical maintenance dose (3.75 mg once daily) in humans showed that the safety margin was 255 to 628 fold for R-138727 and 107 to 399 fold for R-106583. In the 2-year carcinogenicity study in rats, prasugrel hydrochloride did not show tumorigenic activity. Based on the above, prasugrel hydrochloride is considered unlikely to cause any increase in liver tumor in humans as observed in mice. However, the draft package insert includes the statement that frequency of liver tumor increased in mice.

PMDA asked the applicant to explain the possibility that gastrointestinal tumor sporadically observed in the 2-year carcinogenicity study in mice was caused by prasugrel hydrochloride, taking account of the facts that hypertrophy of duodenal mucosal epithelium was observed in the 3-month repeated oral dose toxicity study in mice (Attached document 4.2.3.2-2) and the 14-day repeated oral dose toxicity study (Attached document 4.2.3.2-3) and that the incidence of colon cancer was higher in the prasugrel hydrochloride compared with the clopidogrel sulfate group in the foreign ACS phase III study.

The applicant explained as follows:
No hyperplasia suggestive of cell growth or regenerative change caused by mucosal injury was observed in the small or large intestine in the 14-day or 3-month repeated oral dose toxicity study in mice. In the foreign ACS phase III study, the incidence of colon cancer was significantly higher in the prasugrel hydrochloride group compared with the clopidogrel sulfate group, but there was no difference in the incidence of neoplastic lesions in the stomach or in other regions of the gastrointestinal tract. Although the reason for the higher incidence of colon cancer in patients treated with prasugrel hydrochloride is unknown, prasugrel hydrochloride is considered not to have a cancer-promoting effect since neither the active metabolite in humans (R-138727) nor the major metabolite in humans (R-106583) affected the growth rate of several types of human cancer cells in *in vitro* systems (Attached document 4.3.1-12), and since prasugrel hydrochloride does not affect the growth of cancer in mice transplanted with human lung cancer, colon cancer, or prostate cancer (Attached document 4.3.1-13). In $B6C3F_1$ mice, the strain used in the carcinogenicity study of prasugrel hydrochloride in mice, it is reported that epithelial tumor of the small intestine occurs spontaneously, albeit at a low frequency (0%-4%), and adenocarcinoma was observed in the duodenum in 1 animal in the control group in the 2-year carcinogenicity study in mice. Also taking account of the fact that the frequency of epithelial tumor in the prasugrel hydrochloride group was similar to the frequency of spontaneous lesion (0%-2%), the applicant considered that prasugrel hydrochloride is unlikely to induce the growth of mucosal epithelium either directly or indirectly.

PMDA considers as follows:
As regards liver tumor, the applicant explained that it was not observed in the carcinogenicity study in rats and that the tumor was a change related to phenobarbital-type induction of hepatic drug-metabolizing enzymes, and phenobarbital and other related drugs are not carcinogenic according to the epidemiological survey in humans. Based on the above explanation of the applicant, at present it will suffice to provide the information in the package insert. As for gastrointestinal tumor, there is no significant difference in the extent or incidence of the tumor between animals treated with prasugrel hydrochloride and untreated animals. Also, there was no increase in the number of animals with tumor in the carcinogenicity study in rats. In addition, prasugrel hydrochloride was tested negative in genotoxicity studies and no mechanism suggestive of direct involvement of prasugrel hydrochloride in tumorigenicity has been identified. Thus, taking account of the results of nonclinical studies including toxicity studies, prasugrel hydrochloride is unlikely to cause tumor of the digestive tract in humans. However, in light of the observation that, in clinical studies, the incidence of colon cancer was higher in the prasugrel hydrochloride group than in the clopidogrel sulfate group, the incidence of cancer should be carefully investigated by continuing to collect information via post-marketing surveillance.

3.(iii).B.(3) Hepatotoxicity
Since the liver is the main toxicological target organ of prasugrel hydrochloride and effects on the liver are observed in all animal species tested, PMDA asked the applicant to explain whether or not hepatotoxicity-related problems were observed in clinical studies.

The applicant responded as follows:
In the pooled analysis of 2 clinical studies (the Japanese phase III study in patients with ACS-PCI and the Japanese phase III study in patients with elective PCI), the incidence of hepatic function-related adverse events was 10.3% (109 of 1055 patients) in the prasugrel hydrochloride group and 9.8% (103 of 1050 patients) in clopidogrel sulfate group, and the incidence of hepatic function-related adverse events assessed as “treatment-related” was also similar between the 2 treatment groups as follows: 3.8% (40 of 1055 patients) in the prasugrel hydrochloride group and 3.2% (34 of 1050 patients) in the clopidogrel sulfate group. There was no clear difference in the incidence of any individual event included in hepatic function-related adverse events or adverse events assessed as “treatment-related” between the 2 treatment groups. As serious adverse events observed, “liver function tests abnormal” was reported by 1 patient in the prasugrel hydrochloride group in the Japanese phase III study in patients with ACS-PCI and “hepatic function abnormal” was reported by 1 patient in the prasugrel hydrochloride group in the Japanese phase III study in patients with elective PCI. Both events were considered to be not related to the study drug. Thus, no hepatotoxicity-related clinical problems were observed in Japanese clinical studies.

PMDA considers as follows:
The liver is the target organ of prasugrel hydrochloride, and the incidence of hepatic impairment in clinical studies is similar between the prasugrel hydrochloride group and the clopidogrel sulfate group, but hepatic dysfunction and jaundice are listed in “clinically significant adverse reactions” in the package insert of clopidogrel sulfate. Taking account of these facts, information on hepatic impairment should be provided in the package insert in an appropriate manner, be further collected via post-marketing surveillance, and be carefully investigated.

3.(iii).B.(4) Effect on steroid hormones
PMDA asked the applicant to investigate the possible effect of prasugrel hydrochloride on the balance of steroid hormones including sex hormones, taking account of the following observations: (a) weight of the uterus, prostate gland, ovaries, adrenals, etc., decreased in the 3-month repeated oral dose toxicity study in mice, in the 6-month repeated oral dose toxicity study in rats, and in the study of fertility and early embryonic development to implantation in rats; (b) seminiferous epithelia atrophy was found in the 14-day repeated oral dose toxicity study in dogs; and (c) tendency of dose-dependent decrease in the frequency of testicular tumor and dose-dependent increase in the frequency of uterine cancer were found in the 2-year carcinogenicity study in rats.

The applicant responded as follows:

The decreased weight of the reproductive organs observed in mice and rats was considered to be a change caused by decreased body weight. In the 14-day repeated oral dose toxicity study in dogs, decreased weight and atrophy of male reproductive organ were observed in the 1000 mg/kg group, suggesting an effect on testosterone, but there was a sufficient safety margin for this effect. Also, examination of findings possibly affecting the balance of other steroid hormones did not show any consistency between the findings and fluctuation of hormones. Based on the above, the applicant considered that clinical use of prasugrel hydrochloride is unlikely to affect the balance of steroid hormones including sex hormones.

PMDA accepted the above response of the applicant.

3.(iii).B.(5) Phototoxicity

Prasugrel and its major metabolites have an absorption in the ultraviolet-visible spectral region. In addition, R-138727, the metabolite that was eliminated only gradually from the skin and the eyeballs in pigmented rats, was considered to be possibly phototoxic in the *in vitro* phototoxicity study. Therefore, PMDA asked the applicant to discuss the phototoxicity of prasugrel hydrochloride in further detail.

The applicant responded as follows:

In repeat-dose toxicity studies, neither pathological changes of the eyes or skin nor abnormality in electroretinogram was observed. In the *in vitro* phototoxicity study, R-138727 was assessed as "possibly phototoxic" and not as "phototoxic." Also, the results of the study in pigmented rats showed that little or no prasugrel was accumulated either in the skin or in the eyeballs (Attached document 4.2.2.3-2). In Japanese clinical studies, the informed consent document for patients did not contain the precaution of avoiding strong light such as direct sunlight, and subjects were examined for any undesirable signs while hospitalized for several days after study entry and on an outpatient basis in the subsequent examination period. Thus, adverse drug reactions involving the skin or eyes, if any, should have been detected, but none were noted. Based on the above, the applicant considered that prasugrel hydrochloride is unlikely to cause phototoxicity in clinical settings.

In foreign countries, prasugrel hydrochloride is estimated to have been used in approximately 1,400,000 patients since March 2009, and a serious adverse event suggestive of phototoxicity for which a causal relationship to the study drug could not be ruled out was reported by 1 patient. "Urticaria" and "photosensitivity reaction" were reported in this patient. At approximately 5 weeks after the start of treatment with prasugrel hydrochloride, the symptoms appeared on the face, neck, upper chest region, forearm, and back of the hands, and the symptoms spread from the light-exposed regions to other regions, whereupon administration of prasugrel hydrochloride was discontinued. Although possible involvement of prasugrel hydrochloride cannot be ruled out from the temporal relationship, no detailed information such as outcome is available, leaving the causative agent unidentified. Currently, there are no reports of serious adverse events clearly caused by the phototoxicity of prasugrel hydrochloride in foreign countries after the market launch, and only a little amount of data on non-serious adverse events is available.

PMDA accepted the above response of the applicant.

4. Clinical data

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

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

After oral administration of prasugrel hydrochloride to humans, prasugrel is rapidly converted to R-95913 by carboxylesterase, then to the active metabolite R-138727, which is further metabolized to R-119251 or R-106583. In clinical studies, plasma concentrations of the active metabolite R-138727 and inactive metabolites R-95913, R-119251, R-106583, R-100932, and R-118443 were measured by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS); the lower limit of quantification was 0.500 ng/mL for all of these metabolites. In "4. Clinical data" below, the dose of prasugrel hydrochloride is expressed as the free base (prasugrel). Hereinafter, prasugrel hydrochloride is referred to as "prasugrel."

Pharmacokinetic parameters are expressed as the mean value ± standard deviation (SD) unless otherwise specified.

4.(i).A.(1) Bioequivalence between the to-be-marketed formulation and the formulation used for phase II and phase III studies

The formulation change between 3.75 mg tablets "for clinical studies," i.e., the formulation used in the Japanese phase III study in patients with ACS-PCI (Study CS0747S-B-J301), the Japanese phase III study in patients with elective PCI (Study CS0747S-B-J302), and the Japanese phase II dose-finding study (Study CS0747-B-J202), and the to-be-marketed 3.75 mg tablets, as well as the formulation change between 5 mg tablets for clinical studies and the to-be-marketed 5 mg tablets, fell under the level ■ category stipulated by the "Guidelines for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 67 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012) (BE Guidelines for Formulation Changes). The results of the dissolution test performed according to the method stipulated in the BE Guidelines for Formulation Changes demonstrated the bioequivalence (BE) between 3.75 mg tablets for clinical studies and the to-be-marketed 3.75 mg tablets, and between 5 mg tablets for clinical studies and the to-be-marketed 5 mg tablets.

4.(i).A.(2) Relative bioavailability

4.(i).A.(2).1) Comparison between 3.75 mg tablets for clinical studies and 3.75 mg tablets for phase I and clinical pharmacology studies (Study CS0747S-A-J108, Attached document 5.3.1.2-1)

A two-treatment, two-period, crossover study was conducted in which one 3.75 mg tablet for clinical studies and one 3.75 mg tablet for early stage clinical studies, i.e., the old formulation used in the phase I and clinical pharmacology studies were each administered orally in a single dose to 20 Japanese healthy adult male subjects (washout period, 9-15 days). The geometric mean ratios (90% confidence interval [CI]) of C_{max} and $AUC_{0\text{-}8h}$ of R-138727 for the formulation for clinical studies to those for the old formulation for early stage clinical studies were 0.942 (0.796-1.116) and 0.996 (0.933-1.065), respectively (n = 19).

4.(i).A.(2).2) Comparison between old formulation of 2.5 mg tablets for early stage clinical studies and 2.5 mg tablets or 5 mg tablets for clinical studies (Study CS0747S-A-J109, Attached document 5.3.1.2-2)

A six-sequence, three-period, crossover study was conducted in which two 2.5 mg tablets for early stage clinical studies, two 2.5 mg tablets for clinical studies, and one 5 mg tablet for clinical studies were each administered orally in a single dose to 24 Japanese healthy adult male subjects (washout period, 9-15 days). The geometric mean ratios (90% CI) of C_{max} and $AUC_{0\text{-}8h}$ of R-138727 for two 2.5 mg tablets for clinical studies to those for two old 2.5 mg tablets for early stage clinical studies were 0.907 (0.754-1.091) and 0.969 (0.927-1.014), respectively, and the geometric mean ratios (90% CI) of C_{max} and $AUC_{0\text{-}8h}$ of R-138727 for one 5 mg tablet for clinical studies to those for two old 2.5 mg tablets for early stage clinical studies were 0.928 (0.833-1.034) and 0.952 (0.906-1.001), respectively, (n = 21).

4.(i).A.(3) Food effect (Study CS0747S-A-J112, Attached document 5.3.1.1-1)

A two-treatment, 2-period, crossover study was conducted in which four 5 mg tablets for clinical studies were administered orally in a single dose to 24 Japanese healthy adult male subjects in order to investigate the inhibitory effect against platelet aggregation and to evaluate the effect of food on the pharmacokinetics and the pharmacodynamics of R-138727 (washout period 10-14 days). Following the single oral administration of four 5 mg tablets for clinical studies under fasting conditions and after a high fat diet, the median t_{max} of R-138727 was 0.500 and 2.000 hours, respectively; the geometric mean of C_{max} (coefficient of variation [CV]%) was 168.887 (45.2) and 51.214 (57.6) ng/mL, respectively; $AUC_{0\text{-}\infty}$ was 170.410 (29.6) and 146.380 (57.0) ng·h/mL, respectively; and $t_{1/2}$ was 1.835 (51.1) and 1.357 (80.6) hours, respectively. The ratio (90% CI) of the least squares mean of C_{max} and $AUC_{0\text{-}\infty}$ in fed administration to that in fasted administration was 0.302 (0.237-0.385) and 0.859 (0.720-1.026), respectively (n = 23).

The maximum platelet aggregation (MPA) rate before administration was 86.83% in fasted administration and 87.30% in fed administration. The rate of inhibition of platelet aggregation (IPA)

induced by 20 μM ADP (20 μM ADP-induced IPA) in fasted administration and in fed administration was 49.58% and 11.39%, respectively, at 1 hour post-dose; 58.17% and 33.15%, respectively, at 2 hours post-dose; and 61.07% and 54.73%, respectively, at 4 hours post-dose. After this, no significant difference was observed in the inhibition rate between fasted administration and fed administration up to 24 hours post-dose (the last time point of measurement) (n = 23).

4.(i).B Outline of the review by PMDA

4.(i).B.(1) BE between 3.75 mg tablets and 5 mg tablets of the to-be-marketed formulation

PMDA asked the applicant to explain the BE between 3.75 mg tablet and 5 mg tablet of the to-be-marketed formulation.

The applicant responded as follows:
The formulation changes between the to-be-marketed 3.75 mg tablets and the to-be-marketed 5 mg tablets fell under the level [redacted] category according to the "Guidelines for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (BE Guideline for Different Strengths) (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012). [redacted]. Based on the above, the applicant considered that the to-be-marketed 3.75 mg tablet and the to-be-marketed 5 mg tablet are bioequivalent to each other.

PMDA considers as follows:
[redacted]. Also, PMDA accepts the applicant's explanation that the to-be-marketed 3.75 mg tablets and 5 mg tablets are bioequivalent to each other based on the results of the dissolution test performed using the vessels containing the drug at the same concentration and on the results of the dissolution tests using other dissolving solutions.

4.(i).B.(2) Food effect

PMDA asked the applicant to explain the reason and the justification for not specifying the timing of administration in relation to food intake in the loading dose, while the fed administration, as a rule, was required in the administration of the maintaining doses, in the Japanese phase III studies. PMDA also asked the applicant to consider providing the caution on the food effect in the package insert, based on the observation that the exposure to R-138727 increased after the fasted administration compared with the fed administration in the food effect study (Study CS0747S-A-J112).

The applicant responded as follows:
In a foreign clinical study (Study H7T-EW-TACT), which was conducted before the start of Japanese phase III studies, differences in the pharmacokinetics of prasugrel were observed between fasted and fed administration, whereas the inhibitory activity against platelet aggregation at 2 hours post-dose was only approximately 15% lower after fed administration compared with fasted administration, and no significant difference was observed at any time point after 2 hours post-dose. Since patients with acute coronary syndrome (ACS) require urgent treatment, there is only a short lag from administration of the loading dose to percutaneous coronary intervention (PCI), physically precluding food intake. Therefore, the timing of administration in relation to food intake was not specified for the loading dose in the Japanese phase III study in patients with ACS-PCI. In contrast, no urgent treatment is required for patients with coronary artery disease who need elective intracoronary stenting. Therefore, in the Japanese phase III studies in patients with elective PCI, PCI was to be performed at ≥6 hours after the administration of the first loading dose, the timing considered not to be affected by food intake from the

results of Study H7T-EW-TACT. Based on the above, the timing of the loading dose in relation to food intake was not specified in the Japanese phase III studies.

The Japanese phase III studies required that aspirin (the basal treatment) and prasugrel (at the maintenance dose) be concomitantly administered for a long-term period. Taking account of the fact that aspirin is usually administered postprandially in actual clinical settings because of its adverse drug reaction causing gastrointestinal disorder, the maintenance dose was to be administered postprandially, as a rule, to prevent aspirin-induced gastrointestinal disorder and to ensure the compliance of the long-term concomitant use. The results of the food effect study (Study CS0747S-A-J112) showed that blood R-138727 concentration following the administration of prasugrel 20 mg was lower after fed administration than after fasted administration, but the decrease in $AUC_{0-\infty}$ was only approximately 14%. Also, in Study CS0747S-A-J112, IPA was slightly lower after fed administration than after fasted administration up to 4 hours post-dose but, after that, IPA was similar between fed administration and fasted administration. These results suggest that food has only a clinically insignificant effect on IPA after the loading dose and after multiple administrations of the maintenance dose.

In routine clinical practice, the loading dose is administered during an emergency when PCI is performed. Therefore, it is inappropriate to set a rule for the administration of prasugrel in relation to the timing of food intake. As stated above, in the Japanese phase III study, the maintenance dose was to be administered after a meal as a general rule not because of the pharmacokinetic characteristics of prasugrel but because of the adverse drug reaction due to concomitant use of aspirin. Based on the above, the applicant considered that it was unnecessary to provide a caution on the food effect in the Precaution section in the package insert and, instead, that the results of the food effect study be added in the Pharmacokinetics section.

PMDA considers as follows:
There are no major problems in the applicant's explanation of the justification for the rule for food intake in the Japanese phase III studies. However, the results of the Japanese phase III studies in which the maintenance dose was administered only after a meal as a general rule do not allow the evaluation of the safety and efficacy of multiple doses of prasugrel administered at the maintenance dose in the fasted state. Therefore, it is difficult to conclude that the timing of food intake does not affect the efficacy or safety in the administration of the maintenance dose. Based on the above, in addition to providing the data of the food effect study in the package insert, it is necessary to provide caution, in the "Precautions for Dosage and Administration" section, to preferably avoid administration under fasting conditions because the maintenance dose was administered after food intake, as a general rule, in the Japanese phase III studies. PMDA concluded that it is unnecessary to repeat a food effect study using the to-be-marketed 5 mg tablets, final formulation, because 5 mg tablets for clinical studies used in the food effect study (Study CS0747S-A-J112) and the to-be-marketed 5 mg tablets have been shown to be bioequivalent to each other.

4.(ii) Summary of clinical pharmacology studies

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

4.(ii).A.(1) *In vitro* studies using human biomaterials

4.(ii).A.(1).1) Protein binding (Attached document 5.3.2.1-1)

R-95913, R-100932, R-106583, or R-119251 was added to human plasma at a final concentration of 50, 100, or 500 ng/mL, and the mixture was incubated at 37°C. As a result, the protein binding rate of each metabolite was 93.86% to 95.59%, 90.66% to 93.98%, 94.60% to 95.61, and 76.13% to 76.86%, respectively. R-138727, which is unstable in human plasma, was added to 4% human serum albumin solution to a final concentration of 100 or 500 ng/mL, and the mixture was incubated at 37°C for 5 minutes. The results showed that the protein binding rate was 97.96% to 97.99%.

4.(ii).A.(1).2) *In vitro* metabolism

(a) Hydrolysis of prasugrel by carboxylesterase (Attached document 5.3.2.2-1)

Prasugrel (in the free base form) was added to human carboxylesterase (hCE) 1 or the hCE2-expressing system at a final concentration of 0.855 to 109 μM, and the mixture was incubated at 37°C. The Michaelis-Menten constant (estimate ± SE) for hCE1-catalyzed R-95913 formation reaction was 9.25 ± 0.78 μM, and the maximum reaction velocity (V_{max}) was 0.725 ± 0.035 nmol/min/μg protein, as

calculated from the Michaelis-Menten equation. The dissociation constant in hCE2-catalyzed R-95913 formation reaction was 11.1 ± 2.8 μM, V_{max} was 19.0 ± 2.8 nmol/min/μg protein, and the Hill coefficient was 1.42 ± 0.12, as calculated by the Hill equation.

(b) R-138727 formation by human cytochrome P450 (Attached documents 5.3.2.2-2 to 5.3.2.2-5)
R-95913 was added to the system expressing human cytochrome P450 (CYP) isoform (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) at a final concentration of 20 μM, and the mixture was incubated at 37°C. The rate of R-138727 formation was the highest with CYP3A4, followed by CYP2B6, then by CYP2C19 and CYP2C9 at a comparable rate with each other.

R form, S form, or racemate of prasugrel was added to human liver microsomes at a final concentration of 200 μM, and the mixture was incubated at 37°C. As a result, 4 types of the stereoisomers of R-138727 (RS, RR, SR, and SS forms) were formed.

Racemates of R-95913 were added to human CYP-expression system (CYP2B6, 2C9, 2C19, 3A4, 3A5) at a final concentration of 20 μM, and the mixture was incubated at 37°C. The rate of formation of RS or RR form and SR or SS form of R-138727 was highest with CYP2B6, followed in descending order by CYP2C19, CYP3A4, CYP3A5, and CYP2C9. The ratio of the rate of RS or RR form formation to the rate of SR or SS form formation was 0.64, 0.85, 0.49, 1.6, and 1.6, respectively, for CYP2B6, 2C19, 2C9, 3A4, and 3A5.

R-95913 (final concentration 1.25-160 μM) was added to human liver microsomes derived from 12 subjects who had either one of the genetic polymorphisms of CYP isoforms (CYP2B6*6, CYP2C9*2, CYP2C9*3, CYP2C19*2, CYP2C19*17, CYP3A5*1) in homo type, and the mixture was incubated at 37°C. As a result, the order of the liver's intrinsic clearance of RS or RR form of R-138727 in the above microsomes after R-95913 addition was the same as the order of the activity of CYP3A assessed using midazolam 1'-hydroxylation as the index.

(c) Contribution of intestinal metabolism to metabolic activation of prasugrel (Attached document 5.3.2.3-1)
Prasugrel was added to human small intestinal microsomes at a final concentration of 50 μM in the absence of reduced nicotinamide adenine dinucleotide phosphate (NADPH) and of glutathione, and the mixture was incubated at 37°C. R-95913 was formed after the incubation. In the presence of both NADPH and glutathione, R-138727 was formed in addition to R-95913.

(d) S-methylation of R-138727 (Attached document 5.3.2.2-6)
R-138727 was added to human liver microsomes and to human liver cytosol at a final concentration of 50 μM, and the mixtures were incubated at 37°C. R-106583 was formed under both conditions, but the rate of the formation was higher in the microsomes than in the cytosol. R-138727was added to human liver microsomes at a final concentration of 50 μM, and the mixture was incubated at 37°C in the presence of (±)-2,3-dichloro-alpha-methylbenzylamine hydrochloride (5, 50, 500 μM), a thiol *S*-methyltransferase inhibitor. Formation of R-106583 was completely inhibited under this condition.

A stereoisomer (RS, SR, RR, or SS form) of R-138727 was added to human liver microsomes at a final concentration of 100 μM, and the mixture was incubated at 37°C. R-106583 was detected when SS or SR form was added, but little was detected when RR or RS form was added.

4.(ii).A.(1).3) *In vitro* drug-drug interactions

(a) Inhibitory effect of metabolites against metabolic activities of CYP (Attached documents 5.3.2.2-7, 5.3.2.2-8)
Using human liver microsomes, the inhibitory effect of R-138727, R-95913, and R-106583 against metabolic activities specific to each CYP isoform (CYP1A2, phenacetin-*O*-deethylation; CYP2C9, diclofenac 4'-hydroxylation; CYP2C19, *S*-mephenytoin 4'-hydroxylation; CYP2D6, bufuralol 1'-hydroxylation; CYP3A, midazolam 1'-hydroxylation and testosterone 6β-hydroxylation) was investigated. The inhibition constant (Ki) of R-95913 against CYP2D6, CYP2C9, CYP2C19, and CYP3A activities was 40.8, 82.3, 7.2, and 12.6 μM, respectively, whereas the metabolite did not inhibit CYP1A2. R-138727 and R-106583 did not inhibit any of the CYP isoforms tested.

(b) CYP induction by metabolites (Attached document 5.3.2.2-9)
R-95913 (final concentration, 0.1, 1.0, 10, 100 μM) was added to human primary cultured hepatocytes obtained from 4 donors, and the mixtures were incubated at 37°C for 72 hours. Addition of R-95913 had no effect on the formation rate of the deethylated metabolite of 7-ethoxyresorufin (CYP1A2 activity), whereas addition of 10 μM of R-95913 increased the formation rate of the 6β-hydroxylated metabolite of testosterone (CYP3A activity) 3.2 to 8.4 fold compared with the rate in the absence of R-95913.

4.(ii).A.(1).4) Permeability of the metabolites of prasugrel in MDR1-expressing cells (Attached document 5.3.2.3-2)
^{14}C-labeled prasugrel (in the free base form), R-95913, or R-138727 (20 μM) was added to human MDR1-expressing or non-expressing LLC-PK1 cells, and the ratio of the apparent permeability coefficient from basal to apical side (B to A) to that from apical to basal side (A to B) ([B to A]/[A to B], P_{app} ratio) was compared between MDR1-expressing and non-expressing cells. The ratio (MDR1-expressing cells/non-expressing cells) of P_{app} ratio for ^{14}C-labeled R-95913 and R-138727 was 1.05 and 1.27, respectively, demonstrating that P-glycoprotein was not involved in the directional transport of these metabolites.

4.(ii).A.(2) Pharmacokinetics and pharmacodynamics in healthy subjects
Of the submitted data of 6 studies in healthy adult subjects, major results are presented below.

4.(ii).A.(2).1) Single dose study (Study CS0747S-A-J101, Attached document 5.3.3.1-1)
Prasugrel (2, 5, 10, 20, 30 mg) was administered orally in a single dose under fasting conditions to 39 Japanese healthy adult male subjects (8 subjects/group except for the 10 mg group [7 subjects]). Pharmacokinetic parameters were as shown in Table 7.

Table 7. Pharmacokinetic parameters of each metabolite following a single-dose administration of prasugrel (Adapted from submitted data)

Dose (mg)	n	C_{max} (ng/mL)	t_{max}[a] (h)	$AUC_{0-\infty}$ (ng·h/mL)	$t_{1/2}$ (h)
R-95913					
2	8	5.08 ± 2.74	0.50	7.53 ± 3.15[b]	0.76 ± 0.33[b]
5	8	16.08 ± 9.52	0.50	27.46 ± 10.85	2.70 ± 1.28
10	7	48.31 ± 23.33	0.50	71.74 ± 26.55	3.88 ± 0.94
20	8	107.79 ± 42.07	0.50	173.91 ± 60.61	5.67 ± 2.22
30	8	69.48 ± 27.94	0.75	134.29 ± 40.25	4.71 ± 1.49
R-138727 (active metabolite)					
2	8	21.83 ± 6.24	0.50	19.31 ± 4.80[c]	0.74 ± 0.26[c]
5	8	72.21 ± 35.31	0.50	71.81 ± 14.74	2.01 ± 0.88
10	7	187.76 ± 105.63	0.50	166.97 ± 40.70	4.34 ± 1.20
20	8	403.11 ± 102.99	0.50	367.32 ± 41.22	5.97 ± 1.50
30	8	587.37 ± 257.01	0.75	708.09 ± 143.02	6.18 ± 1.45
R-119251					
2	8	14.87 ± 5.03	0.50	18.09 ± 4.47	1.04 ± 0.16
5	8	37.35 ± 13.96	0.50	50.77 ± 8.70	2.06 ± 0.76
10	7	51.39 ± 22.12	0.50	72.98 ± 13.86	4.46 ± 1.57
20	8	140.67 ± 34.68	0.50	202.73 ± 28.12	7.70 ± 2.40
30	8	314.64 ± 147.87	0.75	453.72 ± 95.42	8.20 ± 1.59
R-106583					
2	8	23.44 ± 5.68	1.00	196.85 ± 61.72[b]	12.12 ± 3.92
5	8	70.02 ± 6.53	1.50	538.11 ± 88.01[c]	9.15 ± 2.27
10	7	130.78 ± 40.08	1.00	954.53 ± 259.25	8.90 ± 1.39
20	8	233.93 ± 47.36	1.00	1929.40 ± 386.27[b]	10.93 ± 1.70
30	8	370.75 ± 122.40	1.25	2958.82 ± 939.35	7.92 ± 1.79

Mean ± SD; a, Median; b, n = 5; c, n = 7

IPA induced by 20 μM ADP increased in a manner dependent on the dose of prasugrel, reaching the maximum level at 4 hours post-dose at ≥5 mg, after which the level remained almost unchanged up to 24 hours post-dose. The maximum level of 20 μM ADP-induced IPA was 2.45%, 6.86%, 16.41%, 43.14%, 66.71%, and 73.78% in the placebo group (n = 10) and the prasugrel 2, 5, 10, 20, and 30 mg

groups, respectively. Compared with the placebo group, IPA was significantly higher in the 5 mg group only at 4 hours post-dose, in the 10 mg group from 1 to 96 hours post-dose, and in the 20 and 30 mg groups from 1 to 168 hours post-dose. In the 2 mg group, no significant difference from the placebo group was observed at any time point up to 168 hours post-dose. Inhibition of 5 μM ADP-induced platelet aggregation (5 μM ADP-induced IPA) and inhibition of 2 μg/mL collagen-induced platelet aggregation (2 μg/mL collagen-induced IPA) showed similar time-course changes as observed with 20 μM ADP-induced IPA.

The median baseline bleeding time (Ivy method) in each group was 99.0 to 132.5 seconds. The bleeding time increased to 184.0 seconds at 24 hours post-dose in the prasugrel 10 mg group, to 252.5 and 287.5 seconds at 4 hours post-dose in the prasugrel 20 and 30 mg groups, respectively, then decreased almost to the baseline level by 168 hours post-dose in all groups.

4.(ii).A.(2).2) Multiple dose studies

(a) Multiple dose study (Study CS0747S-A-J102, Attached document 5.3.3.1-2)

Prasugrel (2.5, 5, 7.5, 10 mg) was administered orally once daily for 7 days to 32 Japanese healthy adult male subjects (8 subjects/group). Table 8 shows the pharmacokinetic parameters obtained. Prasugrel was orally administered after fasting for ≥10 hours on Day 1 and Day 7, and after breakfast from Day 2 to Day 6.

Table 8. Pharmacokinetic parameter of each metabolite following multiple administrations of prasugrel (Adapted from submitted data)

Dose (mg)	Day	n	C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{tau} (ng·h/mL)	$t_{1/2}$ (h)
R-95913						
2.5	1	8	6.83 ± 2.00	0.50	9.69 ± 2.70	1.06 ± 0.12
	7	8	5.59 ± 3.05	0.75	9.79 ± 3.49	1.57 ± 0.61
5	1	7	15.05 ± 5.89	0.50	23.76 ± 9.77	1.91 ± 0.98
	7	8	160.3 ± 7.08	0.50	27.44 ± 9.70	3.56 ± 1.40
7.5	1	8	34.39 ± 29.00	0.50	43.24 ± 33.55	2.62 ± 0.82
	7	8	29.62 ± 16.49	0.50	49.22 ± 28.37	3.55 ± 0.87
10	1	8	28.72 ± 14.39	0.50	41.08 ± 19.70	2.62 ± 0.91
	7	8	26.71 ± 10.72	0.50	47.73 ± 20.55	4.26 ± 1.86
R-138727 (active metabolite)						
2.5	1	8	31.37 ± 10.61	0.50	27.3 ± 8.41	0.67 ± 0.19
	7	8	35.42 ± 19.66	0.50	32.23 ± 11.06	1.07 ± 0.37
5	1	8	76.22 ± 23.30	0.50	73.44 ± 13.85	2.31 ± 0.70
	7	8	79.51 ± 34.40	0.50	79.50 ± 17.05	2.80 ± 0.96
7.5	1	8	151.13 ± 29.07	0.50	134.24 ± 17.32	3.12 ± 0.83
	7	8	145.63 ± 44.73	0.50	146.81 ± 17.90	5.11 ± 1.84
10	1	8	77.65 ± 28.38	0.50	70.86 ± 24.65	1.56 ± 0.76
	7	8	74.46 ± 26.64	0.50	73.08 ± 23.17	2.95 ± 2.63
R-119251						
2.5	1	8	5.79 ± 2.12	0.50	7.60 ± 3.09	0.89 ± 0.27
	7	8	9.26 ± 7.47	0.50	10.05 ± 4.06	1.11 ± 0.33
5	1	7	17.51 ± 5.63	0.50	22.29 ± 5.52	0.97 ± 0.22
	7	8	11.99 ± 4.46	0.50	15.51 ± 3.70	0.89 ± 0.03
7.5	1	8	24.86 ± 5.42	0.50	32.40 ± 7.45	1.47 ± 0.54
	7	8	24.75 ± 5.20	0.50	35.77 ± 7.32	2.01 ± 0.86
10	1	8	35.73 ± 8.33	0.50	49.94 ± 11.43	2.74 ± 1.33
	7	8	31.59 ± 8.14	0.50	54.97 ± 15.45	5.58 ± 3.56
R-106583						
2.5	1	8	13.52 ± 2.74	1.00	87.21 ± 20.89	9.75 ± 2.69
	7	8	14.69 ± 4.34	1.00	106.19 ± 31.78	15.24 ± 8.29
5	1	8	33.68 ± 9.81	1.00	207.14 ± 54.94	9.89 ± 1.48
	7	8	36.65 ± 11.63	1.00	239.13 ± 65.36	10.46 ± 2.74
7.5	1	8	53.71 ± 10.60	0.50	335.80 ± 49.92	9.69 ± 1.50
	7	8	58.30 ± 11.87	1.00	398.03 ± 74.64	11.38 ± 2.31
10	1	8	100.72 ± 35.75	1.00	637.12 ± 218.83	9.66 ± 1.38
	7	8	114.08 ± 39.16	1.00	804.77 ± 330.51	11.99 ± 2.79

Mean ± SD; a, Median

AUC_{tau}, Area under the plasma concentration-time curve over each dosing interval in multiple administrations

Figure 1 shows the time-course change in 20 μM ADP-induced IPA following multiple oral administration of prasugrel or placebo once daily for 7 days.

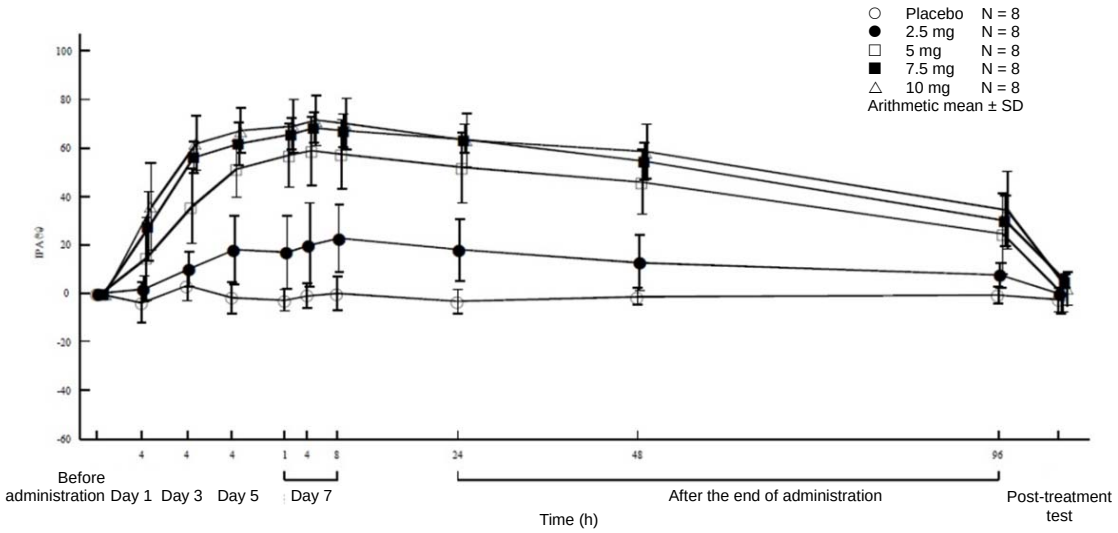


Figure 1. Time-course change in 20 μM ADP-induced IPA following multiple oral administration of prasugrel

IPA induced by 20 μM ADP increased with the duration of treatment. On Day 1 of administration, the IPA level was -3.91%, 1.91%, 14.45%, 27.56%, and 35.89%, respectively, at 4 hours post-dose in the placebo group (n = 8) and the prasugrel 2.5, 5, 7.5, and 10 mg groups and, on Day 7 of administration, -0.90%, 20.00%, 58.90%, 68.29%, and 71.35%, respectively, at 4 hours post-dose. IPA reached the maximum level at 4 to 8 hours post-dose on Day 7, then decreased gradually up to 96 hours after the end of administration. Compared with the placebo group, IPA was significantly higher in the 2.5 mg group from 4 hours post-dose on Day 5 up to 48 hours post-dose on Day 7 and, in the ≥5 mg groups, from 4 hours post-dose on Day 1 up to 96 hours post-dose on Day 7. Similarly, 5 μM ADP-induced IPA and 2 μg/mL collagen-induced IPA generally increased with days of administration. The median baseline bleeding time (Ivy method) in each group was 94.5 to 123.5 seconds. In the ≥5 mg groups, the bleeding time tended to be prolonged; the median bleeding time in the 5, 7.5, and 10 mg groups increased up to 175.0 seconds (4 hours post-dose on Day 7), 194.5 seconds (24 hours after the end of administration), and 190.0 seconds (4 hours post-dose on Day 7), respectively. Platelet reactivity index (PRI), calculated by the measurement of vasodilator-stimulated phosphoprotein (VASP), decreased with dose increase to 80.63%, 80.93%, 73.94%, 61.53%, and 52.60% at 4 hours post-dose on Day 1 in the placebo group and the prasugrel 2.5, 5, 7.5, and 10 mg groups, respectively, and 84.34%, 61.35%, 30.39%, 14.96%, and 4.23%, respectively, at 4 hours post-dose on Day 7.

(b) Study in Asian and Caucasian healthy adult subjects (Study H7T-EW-TABZ, Attached document 5.3.3.3-2)

Caucasian, Japanese, Chinese, and Korean healthy adult male and female subjects (19 subjects, 25 subjects, 22 subjects, and 22 subjects, respectively) received orally prasugrel at 60 mg loading dose on Day 1, and then orally once daily at 10 mg from Day 2 to Day 8 and orally once daily at 5 mg from Day 9 to Day 18 as the maintenance dose. Table 9 shows the geometric mean ratios of pharmacokinetic parameters of R-138727 in Asians to those in Caucasians after the loading dose of 60 mg and after multiple administration of the maintenance dose at 5 mg and at 10 mg, at a steady state.

Table 9. Geometric mean ratios of pharmacokinetic parameters of R-138727 in Asians to those in Caucasians following multiple administrations of prasugrel (Adapted from submitted data)

Dose	Parameter	Race	Least squares geometric mean (90% CI)	Ratio to Caucasians (90% CI)
60 mg	AUC_{last} (ng·h/mL)	Caucasians	486 (427-553)	-
		Japanese	643 (567-730)	1.32 (1.10-1.58)
		Chinese	653 (583-733)	1.34 (1.13-1.60)
		Koreans	611 (533-700)	1.26 (1.04-1.52)
	C_{max} (ng/mL)	Caucasians	476 (405-560)	-
		Japanese	565 (478-668)	1.19 (0.94-1.49)
		Chinese	614 (531-710)	1.29 (1.04-1.60)
		Koreans	586 (477-719)	1.23 (0.94-1.59)
10 mg	AUC_{last} (ng·h/mL)	Caucasians	69.6 (61.1-79.2)	-
		Japanese	89.9 (79.3-102)	1.29 (1.08-1.55)
		Chinese	97.9 (86.8-111)	1.41 (1.18-1.68)
		Koreans	83.9 (73.9-96.2)	1.21 (1.00-1.46)
5 mg	AUC_{last} (ng·h/mL)	Caucasians	30.3 (26.7-34.5)	-
		Japanese	41.6 (36.7-47.2)	1.37 (1.15-1.64)
		Chinese	42.4 (37.8-47.6)	1.40 (1.18-1.66)
		Koreans	40.4 (35.2-46.3)	1.33 (1.10-1.61)

AUC_{last}, Area under the plasma concentration-time curve from 0 hours post-dose up to the last quantifiable time point

4.(ii).A.(2).3) Mass balance study (Study H7T-LC-TAAB, Attached document 5.3.3.1-5)

Following a single oral administration of ^{14}C-labeled prasugrel (15 mg) to 5 foreign healthy adult male subjects, AUC_{0-12h} of the radioactivity from R-95913, R-138727, R-119251, and R-106583 accounted for approximately 40% of total AUC_{0-12h}, and the sum of the radioactivity concentrations of these 4 metabolites at 0.5 hours post-dose accounted for approximately 60% of the total radioactivity concentration. In addition to the above 4 metabolites, the following metabolites were observed in the plasma: R-104434 which is formed via an R-95913 isomer and is inactive although it has a thiol group as is the case with R-138727, R-100932 which is formed by S-methylation, R-118443 which is a cysteine conjugate, as well as M1, M9, M10, M11, M13, M14, M15, M16, M17, M18, M19 which form by oxidation or glucuronidation of the above metabolites. The concentration of R-106583 was the highest at all sampling time points (0.5, 1, 2, 4, and 12 hours post-dose). Total radioactivity concentration was higher in plasma than in whole blood.

Radioactivity recovered in urine within 240 hours post-dose accounted for 68.3% of the radioactivity administered, and 61.3% of the administered radioactivity was recovered within 24 hours post-dose. Major metabolites recovered in urine were M1, M11, and M16, which accounted for 21.3%, 6.4%, and 6.0%, respectively, of administered radioactivity, and were recovered within 24 hours post-dose.

Radioactivity recovered in feces within 240 hours post-dose accounted for 27.0% of radioactivity administered, and 24.6% of the administered radioactivity was recovered within 72 hours post-dose. Major metabolites recovered in feces were R-106583 and M1, which accounted for 3.4% and 2.6%, respectively, of administered radioactivity, and were recovered within 72 hours post-dose.

4.(ii).A.(3) Pharmacokinetics and pharmacodynamics in patients

4.(ii).A.(3).1) Phase II dose-finding study (Study CS0747S-B-J202, Attached document 5.3.5.1-1)

A randomized, double-blind, parallel group, comparative study was conducted in Japanese patients with coronary artery disease requiring elective intracoronary stenting. Of 422 randomized Japanese subjects with coronary artery disease, 312 subjects were aged <75 years and weighing >50 kg (ordinary subjects) and 110 subjects were aged ≥75 years, or weighing ≤50 kg (elderly or low body weight subjects). The ordinary subjects were assigned to a group receiving a 20 mg initial dose and 5 mg maintenance doses of prasugrel (20 + 5 mg group), 20 + 3.75 mg group, and a clopidogrel sulfate (clopidogrel) 300 + 75 mg group (the dose of clopidogrel sulfate is expressed in clopidogrel equivalent). The elderly or low body weight subjects were assigned to the prasugrel 20 + 3.75 mg group, 20 + 2.5 mg group, and the clopidogrel 300 + 75 mg group. The loading dose was administered orally in a single dose on Day 1 and, during the subsequent 12 weeks, the maintenance dose was administered orally every morning after

breakfast, as a general rule. In all groups, aspirin (81 or 100 mg/day) was concomitantly administered.

Both in ordinary subjects and in elderly or low body weight subjects, $P2Y_{12}$ reaction unit (PRU) and PRI within 8 hours post-dose at Weeks 4 and 12 decreased with an increase in dose in the prasugrel groups, and % inhibition increased with dose at each time point. In both ordinary subjects and elderly or low body weight subjects of the clopidogrel group, PRU, PRI, and % inhibition were similar to those observed in the elderly or low body weight subjects of the prasugrel 20 + 2.5 mg group.

In the prasugrel 20 + 3.75 mg group, plasma R-138727 concentration tended to be slightly higher in subjects weighing ≤50 kg than in subjects weighing >50 kg up to 8 hours post-dose, but the difference was within the range of inter-individual variability. Plasma R-138727 concentration in subjects aged ≥75 years did not show any tendency for a higher level compared with subjects aged <75 years.

PRU and PRI within 8 hours post-dose at Week 4 were compared among subjects of different CYP2C19 phenotypes. As a result, both in ordinary subjects and in elderly or low body weight subjects, there were no major differences in PRU or PRI among extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM) of CYP2C19 in the prasugrel groups. In the clopidogrel group, in contrast, PRU and PRI increased to greater extent in IM and PM than in EM.

4.(ii).A.(3).2) Japanese phase III study in patients with ACS-PCI (Study CS0747S-B-J301, Attached document 5.3.5.1-2)

A randomized, double-blind, parallel group, comparative study was conducted at 162 centers in Japan to investigate the efficacy and safety of administration of prasugrel or clopidogrel for 24 to 48 weeks in Japanese patients with acute coronary syndrome who were scheduled to undergo PCI. Aspirin was administered orally in a single initial dose of 81 to 330 mg and then 81 to 100 mg orally daily. As a general rule, prasugrel was administered orally at 20 mg single loading dose before PCI and then orally daily at 3.75 mg (after breakfast as a general rule). Clopidogrel was administered orally at 300 mg single loading dose before PCI as a general rule and then orally daily at 75 mg (after breakfast as a rule). PCI was performed within 4 days after the loading dose of prasugrel or clopidogrel.

In the prasugrel group, PRU and PRI decreased up to 5 to 12 hours after the loading dose. At 48 weeks after the start of treatment, PRU and PRI in the prasugrel group remained low at levels similar to those observed at 5 to 12 hours after the loading dose. PRU and PRI in the prasugrel group were lower than those in the clopidogrel group at all time points.

PRU and PRI within 8 hours post-dose at Week 4 were compared among subjects with different CYP2C19 phenotypes. The results showed that, in the prasugrel group, there was no major difference in PRU or PRI among EM, IM, and PM of CYP2C19, whereas in the clopidogrel group, PRU and PRI increased in IM and PM compared with EM.

4.(ii).A.(3).3) Japanese phase III study in patients with elective PCI (Study CS0747S-B-J302, Attached document 5.3.5.1-3)

A randomized, double-blind, parallel group, comparative study was conducted at 100 centers in Japan to investigate the efficacy and safety of prasugrel and clopidogrel administered for 24 to 48 weeks in Japanese patients with coronary artery disease requiring elective intracoronary stenting. Aspirin (81-100 mg) was administered orally once daily. Prasugrel was administered orally at 20 mg single loading dose and then orally daily at 3.75 mg (after breakfast as a general rule). If the loading dose was not administered, 3.75 mg was administered orally daily (after breakfast as a general rule) from the first day of study drug treatment. Clopidogrel was administered orally at 300 mg single loading dose and then orally daily at 75 mg (after breakfast as a general rule). If the loading dose was not administered, 75 mg was administered orally daily (after breakfast as a general rule) from the first day of study drug treatment.

In the prasugrel group, PRU and PRI decreased at 3 to 6 hours after the loading dose and, at 48 weeks after the start of treatment, remained at low levels similar to those observed at 3 to 6 hours after the loading dose. PRU and PRI in the prasugrel group were lower than in the clopidogrel group at all time points measured.

PRU and PRI within 8 hours post-dose at Week 4 were compared among subjects with different CYP2C19 phenotypes. The results showed that, in the prasugrel group, there was no significant difference in PRU or PRI among EM, IM, and PM of CYP2C19, whereas in the clopidogrel group, PRU and PRI increased to greater extent in IM and PM than in EM.

4.(ii).A.(3).4) Population pharmacokinetic/pharmacodynamic analysis (Attached document 5.3.3.5-1)

A population pharmacokinetic (PPK) analysis was performed using plasma R-138727 concentration data (3329 points consisting of 2985 observed values and 344 values predicted by the multiple regression model) and plasma R-95913 concentration data (3272 points) obtained from a total of 501 subjects in 2 Japanese studies (Studies CS0747S-B-J107 and CS0747S-B-J202) conducted in Japanese patients with coronary artery disease requiring elective intracoronary stenting and 7 Japanese studies (Studies CS0747S-A-J101, CS0747S-A-J102, CS0747S-A-J103, CS0747S-A-J105, CS0747S-A-J108, CS0747S-A-J109, and CS0747S-B-J110) conducted in Japanese healthy adult subjects. Pharmacodynamic data were obtained from 494 out of a total of 501 subjects, and the population pharmacodynamic analysis was performed using 2221values of MPA, 1439 values of PRI, and 707 values of % inhibition. The dosage and administration methods in the above 9 studies were a single-dose administration of 2, 3.75, 5, 10, 20, and 30 mg; once daily multiple administrations of 2.5, 5, 7.5, and 10 mg; and 10 + 2.5, 15 + 3.75, 20 + 2.5, 20 + 3.75, 20 + 5, 30 + 7.5 mg.

Patient characteristics of 501 subjects analyzed were as follows: age, 63 [20-86] years (median [minimum-maximum]); body weight, 62 [40.5-123.2] kg; body mass index (BMI), 23.2 [16-43.8] kg/m^2; body surface area (BSA), 1.69 [1.25-2.28] m^2; ALP, 215 [87-488] U/L; ALT, 19 [4-84] U/L; aspartate aminotransferase (AST), 20 [8-70] U/L; total bilirubin, 11.97 [3.42-34.2] μM; γ-glutamyl transferase, 24 [6-281] U/L; serum creatinine, 70.72 [34.48-151.2] μM; urea nitrogen, 13.7 [5-31.9] mg/dL; creatinine clearance (CL_{CR}, estimated by Cockcroft-Gault equation), 87.6 [38-211.7] mL/min; and estimated glomerular filtration rate, 102.2 [40.1-233.2] mL/min. Subjects consisted of 414 males and 87 females; 381 non-smokers, 35 past smokers, 80 current smokers, and status of 5 subjects were unknown; 344 were on aspirin and 157 were not; 191 had no underlying disease (healthy subjects) and 310 had coronary artery disease requiring elective intracoronary stenting.

The above factors were evaluated as candidates for covariates of pharmacokinetic parameters. Since the study drug was administered under fasting conditions in studies in healthy adult subjects and under fed conditions in studies in patients without exception, resulting in complete confounding of the 2 parameters, events that were initially interpreted as a food effect were regarded as those caused by the disease condition.

Pharmacokinetics of R-138727 was described by the 1-compartment model with a first order elimination process, with metabolism from R-95913 in the circulating blood and the first pass metabolism taken into consideration. Pharmacokinetics of R-95913 was described by the 2-compartment model with a first order absorption process and first order elimination process. The model shown in Figure 2 was used as the structural model for PPK.

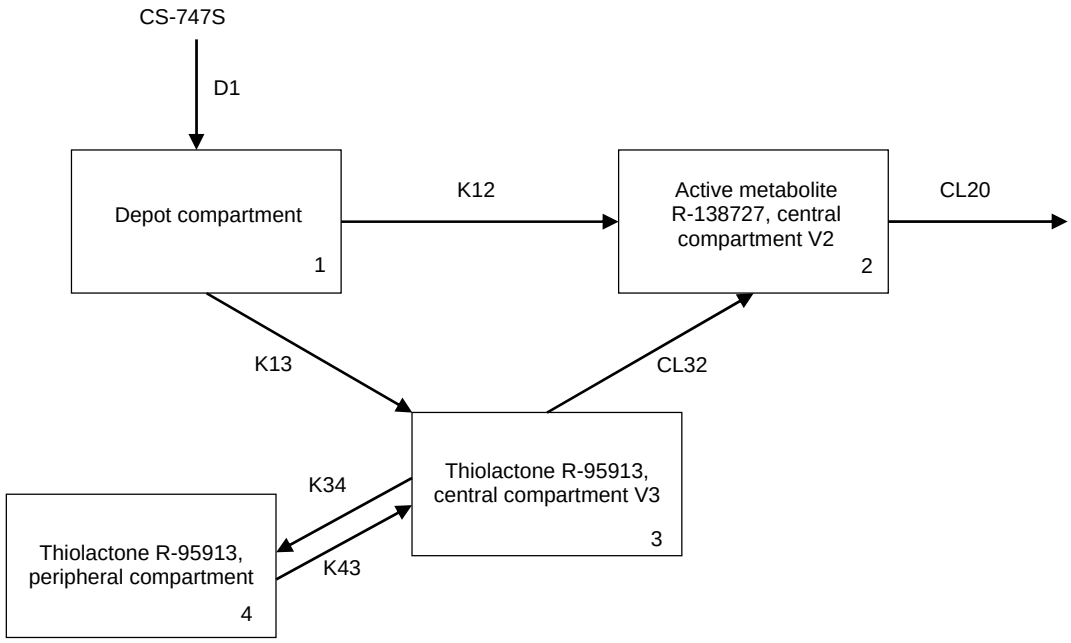


Figure 2. Structural model for PPK

CL20, Clearance of R-138727; V2, Distribution volume of the central compartment of R-138727; CL32, Clearance of R-95913; V3, Distribution volume of the central compartment of R-95913; D1, Zero-order absorption time; K12, Absorption rate constant of R-138727 by first-pass metabolism; K13, Absorption rate constant of R-95913; K34, Distribution rate constant of R-95913 from the central compartment to peripheral compartments; K43, Distribution rate constant of R-95913 from peripheral compartments to the central compartment

In the final PPK model, body weight, age, and food were selected as covariates significantly affecting the following parameters: body weight for CL20, CL32, and V3; age for CL32 and V3; and food for K12, K13, and D1.

AUC of R-138727 following 20 + 3.75 mg administration increased by 54% and decreased by 32% in patients with coronary artery disease weighing 40 kg and 100 kg, respectively, compared with in those weighing 65 kg. C_{max} of R-138727 was approximately 49% lower in the fed state than in the fasted state, and t_{max} of R-138727 was longer in the fed state than in the fasted state (in the fed state, 1.25 hours; in the fasted state, 0.5 hours). AUC of R-138727 was not affected by food. Age did not affect the pharmacokinetic parameters of R-138727.

Population pharmacodynamic analysis was performed by a stepwise approach, and the population parameters of the PPK model were used as the fixed estimated values in the final model. In the population pharmacodynamic model analysis, the relationship between the time-course of plasma R-138727 concentration and the time-course of pharmacodynamic parameters was described and analyzed by an indirect response model.

Body weight, BMI, age, sex, smoking habit, presence/absence of concurrent diabetes mellitus, presence/absence of coronary artery disease requiring elective intracoronary stenting (patients or healthy subjects), and concurrent use/non-use of aspirin were investigated as candidates of covariates for pharmacodynamic parameters. Concomitant use of aspirin affected baseline MPA, but there were no covariates that significantly affected pharmacodynamic parameters.

IPA at 24 hours after administration of the 20 mg loading dose increased by 11% and decreased by 13% in coronary artery disease patients weighing 40 kg and 100 kg, respectively, compared with in those weighing 65 kg. Trough IPA following multiple administrations of the maintenance dose at 3.75 mg increased by 12% and decreased by 12% in patients with coronary artery disease weighing 40 kg and 100 kg, respectively, compared with in those weighing 65 kg. When the loading dose of 20 mg was administered under fed conditions, onset of an inhibitory effect against platelet aggregation was delayed compared with the effect observed following the fasted administration but, from 2 hours post-dose, the extent of the inhibitory effect was similar between the 2 administration methods. Following the

administration of 3.75 mg maintenance dose, the difference in the time course of MPA, IPA, PRI, and % inhibition between fed administration and fasted administration was minimal throughout the treatment period. In typical Japanese patients with coronary artery disease (68 years, 63 kg), time to reach 20% IPA after 20 mg loading dose was 0.6 hours under fasted conditions while 1.2 hours under fed conditions.

4.(ii).A.(3).5) Japanese clinical pharmacology study in patients with elective PCI (Study CS0747S-B-J107, Attached document 5.3.4.2-1)

A randomized, double-blind, parallel group, comparative study was conducted in Japanese patients with coronary artery disease requiring elective intracoronary stenting who were receiving aspirin (81-100 mg/day) for ≥5 days. A total of 84 Japanese patients with coronary artery disease were randomized to the prasugrel 20 + 5 mg group, 15 + 3.75 mg group, 10 + 2.5 mg group, and clopidogrel 300 + 75 mg group (clopidogrel was to be administered open-lable). The single loading dose was administered orally on Day 1 after breakfast, and the maintenance dose was administered orally daily after breakfast for the succeeding 28 days.

The maximum platelet aggregation induced by 20 μM ADP (20 μM ADP-induced MPA) in the prasugrel 10 + 2.5, 15 + 3.75, 20 + 5 mg groups, and in the clopidogrel group was 52.8%, 43.8%, 39.6%, and 59.2%, respectively, at 24 hours after the loading dose, and 53.6%, 45.4%, 42.9%, and 52.1%, respectively, on Day 28 of the maintenance period (within 8 hours post-dose). Inhibition of 20 μM ADP-induced platelet aggregation (20 μM ADP-induced IPA) in the prasugrel 10 + 2.5, 15 + 3.75, and 20 + 5 mg groups, and in the clopidogrel group was 22.91%, 34.48%, 41.71%, and 9.96%, respectively, at 24 hours after the loading dose, and 21.46%, 32.08%, 37.74%, and 21.69%, respectively, on Day 28 of the maintenance period. Similarly, 5 μM ADP-induced IPA tended to increase with dose as was the case with 20 μM ADP-induced IPA. PRI in the prasugrel 10 + 2.5, 15 + 3.75, 20 + 5 mg groups and in the clopidogrel group was 83.32%, 82.21%, 81.57%, and 80.26%, respectively, during the observation period, 62.67%, 48.37%, 29.31%, and 73.28%, respectively, at 24 hours after the loading dose, and 57.37%, 42.04%, 29.18%, and 53.33%, respectively, on Day 28 of the maintenance period.

4.(ii).A.(4) Studies of intrinsic factors

4.(ii).A.(4).1) Study in healthy elderly subjects (Study CS0747S-B-J110, Attached document 5.3.3.3-1)

Prasugrel (20 mg) was administered orally to 23 Japanese elderly subjects aged ≥75 years and to 23 non-elderly subjects aged ≥45 and <65 years on Day 1 of the treatment and then 3.75 mg orally once daily from Day 2 to Day 7. Table 10 shows the pharmacokinetic parameters of R-138727 observed.

Table 10. Pharmacokinetic parameters of R-138727 following the administration of prasugrel to elderly subjects aged ≥75 years and to non-elderly subjects (Adapted from submitted data)

Parameter	Elderly subjects aged ≥75 years		Non-elderly subjects	
	n	Geometric mean (CV%)	n	Geometric mean (CV%)
Day 1				
C_{max} (ng/mL)	22	134.331 (62.1)	23	153.319 (62.1)
t_{max}[a] (h)	22	0.568 (0.269)	23	0.587 (0.234)
AUC_{last} (ng·h/mL)	22	173.515 (34.7)	23	174.523 (35.9)
$t_{1/2}$ (h)	22	4.361 (60.9)	23	3.456 (90.3)
Day 7				
C_{max} (ng/mL)	23	25.227 (44.7)	23	24.942 (68.7)
t_{max}[a] (h)	23	0.587 (0.278)	23	0.609 (0.360)
AUC_{last} (ng·h/mL)	23	26.041 (31.2)	23	24.673 (38.8)
$t_{1/2}$ (h)	23	0.982 (65.7)	22	0.835 (50.5)

a, Arithmetic mean (SD)

Both in the elderly subjects (aged ≥75 years) and in the non-elderly subjects, 20 μM ADP-induced IPA following administration of prasugrel reached the maximum level at 8 hours after the loading dose and the profile were similar up to 24 hours post-dose, whereas at 24 hours after the loading dose and at 4 and 8 hours after the maintenance dose, 20 μM ADP-induced IPA was significantly higher in the elderly

subjects than in the non-elderly subjects (difference in arithmetic mean [elderly subjects aged ≥75 years – non-elderly subjects], 5.10%-7.57%).

4.(ii).A.(4).2) Study in patients with renal impairment (a) (Study H7T-EW-TABW, Attached document 5.3.3.3-3)

Prasugrel (60 mg) was administered orally in a single dose to 28 foreign subjects with normal renal function (CL_{CR} estimated by Cockroft-Gault equation, >80 mL/min), 10 subjects with mild renal impairment (CL_{CR} estimated, 30-50 mL/min), and 5 subjects with end-stage renal impairment receiving hemodialysis for ≥3 months. Table 11 shows the comparison of pharmacokinetic parameters of R-138727 among subject groups matched for patient characteristics (age, sex, and body weight).

Table 11. Pharmacokinetic parameters of R-138727 following the administration of prasugrel to subjects with normal renal function, moderate renal impairment, or end-stage renal impairment (Adapted from submitted data)

	C_{max} (ng/mL)	t_{max}[c] (h)	AUC_{last} (ng·h/mL)
Subjects with normal renal function (n = 20)[a]	433	0.638	506
Subjects with moderate renal impairment (n = 10)	385	0.500	464
Subjects with normal renal function (n = 8)[b]	460	0.500	487
Subjects with end-stage renal impairment (n = 5)	274	0.500	259

Least squares geometric mean; a, Subjects with normal renal function matched for background characteristics with subjects with moderate renal impairment; b, Subjects with normal renal function matched for background characteristics with subjects with end-stage renal impairment; c, Median

Following the administration of prasugrel, 20 μM ADP-induced IPA in subjects with moderate or end-stage renal impairment changed over time in a similar manner as that observed in subjects with normal renal function matched for background characteristics (age, sex, body weight).

4.(ii).A.(4).3) Study in subjects with renal impairment (b) (Study H7T-EW-TACJ, Attached document 5.3.3.3-4)

Prasugrel (5, 10, 30, 60 mg) was administered orally in a single dose to 16 foreign subjects with normal renal function (CL_{CR}, ≥80 mL/min) and to 16 subjects with end-stage renal impairment receiving hemodialysis for ≥3 months (4 subjects each/dose group). Table 12 shows pharmacokinetic parameters of R-138727 obtained.

Table 12. Pharmacokinetic parameters of R-138727 following the administration of prasugrel to subjects with normal renal function and subjects with end-stage renal impairment (Adapted from submitted data)

Parameter	Dose (mg)	Subjects with normal renal function (n = 4)	Subjects with end-stage renal impairment (n = 4)
C_{max} (ng/mL)	5	19.6 (9.30)	15.9 (57.5)
	10	85.9 (38.1)	42.4 (31.5)
	30	131 (31.1)	93.7 (76.7)
	60	229 (55.1)	110 (177)
t_{max}[a] (h)	5	0.50	0.50
	10	0.50	0.50
	30	0.62	0.50
	60	0.75	1.00
AUC_{last} (ng·h/mL)	5	17.1 (13.1)	10.3 (46.5)
	10	64.5 (25.3)	34.7 (16.4)
	30	154 (32.4)	107 (66.4)
	60	295 (29.9)	197 (78.5)

Geometric mean (CV%); a, Median

Before the administration of prasugrel, 20 μM ADP-induced MPA was 12% lower in subjects with end-stage renal impairment than in subjects with normal renal function but, after the administration, changed over time in a similar manner between the 2 groups. Also, changes over time in IPA after the administration of prasugrel were similar between subjects with normal renal function and subjects with end-stage renal impairment.

4.(ii).A.(4).4) Study in patients with hepatic impairment (a) (Study H7T-EW-TAAN, Attached document 5.3.3.3-5)

Prasugrel 60 mg was administered orally in a single dose to 10 foreign subjects with normal hepatic function, to 4 foreign subjects with mild hepatic impairment (Child-Pugh class A) and to 8 foreign subjects with moderate hepatic impairment (Child-Pugh class B). After a washout period of 2 weeks, prasugrel was administered orally at 60 mg single loading dose to 7 of 8 subjects with moderate hepatic impairment and then orally once daily at 10 mg maintenance dose for 5 days starting from the next day. Table 13 shows the pharmacokinetic parameters of R-138727.

Table 13. Pharmacokinetic parameters of R-138727 following the administration of prasugrel to subjects with normal hepatic function, mild hepatic impairment, and moderate hepatic impairment (Adapted from submitted data)

Parameter	Subjects with normal hepatic function	Subjects with mild hepatic impairment	Subjects with moderate hepatic impairment		
	60 mg single dose (n = 10)	60 mg single dose (n = 4)	60 mg single dose (n = 8)	60 mg loading dose (n = 7)	10 mg maintenance dose[b] (n = 7)
C_{max} (ng/mL)	438 (40.7)	384 (35.6)	430 (44.6)	486 (46.7)	62.4 (48.8)
t_{max}[a] (h)	0.50	0.50	0.50	0.50	0.50
AUC_{last} (ng·h/mL)	464 (34.7)	361 (47.6)	484 (53.3)	470 (41.9)	67.1 (36.2)

Geometric mean (CV%); a, Median; b, Post-dose of the last maintenance dose

After the administration of prasugrel, changes over time in 20 μM ADP-induced IPA were similar among subjects with normal hepatic function, subjects with mild hepatic impairment, and subjects with moderate hepatic impairment.

4.(ii).A.(4).5) Study in subjects with hepatic impairment (b) (Study H7T-EW-TABV, Attached document 5.3.3.3-6)

Prasugrel was administered orally on Day 1 at 60 mg single loading dose to 20 foreign subjects with normal hepatic function and to 10 foreign subjects with moderate hepatic impairment (Child-Pugh class B) and then orally once daily at 10 mg maintenance dose from Day 2 to Day 6. Table 14 shows the pharmacokinetic parameters of R-138727.

Table 14. Pharmacokinetic parameters of R-138727 following the administration of prasugrel to subjects with normal hepatic function and subjects with moderate hepatic impairment (Adapted from submitted data)

Parameter	Subjects with normal hepatic function (n = 20)	Subjects with moderate hepatic impairment (n = 10)
Day 1		
C_{max} (ng/mL)	403 (62.1)	368 (49.8)
t_{max}[a] (h)	0.50	0.50
AUC_{last} (ng·h/mL)	477 (29.5)	466 (38.7)
Day 6		
C_{max} (ng/mL)	51.8 (90.3)	59.3 (62.9)
t_{max}[a] (h)	0.50	0.50
AUC_{last} (ng·h/mL)	56.9 (66.3)	61.5 (43.2)

Geometric mean (CV%); a, Median

In subjects with moderate hepatic impairment, 20 μM ADP-induced IPA was lower compared with in subjects with normal hepatic function at 4 and 6 hours after the last dose of prasugrel 10 mg (63.8% vs. 76.9% after 4 hours, 56.7% vs. 82.1% after 6 hours), but was similar at all other time points.

4.(ii).A.(5) Drug-drug interactions

4.(ii).A.(5).1) Lansoprazole (Study H7T-EW-TAAI, Attached document 5.3.3.4-7)

A four-treatment, four-period, crossover study was conducted in 24 foreign healthy adult male and female subjects in which (i) prasugrel (60 mg) was administered orally in a single dose, (ii) lansoprazole

(30 mg) was administered orally once daily for 7 days, and on Day 7 of administration, prasugrel (60 mg) was concomitantly administered orally in a single dose, (iii) clopidogrel (300 mg) was administered orally in a single dose, and (iv) lansoprazole (30 mg) was administered orally once daily, and on Day 7, clopidogrel (300 mg) was concomitantly administered orally in a single dose (washout period ≥14 days).

The geometric mean ratios (90% CI) of C_{max} and AUC_{last} of R-138727 when prasugrel was administered concomitantly with lansoprazole to those when administered alone were 0.711 (0.622-0.813) and 0.869 (0.823-0.916), respectively. Changes over time in 20 μM ADP-induced IPA or 5 μM ADP-induced IPA were not significantly different between single-agent use of prasugrel and the concomitant use with lansoprazole. There were no significant differences in IPA level between the single-agent use of clopidogrel and the concomitant use with lansoprazole except that 20 μM ADP-induced IPA at 4 hours post-dose was 10.85% lower, and 5 μM ADP-induced IPA at 24 hours post-dose was 10.39% lower in the concomitant use with lansoprazole than in the single-agent use of clopidogrel.

4.(ii).A.(5).2) Ranitidine (Study H7T-EW-TABS, Attached document 5.3.3.4-8)

Prasugrel was administered orally on Day 1 at 60 mg single loading dose to 23 foreign healthy adult male subjects and then orally once daily at 10 mg maintenance dose from Day 2 to Day 8. After a washout period of ≥14 days, prasugrel was administered, in a similar manner as before the washout period, together with ranitidine (150 mg) twice daily for 8 days. The geometric mean ratios (90% CI) of C_{max} and AUC_{last} of R-138727 when prasugrel was administered concomitantly with ranitidine to those when administered alone were 0.856 (0.704-1.04) and 0.901 (0.835-0.971), respectively, after the loading dose, and 1.02 (0.894-1.17) and 0.983 (0.931-1.04), respectively, after the maintenance dose (on Day 8). There wer no significant differences in IPA level between the single-agent use of prasugrel and the concomitant use with ranitidine except that 20 μM ADP-induced IPA at 0.5 hours after the loading dose was 12.34% lower in the concomitant use with ranitidine, than in the single-agent use of prasugrel.

4.(ii).A.(5).3) Ketoconazole (Study H7T-EW-TAAK, Attached document 5.3.3.4-3)

A two-treatment, two-period crossover study was conducted in 18 foreign healthy adult male subjects in which (i) prasugrel was administered orally at 60 mg single loading dose on Day 1, and then orally once daily at 15 mg maintenance dose from Day 2 to Day 6, and (ii) prasugrel was administered in a similar manner, and ketoconazole (400 mg) was administered orally once daily from 3 days before the loading dose of prasugrel to Day 6 of prasugrel administration (washout period ≥14 days). The geometric mean ratios (90% CI) of C_{max} and AUC_{0-24} of R-138727 when prasugrel was administered concomitantly with ketoconazole to those when administered alone were 0.54 (0.45-0.66) and 0.89 (0.80-0.99), respectively, after the loading dose, and 0.66 (0.56-0.79) and 1.07 (0.97-1.18), respectively, after the maintenance dose (on Day 6). There were no significant differences in 20 μM ADP-induced IPA between the single-agent use of prasugrel and the concomitant use with ketoconazole at any time point up to 48 hours after the dose on Day 6.

4.(ii).A.(5).4) Rifampicin and bupropion (Study H7T-EW-TAAS, Attached document 5.3.3.4-4)

The study drugs were administered to 30 foreign healthy adult male subjects in 3 treatment periods. In treatment period 1, bupropion (150 mg), a substrate of CYP2B6, was administered orally in a single dose. In treatment period 2, prasugrel was administered orally at 60 mg single loading dose on Day 1, and then orally once daily at 10 mg maintenance dose from Day 2 to Day 11, together with a single oral dose of bupropion (150 mg) on Day 7. In treatment period 3, rifampicin (600 mg) was administered orally once daily for 15 days, and prasugrel was administered orally at 60 mg single loading dose on Day 9, and then orally once daily at 10 mg maintenance dose from Day 10 to Day 14. The washout period was ≥7 days between treatment periods 1 and 2, and ≥14 days between treatment periods 2 and 3.

The geometric mean ratios (90% CI) of C_{max} and AUC_{last} of R-138727 when prasugrel was administered concomitantly with rifampicin to those when administered alone were 1.02 (0.856-1.21) and 0.966 (0.898-1.04), respectively, after the loading dose, and 0.883 (0.747-1.05) and 1.00 (0.933-1.08), respectively, after the maintenance dose (on Day 5). The geometric mean ratios (90% CI) of C_{max} and AUC_{last} of R-95913 when prasugrel was administered concomitantly with rifampicin to those when administered alone were 0.318 (0.282-0.358) and 0.265 (0.241-0.291), respectively, after the loading dose, and 0.209 (0.181-0.242) and 0.159 (0.138-0.182), respectively, after the maintenance dose. In

concomitant use with rifampicin, 20 μM ADP-induced IPA after the loading dose and after the maintenance dose of the prasugrel was lower than in single-agent use of prasugrel, with the difference in the geometric mean being 4.10% to 16.5% at each time point up to 24 hours after the dose on Day 6 of prasugrel administration. The geometric mean ratios (90% CI) of C_{max} and AUC_{last} of bupropion when administered concomitantly with prasugrel to those when administered alone 1.14 (1.06-1.22) and 1.18 (1.10-1.26), respectively. The geometric mean ratios (90% CI) of C_{max} and AUC_{last} of hydroxy bupropion, a metabolite of bupropion, in concomitant use with prasugrel to those in single-agent use of bupropion were 0.682 (0.650-0.716) and 0.760 (0.718-0.803), respectively.

4.(ii).A.(5).5) Digoxin (Study H7T-EW-TAAX, Attached document 5.3.3.4-5)

To 18 foreign healthy adult male subjects, digoxin and prasugrel were orally administered in the following manner: digoxin 0.5 mg twice on Day 1, 0.25 mg twice on Day 2, and 0.25 mg once daily from Day 3 to Day 17; prasugrel 60 mg once as the loading dose on Day 8, and 10 mg once daily as the maintenance dose from Day 9 to Day 17. The geometric mean ratios (90% CI) of C_{max}, AUC_{tau}, and renal clearance under steady state of digoxin when administered concomitantly with prasugrel to those when administered alone were 0.888 (0.786-1.00), 0.895 (0.850-0.943), and 1.03 (0.964-1.10), respectively, after the loading dose of prasugrel, and 0.829 (0.734-0.936), 0.857 (0.813-0.903), and 0.957 (0.893-1.03), respectively, after the maintenance dose (on Day 17).

4.(ii).A.(5).6) Atorvastatin (Study H7T-EW-TAAV, Attached document 5.3.3.4-6)

A two-treatment, two-period, crossover study was conducted in 34 foreign healthy adult male subjects in which (i) prasugrel was administered orally at 60 mg single loading dose on Day 1, and then orally once daily at 10 mg maintenance dose from Day 2 to Day 11, and (ii) atorvastatin (80 mg) was administered orally from 6 days before the loading dose of prasugrel to Day 11 of prasugrel administration (washout period ≥14 days). The geometric mean ratios (90% CI) of C_{max} and AUC_{last} of R-138727 when the product was concomitantly administered with atorvastatin to those when administered alone 0.866 (0.744-1.01) and 0.959 (0.870-1.06), respectively, after the loading dose of prasugrel, and 1.11 (0.917-1.33) and 1.17 (1.10-1.24), respectively, after the maintenance dose (on Day 11). Concomitant use of atorvastatin did not affect 20 μM ADP-induced IPA.

4.(ii).A.(5).7) Aspirin (a) (Study CS0747S-A-J103, Attached document 5.3.3.4-1)

To 23 Japanese healthy adult male subjects (5 subjects in the placebo group, 9 subjects each in the prasugrel groups), aspirin (100 mg) was orally administered once daily for 6 days, and on Day 6 of aspirin administration, placebo or prasugrel (20, 30 mg) was administered orally in a single dose. In the prasugrel 20 and 30 mg groups, median t_{max} of R-138727 was 0.5 hours in both groups; C_{max} was 144.92 ± 86.81 and 251.34 ± 104.05 ng/mL, respectively; AUC_{last} was 140.70 ± 51.40 and 246.25 ± 66.36 ng·h/mL, respectively; and $t_{1/2}$ was 4.35 ± 2.12 and 4.37 ± 1.89 hours, respectively. In both the prasugrel 20 and 30 mg groups, 20 μM ADP-induced IPA significantly increased compared with the placebo group and reached the maximum level (61.49% ± 4.52% and 73.28% ± 8.05%, respectively) at 4 hours after concomitant use, then decreased gradually over time. Bleeding time tended to increase in both the prasugrel 20 and 30 mg groups as compared to the placebo group but, at 144 hours after concomitant use, returned to a level similar to that before aspirin administration and before concomitant use.

4.(ii).A.(5).8) Aspirin (b) (Study CS0747S-A-J105, Attached document 5.3.3.4-2)

To 20 Japanese healthy adult male subjects (4 subjects in the placebo group, 8 subjects each in the prasugrel groups), aspirin (100 mg) was orally administered once daily for 10 days, and on Day 6 to Day 10 of aspirin administration, placebo or prasugrel (20 + 5, 30 + 7.5 mg) was orally administered once daily. On Day 1 of concomitant use, median t_{max} of R-138727 was 0.5 hours in both prasugrel 20 + 5 and 30 + 7.5 mg groups; C_{max} was 363.61 ± 98.51 and 566.15 ± 197.29 ng/mL, respectively, in the prasugrel 20 + 5 and 30 + 7.5 mg groups; AUC_{last} was 341.32 ± 45.20 and 594.41 ± 127.66 ng·h/mL, respectively; and $t_{1/2}$ was 6.41 ± 2.40 and 7.13 ± 0.51 hours, respectively. On Day 5 of concomitant use, median t_{max} of R-138727 was 0.5 hours in both groups; C_{max} was 72.30 ± 34.19 and 110.98 ± 39.80 ng/mL, respectively, in the prasugrel 20 + 5 and 30 + 7.5 mg groups; AUC_{last} was 61.28 ± 20.91 and 124.32 ± 37.80 ng·h/mL, respectively; and $t_{1/2}$ was 2.66 ± 1.09 and 4.56 ± 2.24 hours, respectively.

In the prasugrel 20 + 5 and 30 + 7.5 mg groups, 20 μM ADP-induced IPA increased rapidly after the start of concomitant use, reaching a significantly higher level compared with the placebo group from 1

hour post-dose on Day 1 of concomitant use until 72 hours (20 + 5 mg group) or 144 hours (30 + 7.5 mg group) after the end of administration. In the prasugrel 20 + 5 and 30 + 7.5 mg groups, IPA reached the maximum level (63.69% and 70.76%, respectively) at 4 hours after the loading dose, remained at >50% up to 24 hours after the end of administration, then gradually decreased until 144 hours after the end of administration. There was little change in the bleeding time in the placebo group after the start of concomitant use, whereas in the prasugrel 20 + 5 and 30 + 7.5 mg groups, median bleeding time was 244.5 and 182.0 seconds, respectively, at 4 hours post-dose on Day 1 of concomitant use, and 134.0 and 112.5 seconds at 4 hours post-dose on Day 5 of concomitant use, showing prolongation compared with the time before the use of prasugrel (112.5 and 79.0 seconds, respectively). At 144 hours after the end of administration, the bleeding time in all treatment groups returned to a level similar to that before aspirin administration.

4.(ii).A.(5).9) Warfarin (Study H7T-EW-TAAR, Attached document 5.3.3.4-9)

A two-treatment, two-period, crossover study was conducted in 14 foreign healthy adult male subjects in which (i) warfarin (15 mg) was administered orally in a single dose, and (ii) prasugrel was administered orally at 60 mg single loading dose on Day 1, and then orally once daily at 10 mg maintenance dose on Day 2 to Day 11, while warfarin 15 mg in a single oral dose was administered on Day 6 of prasugrel administration (washout period, 14 days). The geometric mean ratios (90% CI) of C_{max} and AUC_{last} of R-form of warfarin when administered concomitantly with prasugrel to those when administered alone were 0.921 (0.815-1.04) and 0.997 (0.972-1.02), respectively, and the geometric mean ratios (90% CI) of C_{max} and AUC_{last} of S-form of warfarin were 0.923 (0.803-1.06) and 1.08 (1.05-1.10), respectively. Concomitant use of prasugrel had no effect on the maximum level of the international normalized ratio of prothrombin time (PT-INR) or PT after warfarin administration, or on the area under PT-INR-time curve. The ratio at each measuring time point (ratio of bleeding time after concomitant use of prasugrel to that at baseline/ratio of bleeding time after single-agent use of warfarin to that at baseline) was 1.40 to 1.73.

4.(ii).A.(5).10) Unfractionated heparin (Study H7T-EW-TAAT, Attached document 5.3.3.4-10)

A three-treatment, three-period, crossover study was conducted in 18 foreign healthy adult male subjects in which (i) prasugrel (60 mg) was administered orally in a single dose; (ii) prasugrel (60 mg) was administered orally in a single dose, and then a single intravenous administration of unfractionated heparin (100 U/kg) at 2 hours after the administration of prasugrel; and (iii) unfractionated heparin (100 U/kg) was administered intravenously in a single dose (washout period, 14 days). Mean changes over time in activated partial thromboplastin time, rate of inhibition of activated blood coagulation factor X, and activated coagulation time were similar between after administration of unfractionated heparin alone and after concomitant administration of prasugrel. The level of 20 μM ADP-induced IPA was similar between after administration of prasugrel alone and after concomitant administration of unfractionated heparin. The ratio at 4 and 6 hours after prasugrel administration (ratio of bleeding time after concomitant use of unfractionated heparin to that at baseline/ratio of bleeding time after administration of prasugrel alone to that at baseline) was 1.28 and 1.16, respectively.

4.(ii).A.(6) Foreign QT study (Study H7T-EW-TAAP, Attached document 5.3.4.1-1)

A moxifloxacin (400 mg) and placebo-controlled, randomized, three-treatment, three-period, crossover study was conducted to investigate the effect of a single oral administration of prasugrel (80 mg) on ventricular repolarization based on QT/QTc interval in 60 foreign healthy adult male and female subjects (washout period, 10 days).

Median t_{max} of R-138727 following the administration of prasugrel (80 mg) was 0.90 hours; C_{max} was 488 ± 189 ng/mL; and AUC_{last} was 724 ± 264 ng·h/mL. For parameters QTc interval corrected by the Fridericia method (QTcF), QTc interval corrected by the Bazet method (QTcB), and QTc interval adjusted using the correcting formula for individual subjects (QTcI), the least squares means of changes from baseline at 1, 2, and 6 hours after the administration of prasugrel were compared with those after placebo administration. As a result, the change in QTcB at 2 and 6 hours post-dose was significantly greater compared to the value after placebo administration, with the difference (90% CI) being 2.95 (0.684-5.22) and 3.00 (0.734-5.27) msec, respectively. At any other time points, the change in QTcF, QTcB, or QTcI from baseline was not significantly different between after prasugrel administration and after placebo administration, with the difference being <5 msec. The least squares means of changes

from baseline of QTcF, QTcB, and QTcI after administration of the positive control moxifloxacin were significantly greater compared with those after placebo administration at all time points, with the difference being 7.97 (5.90-10.0) to 12.6 (10.3-14.9) msec.

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Difference in pharmacokinetics and pharmacodynamics between Japanese subjects and foreign subjects

Regarding the applicant's explanation of the efficacy and safety of prasugrel in Japanese patients based on the results of foreign clinical studies, PMDA asked the applicant to explain whether or not such an explanation is appropriate from the view point of the difference in the pharmacokinetics and the pharmacodynamics of prasugrel between Japanese and foreign subjects.

The applicant responded as follows:
From the results of the phase I single dose study (Study CS0747S-A-J101) and the foreign single-dose PK dose comparison study (Study H7T-EW-TAAW), the applicant inferred that, after single-dose administration of prasugrel, plasma R-138727 concentration increased roughly in a dose-proportional manner within the dose range of 2 to 30 mg, both in Japanese subjects and in foreign subjects. Also, the results of the phase I single dose study showed that 20 μM ADP-induced IPA increased with dose. The result of the study in healthy Asian and Caucasian adult subjects (Study H7T-EW-TABZ) showed that AUC of plasma R-138727 in Japanese subjects was 1.3 to 1.4 times higher than that in Caucasian subjects, and C_{max} was approximately 1.2 times higher. IPA following the administration of prasugrel 5 and 10 mg was higher in Japanese subjects (67.1%, 75.8%) than in Caucasian subjects (54.6%, 70.0%). In contrast, no clear racial difference was observed in the relationship between exposure to R-138727 and platelet aggregation. The results of the population pharmacokinetics/pharmacodynamics (PPK/PD) analysis indicated that body weight was the covariate that had the strongest effect on changes over time of plasma R-138727 and pharmacodynamic parameters (MPA, IPA, PRI, % Inhibition) after the administration of prasugrel, which suggests that the higher AUC, C_{max}, and IPA in Japanese subjects observed in the above study in Asian and Caucasian healthy adult subjects were mainly due to the difference in body weight between races.

Although mean IPA following the loading dose and following the maintenance dose obtained in main Japanese and foreign clinical pharmacology studies varied among studies, the value following the administration of the dose approved in the US and Europe (loading dose 60 mg, maintenance dose 10 mg) tended to be higher in Japanese subjects than in Caucasian subjects (83.0% vs. 57.9%-77.9%); a similar tendency was observed at other doses as well. In the Japanese phase III study, the loading dose of prasugrel was 20 mg and the maintenance dose was 3.75 mg. The results of this clinical pharmacology study showed that IPA achieved in Japanese subjects (41.7%-63.7% and 32.1%-38.5%, respectively) by administration of 20 mg prasugrel as the loading dose and 3.75 mg as the maintenance dose tended to be lower than IPA achieved in Caucasian subjects (57.9%-77.9% and 42.8%-70.0%, respectively) by administration of prasugrel 60 mg as the loading dose and 10 mg as the maintenance dose but was higher than that achieved in Caucasian subjects (24.1%-37.8% and 26.2%-43.2%, respectively) by administration of clopidogrel 300 mg as the loading dose and 75 mg as the maintenance dose, and therefore the applicant considered that prasugrel has a sufficient activity to IPA in Japanese subjects as observed in Caucasian subjects. Thus, although the exposure to R-138727 in plasma achieved in Japanese subjects after administration of prasugrel at doses investigated in Japanese phase III studies was lower than the level achieved in Caucasian subjects after administration of prasugrel at the approved dose in the US and Europe, the inhibitory effect against platelet aggregation in Japanese subjects was more potent than clopidogrel, as was the case in Caucasian subjects. Therefore, the applicant considers that there is no problem in explaining the efficacy and safety of prasugrel in Japanese patients by referring to the results of foreign clinical studies.

PMDA considers as follows:
The results of the Japanese and foreign clinical studies showed different tendencies in the pharmacokinetics and pharmacodynamics of prasugrel between Japanese and foreign subjects. In addition, the doses selected in the Japanese phase III studies were lower than the approved dose in the US and Europe. Taking account of these facts, PMDA considers that it is practically impossible to explain the appropriateness of using the data of foreign clinical studies merely from the relative order

of the inhibitory activity of prasugrel and clopidogrel against platelet aggregation, and that the appropriateness should be further investigated also taking account of the difference in the efficacy and safety of prasugrel between Japanese and foreign subjects [see "4.(iii).B.(2).2) Use of the data of foreign ACS phase III study for application in Japan"]. The applicant pointed out body weight as the main cause of the higher plasma R-138727 concentration in Japanese subjects compared with foreign subjects, based on the results of clinical pharmacology studies and of PPK/PD analysis. In foreign ACS phase III studies, body weight was related to bleeding risk, and the approved dosage regimen in foreign countries require that consideration be given to dose reduction in patients with a body weight of <60 kg. Taking account of these facts, PMDA considers it necessary to determine the necessity of dose reduction in Japanese patients with low body weight and of providing caution, based on the results of the efficacy and safety in patient groups stratified according to body weight in the Japanese phase II dose-finding study and in the Japanese phase III studies. The necessity of dose reduction in Japanese patients with low body weight and of providing caution will be further discussed in the clinical section [see 4.(iii).B.(4).2) Administration in patients with body weight of ≤50 kg].

4.(ii).B.(2) Effect of prasugrel administration on the metabolism of substrates of CYP3A4

Taking account of the observation that the *in vitro* study using human-derived hepatocytes suggested the possible induction of CYP3A4 by prasugrel administration, PMDA asked the applicant to explain the effect of concomitant use of a drug that serves as a substrate for CYP3A4 with prasugrel on the blood concentration of the concomitant drug.

The applicant responded as follows:

In the CYP enzyme-inducing study using human primary cultured hepatocytes, CYP1A2 was not induced, whereas the activity of CYP3A4 was increased by 10 μM R-95913. Therefore, it cannot be ruled out that prasugrel may induce CYP3A4.

On the other hand, when prasugrel was administered in Study CS0747S-B-J110 according to the proposed dosage and administration, i.e., 20 mg in a single dose on Day 1, and then 3.75 mg orally once daily from Day 2 to Day 7, C_{max} of R-95913 on Day 7 of administration was 13.9 to 16.4 ng/mL (0.04-0.05 μM), which was not more than one two-hundredth times the concentration that increased CYP3A4 in the *in vitro* induction study using cultured hepatocytes (10 μM).

In the metabolism of prasugrel, CYP3A4 is mainly involved in the formation of the active metabolite R-138727 from R-95913. In Study H7T-EW-TAAS, pre-administration of a CYP3A4 inducer rifampicin did not affect C_{max} and AUC of R-138727, but decreased C_{max} and AUC of R-95913. In Study CS0747S-A-J102, blood concentrations of R-138727 and R-95913 following multiple administrations of prasugrel were similar to those following the initial administration. Since the pharmacokinetics of R-95913 did not change after multiple administrations of prasugrel (without concomitant use of other drugs), the applicant considered that, at the clinical dose of prasugrel, R-95913 did not induce CYP3A4 (self induction).

In Study H7T-EW-TAAR, C_{max} and AUC of R-warfarin were not affected by concomitant use of prasugrel. Also, in Japanese and foreign clinical studies so far conducted and in foreign countries after the market launch, prasugrel has been concomitantly administered with atorvastatin (substrate of CYP3A4) in many patients, but there has been no report of clinically significant drug-drug interactions caused by CYP3A4 induction.

Based on the above, the applicant determined that prasugrel does not cause clinically significant enzyme induction as suggested by the induction study using human primary cultured hepatocytes.

PMDA accepted the response of the applicant.

4.(ii).B.(3) Appropriateness of PPK analysis

PMDA asked the applicant to explain 1) to 3) below in order to evaluate the appropriateness of conducting PPK analysis and pharmacokinetic/pharmacodynamic (PK/PD) analysis by including the plasma R-138727 concentration predicted by the multiple regression model in addition to actual measurement of plasma R-138727 concentration.

1) Justification for predicting plasma R-138727 concentration using the multiple regression model and the appropriateness of the predicted values

The applicant explained as follows:

R-138727 is unstable in the plasma. Therefore, in order to measure plasma R-138727 concentration, it is necessary to derivatize the metabolite by a cumbersome procedure immediately after blood sampling. Therefore, in the phase II dose-finding study (Study CS0747S-B-J202), as in the foreign clinical study (Study H7T-MC-TAAL), plasma concentrations of stable metabolites R-119251 and R-106583, instead of R-138727, were measured, and plasma R-138727 concentration was predicted using the multiple regression model established separately. In the phase II dose-finding study, blood samples for R-138727 measurement were collected only from feasible subjects at feasible medical institutions. As a result, information on plasma R-138727 concentration was obtained from 245 subjects corresponding to approximately 90% of the full analysis set as observed values or values predicted by the multiple regression model. Observed values alone of plasma R-138727 concentration were obtained from 96 subjects. Based on the above, the values of plasma R-138727 concentration predicted from the multiple regression model were included in the data for the population analysis.

The multiple regression model was constructed using the data of 3 foreign clinical studies, and the predictability of the model was validated by 7 foreign clinical studies. In addition, the good predictability of the model was demonstrated for the plasma R-138727 concentration in the study in Asian and Caucasian healthy adult subjects, including Japanese subjects (Study H7T-EW-TABZ). Before conducting the population analysis on data including those of the phase II dose-finding study, predictability of the multiple regression model on the plasma R-138727 concentration was investigated using the data obtained from Japanese clinical studies. The results showed that the values predicted by the multiple regression model were almost identical with the observed values, demonstrating the good predictability (Attached document 5.3.3.5-1). In 2 studies in patients (Studies CS0747S-B-J107 and CS0747S-B-J202), the values predicted by the multiple regression model tended to be slightly higher than the observed values. However, when the extent of the within-study variation is taken into consideration, the predictability of the multiple regression model is considered to be good as a whole. Based on the above, the applicant determined that it was appropriate to include the values predicted from the multiple regression model in the data for the population analysis.

If the values predicted from the multiple regression model are not used, the empirical Bayesian estimate of pharmacokinetic parameters of R-138727 in subjects who have only values predicted from the multiple regression model shrinks almost completely to the population mean in PPK analysis. If the posterior distribution of the pharmacokinetic parameters of R-138727 is biased toward the population mean, the error in inter-individual variability of the second order rate constant of the irreversible blinding ($K_{irreversible}$) of R-138727 to ADP-sensitive platelets may be overestimated. This is supported by the distribution of the empirical Bayesian estimate in the population analysis using only the observed values of plasma R-138727 concentration. The empirical Bayesian estimates of CL20 and $K_{irreversible}$ in subjects who had both observed values and values predicted from the multiple regression model were compared between those obtained by using the observed values alone and those observed by using the predicted values as well. When only the observed values were used, the empirical Bayesian estimate of CL20 completely shrank to the population mean in PPK analysis and, in the population pharmacodynamic analysis, the empirical Bayesian estimate of CL20 showed a tendency of a slight shrinkage, which was reflected in a slight broadening of the distribution of the empirical Bayesian estimate of $K_{irreversible}$. Based on the above, the applicant considers that, in the population pharmacodynamic analysis as well, the estimate of the population pharmacodynamic parameters is more precise when plasma R-138727 concentration values predicted from the multiple regression model are included in the data than when the analysis is performed using the observed values alone.

2) Presence or absence of imbalance in the distribution of characteristics of subjects whose multiple regression model-predicted values were used, and in the distribution of blood concentration the time points

The applicant explained as follows:

A total of 231 subjects had 1 or more predicted values from the multiple regression model, and 149 subjects had only predicted values, all of whom were patients with coronary artery disease. The

characteristics of these subjects were compared with those of the entire population of patients with coronary artery disease (310 subjects). As a result, the characteristics of the subjects whose predicted values from the multiple regression model were used for analysis distributed in a similar way to those of the entire population of patients with coronary artery disease. Also, no marked difference was noted in the distribution of the time points between the values predicted by the multiple regression model and the observed values in the population of patients with coronary artery disease, and the distribution of the predicted values and that of the observed values overlapped with each other. Thus, the characteristics of subjects whose predicted values from the multiple regression model were used for analysis and the distribution of the blood concentration time points were not different from those in the entire population of patients with coronary artery disease.

3) Comparison between the results of PPK and PD analyses using only observed values of plasma R-138727 concentration and the results of analyses in the documents submitted by the applicant

The applicant explained as follows:
A population analysis was performed using only observed values of plasma R-138727 concentration. As a result, the estimates of PPK parameters and the estimates of population pharmacodynamic parameters (including the estimates of intra-individual variability) were roughly the same as those obtained by the analysis using data including the multiple regression model-predicted values, showing no inconsistency.

PMDA considers as follows taking account of the applicant's explanations 1) to 3) above:
Regarding the analysis to evaluate the predictability of the multiple regression model, the applicant claimed that the predicted values and the observed values were almost identical. However, not a few predicted values tended to be higher or lower than the observed values, in some studies. In addition, the values predicted from the multiple regression model were biased in some studies, failing to show good predictability. Despite these drawbacks, a multiple regression model using the data from Japanese clinical studies was not constructed and validated. Taking account of the above, PMDA concludes that it was inappropriate to have included the predicted values, as used by the applicant, in the PPK analysis in order to construct a model that describes the pharmacokinetics of R-138727 in Japanese subjects. However, given the difficulty in measuring the concentration of R-138727, which is unstable in plasma, it is the second best option to predict plasma R-138727 level, in an exploratory manner, from the concentrations of inactive metabolites, which are stable in plasma. Thus, PMDA concluded that it is acceptable to use, as reference information, pharmacokinetic data of prasugrel in Japanese patients obtained by this population analysis.

4.(ii).B.(4) Pharmacokinetics following multiple administrations of prasugrel

In the phase I multiple dose study (Study CS0747S-A-J102), C_{max} and AUC of R-138727 in the prasugrel 10 mg group were lower than those in the 7.5 mg group, but the applicant explained that no clear cause for the result could be identified. Therefore, PMDA asked the applicant to explain the accumulation and dose-proportionality in multiple administrations of prasugrel in Japanese subjects, taking into account of the results of other clinical studies.

The applicant responded as follows:
In addition to the Japanese multiple dose study (Study CS0747S-A-J102), multiple dose clinical pharmacology studies of prasugrel in Japanese subjects include a study in healthy elderly subjects (Study CS0747S-B-J110) and a multiple dose study with concomitant use with aspirin (Study CS0747S-A-J105). Based on the results of these studies, the applicant considered that R-138727 did not accumulate in the body up to the dose of 7.5 mg.

As regards the dose-proportionality of R-138727, the applicant considers as follows. Plasma R-138727 concentration following a single dose is considered to be roughly dose-proportional, judging from the results of prasugrel 5 and 7.5 mg groups in concomitant use with aspirin in the multiple dose study of concomitant use with aspirin (Study CS0747S-A-J105), as well as from the results of the phase I single dose study (Study CS0747S-A-J101) and the foreign single dose comparative PK study (Study H7T-EW-TAAW). In light of the facts that multiple doses do not cause R-138727 accumulation, as mentioned above, and that the time-course of the concentration in multiple doses is similar to that observed

following the single dose, plasma R-138727 concentration increased roughly in a dose-proportional manner up to the dose of 7.5 mg.

PMDA considers as follows:
In the phase I multiple dose study (Study CS0747S-A-J102), the cause for the lower C_{max} and AUC values of R-138727 in the prasugrel 10 mg group compared with those in the 7.5 mg group could not be identified. Taking account of this fact, it is difficult to evaluate the multiple-dose pharmacokinetics in Japanese subjects from the results of this study. Nevertheless, it is possible to evaluate the pharmacokinetic profile following multiple doses of 3.75 mg, the recommended clinical maintenance dose, from the results of other clinical pharmacology studies, and R-138727 accumulation is unlikely to be clinically significant.

4.(iii) Summary of clinical efficacy and safety

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

As the efficacy and safety evaluation data, the results from 9 Japanese phase I studies, 1 Japanese phase II study, 2 Japanese phase III studies, and 1 foreign phase I study were submitted. As the reference data, the results of 21 Japanese or foreign clinical studies were submitted [for BE and pharmacokinetics, see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. The main study results are summarized below.

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

4.(iii).A.(1).1) Single dose study (Protocol, Study CS0747S-A-J101; Attached document 5.3.3.1-1 [[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, comparative study was conducted at 1 center in Japan to evaluate the safety, pharmacodynamics, and pharmacokinetics of prasugrel following a single oral administration to healthy adult male subjects. Prasugrel (2, 5, 10, 20, 30 mg) or placebo was to be administered orally in a single dose under fasting conditions to 50 Japanese healthy adult male subjects. No subjects discontinued the study prematurely.

Among adverse events, the incidence of signs or symptoms was 37.5% (3 of 8 subjects) in the 2 mg group; 50.0% (4 of 8 subjects) in the 5 mg group; 25.0% (2 of 8 subjects) in the 10 mg group; 12.5% (1 of 8 subjects) in the 20 mg group; 37.5% (3 of 8 subjects) in the 30 mg group; and 30.0% (3 of 10 subjects) in the placebo group. Events reported by ≥2 subjects in any group were headache (2 subjects in the 2 mg group, 0 subjects in the 5 mg group, 0 subjects in the 10 mg group, 0 subjects in the 20 mg group, 1 subject in the 30 mg group, 0 subjects in the placebo group), body temperature increased (0 subjects, 2 subjects, 0 subjects, 0 subjects, 0 subjects, 0 subjects), diarrhoea (0 subjects, 1 subject, 0 subjects, 0 subjects, 2 subjects, 0 subjects), and petechiae (0 subjects, 0 subjects, 0 subjects, 0 subjects, 0 subjects, 2 subjects). Among adverse events, the incidence of laboratory abnormalities was 100% (8 of 8 subjects) in all the prasugrel groups (2, 5, 10, 20, 30 mg) and 90.0% (9 of 10 subjects) in the placebo group. Laboratory abnormalities reported by ≥2 subjects in any group receiving prasugrel were activated partial thromboplastin time shortened, blood bilirubin increased, blood creatine phosphokinase increased, blood creatinine decreased, blood fibrinogen decreased, blood lactate dehydrogenase decreased, blood triglycerides increased, blood urea decreased, C-reactive protein increased, creatine phosphokinase decreased, gamma-glutamyltransferase decreased, haematocrit decreased, haemoglobin decreased, monocyte count decreased, red blood cell count decreased, reticulocyte count increased, specific gravity urine decreased, and specific gravity urine increased. Neither deaths nor serious adverse events were observed.

4.(iii).A.(1).2) Multiple dose study (Protocol, Study CS0747S-A-J102; Attached document 5.3.3.1-2 [[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, comparative study was conducted at 1 center in Japan to evaluate the safety, pharmacodynamics, and pharmacokinetics of prasugrel following multiple oral administration to healthy adult male subjects. Prasugrel (2.5, 5, 7.5, 10 mg) or placebo was to be administered orally once daily for 7 days to 40 Japanese healthy adult male subjects. The study drug was administered after fasting for ≥10 hours on Day 1 and Day 7, and after breakfast on Day 2 to Day 6. No subjects discontinued the study prematurely.

Among adverse events, the incidence of signs or symptoms was 37.5% (3 of 8 subjects) in the 2.5 mg group, 12.5% (1 of 8 subjects) in the 5 mg group, 50.0% (4 of 8 subjects) in the 7.5 mg group, 50.0% (4 of 8 subjects) in the 10 mg group, and 12.5% (1 of 8 subjects) in the placebo group. Events reported by ≥2 subjects in any group were headache (1 subject in the 2.5 mg group, 0 subjects in the 5 mg group, 0 subjects in the 7.5 mg group, 2 subjects in the 10 mg group, 0 subjects in the placebo group) and epistaxis (0 subjects, 1 subject, 3 subjects, 0 subjects, 0 subjects). Among adverse events, the incidence of laboratory abnormalities was 100.0% (8 of 8 subjects) in the prasugrel 5, 7.5, 10 mg groups and the placebo group, and 87.5% (7 of 8 subjects) in the 2.5 mg group. Laboratory abnormalities reported by ≥2 subjects in any group receiving prasugrel were activated partial thromboplastin time shortened, blood bilirubin increased, blood cholesterol decreased, blood creatinine decreased, blood lactate dehydrogenase decreased, blood triglycerides increased, C-reactive protein increased, creatine phosphokinase decreased, haematocrit decreased, haemoglobin decreased, protein total decreased, red blood cell count decreased, white blood cell count decreased, reticulocyte count increased, specific gravity urine decreased, specific gravity urine increased, neutrophil percentage decreased, monocyte percentage decreased, lymphocyte percentage increased, and protein urine present. Neither deaths nor serious adverse events were observed.

4.(iii).A.(1).3) Comparison between 3.75 mg tablets for early clinical studies (old formulation) and 3.75 mg tablets for clinical studies (Study CS0747S-A-J108, Attached document 5.3.1.2-1 [[redacted] to [redacted] 20[redacted]])

In order to investigate the relative bioavailability of the 3.75 mg tablets for early stage clinical studies (old formulation) and the 3.75 mg tablets for clinical studies, a two-treatment, two-period, crossover study was conducted at 1 center in Japan in which each formulation was administered orally in a single dose to 20 Japanese healthy adult male subjects. One subject requested study discontinuation after the end of the first period.

Among adverse events, the incidence of signs or symptoms was 15.0% (3 of 20 subjects) in the old formulation group and 5.3% (1 of 19 subjects) in the formulation for clinical studies group. The symptoms were nasopharyngitis in all of them. Among adverse events, the incidence of laboratory abnormalities was 95.0% (19 of 20 subjects) in the old formulation group and 100.0% (19 of 19 subjects) in the formulation for clinical studies group. Laboratory abnormalities reported by ≥5 subjects in any group were blood fibrinogen decreased, blood lactate dehydrogenase decreased, C-reactive protein increased, and protein urine present. Neither deaths nor serious adverse events were observed.

4.(iii).A.(1).4) Comparison among 2.50 mg tablets for early stage clinical studies (old formulation), 2.50 mg tablets for clinical studies, and 5.00 mg tablets for clinical studies (Study CS0747S-A-J109, Attached document 5.3.1.2-2 [[redacted] to [redacted] 20[redacted]])

A three-treatment, three-period, crossover study was conducted at 1 center in Japan in which two 2.50 mg tablets for clinical studies (old formulation), two 2.50 mg tablets for clinical studies, or one 5.00 mg tablet for clinical studies was administered orally in a single dose to 24 Japanese healthy adult male subjects. Of whom, 1 subject discontinued the study because of violation of the exclusion criteria, and 2 subjects because of adverse events.

Among adverse events, the incidence of signs or symptoms was 9.5% (2 of 21 subjects) in the 2.50 mg tablets old formulation group, 8.7% (2 of 23 subjects) in the 2.50 mg tablets for clinical studies group, and 4.5% (1 of 22 subjects) in the 5.00 mg tablets for clinical studies group. Events reported by ≥2 subjects in any group were epistaxis. Among adverse events, the incidence of laboratory abnormalities was 90.5% (19 of 21 subjects) in the 2.50 mg tablets old formulation group, 100.0% (23 of 23 subjects) in the 2.50 mg tablets for clinical studies group, and 95.5% (21 of 22 subjects) in the 5.00 mg tablets for clinical studies group. Laboratory abnormalities reported by ≥5 subjects in any group were blood creatine phosphokinase increased, blood fibrinogen decreased, blood lactate dehydrogenase decreased, C-reactive protein increased, blood urea decreased, haemoglobin decreased, and protein total decreased. Adverse events leading to study drug discontinuation were reported by 1 subject in the 5.00 mg tablets for clinical studies group (blood creatine phosphokinase increased) and in 1 subject in the 2.50 mg tablets for clinical studies group (C-reactive protein increased/blood fibrinogen increased). Neither deaths nor serious adverse events were observed.

4.(iii).A.(1).5) PK/PD study in elderly subjects (Study CS0747S-B-J110, Attached document 5.3.3.3-1 [[redacted] 20[redacted] to [redacted] 20[redacted]])

In order to compare the pharmacokinetics and pharmacodynamics following prasugrel administration between elderly subjects, aged ≥75 years, and non-elderly subjects, an open-label, parallel group comparative study was conducted at 2 centers in Japan in 23 Japanese elderly subjects, aged ≥75 years, and 24 non-elderly subjects, aged ≥45 and <65 years. Prasugrel was administered orally at 20 mg on Day 1, and orally once daily at 3.75 mg from Day 2 to Day 7. One non-elderly subject discontinued the study because of an adverse event.

Among adverse events, the incidence of signs or symptoms was 39.1% (9 of 23 subjects) in the elderly subjects, aged ≥75 years, and 12.5% (3 of 24 subjects) in the non-elderly subjects. The adverse events included arrhythmia (2 subjects in the elderly subjects, 0 subjects in the non-elderly subjects), retinal haemorrhage (1 subject, 0 subjects), diarrhoea (0 subjects, 2 subjects), enterocolitis (0 subjects, 1 subject), faeces hard (0 subjects, 1 subject), QRS axis abnormal (1 subject, 0 subjects), headache (0 subjects, 1 subject), haemorrhage subcutaneous (4 subjects, 1 subject), rash (1 subject, 0 subjects), and haematoma (1 subject, 0 subjects). Among adverse events, the incidence of laboratory abnormalities was 100% (23 of 23 subjects) in the elderly subjects and 95.8% (23 of 24 subjects) in the non-elderly subjects. Laboratory abnormalities reported by ≥5 subjects in any group were blood albumin decreased, haematocrit decreased, blood urine present, haemoglobin decreased, protein total decreased, prothrombin time shortened, red blood cell count decreased, red blood cells urine positive, occult blood positive, and blood creatine phosphokinase decreased. The adverse event leading to study drug discontinuation was occult blood positive (1 non-elderly subject). Neither deaths nor serious adverse events were observed.

4.(iii).A.(1).6) Food effect (Study CS0747S-A-J112, Attached document 5.3.1.1-1 [[redacted] to [redacted] 20[redacted]])

In order to investigate the inhibitory effect of a single oral administration of prasugrel (20 mg) against platelet aggregation and to evaluate the effect of food on the pharmacokinetics and pharmacodynamics of prasugrel and the active metabolite R-138727, a two-treatment, two-period, crossover comparative study was conducted at 1 center in Japan in 24 Japanese healthy adult male subjects. One day before the administration in the second period, 1 subject withdrew the study voluntarily.

Among adverse events, symptoms or findings were headache in 1 subject who received prasugrel after meal. Among adverse events, the incidence of laboratory abnormalities was 78.3% (18 of 23 subjects) after fasted administration and 87.5% (21 of 24 subjects) after fed administration. Laboratory abnormalities reported by ≥5 subjects in any group were AST decreased, blood lactate dehydrogenase decreased, gamma-glutamyltransferase decreased, protein total decreased, and blood creatine phosphokinase decreased. Neither deaths nor serious adverse events were observed.

4.(iii).A.(1).7) Japanese clinical pharmacology study in patients with elective PCI (Study CS0747S-B-J107, Attached document 5.3.4.2-1 [February to November 2008])

A randomized, double-blind, parallel group comparative study was conducted at 10 centers in Japan to investigate the dose-response of prasugrel using the inhibitory effect against platelet aggregation as the index in patients with coronary artery disease requiring elective intracoronary stenting because of stable angina (SA), old myocardial infarction (OMI), etc., (target sample size: 25 subject/group, 100 subjects in total). The patients received aspirin (81 or 100 mg/day) as the basal treatment. PCI was to be performed within 48 hours after the maintenance dose of prasugrel. At the timing of the study initiation, clopidogrel was not approved for the indication related to SA and OMI that are to be managed with PCI in Japan. Therefore, clopidogrel was to be administered open-label as a reference drug.

A total of 84 subjects were randomized (20 subjects into the prasugrel 10 + 2.5 mg group, 23 subjects into the 15 + 3.75 mg group, 17 subjects into the 20 + 5 mg group; 24 subjects into the clopidogrel 300 + 75 mg group [the clopidogrel group]). The loading dose was to be administered on Day 1, and then multiple oral once daily maintenance doses were to be administered after breakfast for succeeding 28 days. All 84 subjects received at least 1 dose of the study drug, and were therefore included in the safety analysis set. The study was discontinued during the treatment period in 8 subjects (3 subjects in the 15 + 3.75 mg group, 1 subject in the 20 + 5 mg group, 4 subjects in the clopidogrel group). Reasons for the

discontinuation were adverse events (1 subject in the 15 + 3.75 mg group), violation of the inclusion or exclusion criteria (2 subjects in the 15 + 3.75 mg group, 1 subject in the clopidogrel group), consent withdrawal (1 subject in the 20 + 5 mg group), thrombotic event (1 subject in the clopidogrel group), and other reasons including study ineligibility as judged by the investigator or the subinvestigator (2 subjects in the clopidogrel group).

The incidence of adverse events was 70.0% (14 of 20 subjects) in the 10 + 2.5 mg group; 65.2% (15 of 23 subjects) in the 15 + 3.75 mg group; 52.9% (9 of 17 subjects) in the 20 + 5 mg group; and 50.0% (12 of 24 subjects) in the clopidogrel group. Events reported by ≥2 subjects in any group were occult blood positive (6 subjects in the 10 + 2.5 mg group, 1 subject in the 15 + 3.75 mg group, 0 subjects in the 20 + 5 mg group, 3 subjects in the clopidogrel group), haemorrhage subcutaneous (1 subject, 4 subjects, 4 subjects, 0 subjects), blood urine present (urinary occult blood positive) (5 subjects, 0 subjects, 0 subjects, 2 subjects), subcutaneous haematoma (0 subjects, 1 subject, 4 subjects, 1 subject), headache (2 subjects, 0 subjects, 1 subject, 3 subjects), epistaxis (0 subjects, 2 subjects, 2 subjects, 1 subject), puncture site haemorrhage (1 subject, 0 subjects, 0 subjects, 2 subjects), and haemorrhoidal haemorrhage (0 subject, 2 subject, 0 subject, 0 subject).

Serious adverse events were reported by 1 subject in the 15 + 3.75 mg group (coronary artery perforation, pericardial haemorrhage), 1 subject in the 20 + 5 mg group (coronary artery dissection), and in 3 subjects in the clopidogrel group (coronary artery occlusion, prinzmetal angina, thrombosis in device). No deaths occurred.

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

4.(iii).A.(2).1) Japanese phase II dose-response study (Study CS0747S-B-J202, Attached document 5.3.5.1-1 [[redacted] 20[redacted] to [redacted] 20[redacted]])

A randomized, double-blind, parallel group comparative study was conducted at 55 centers in Japan to determine the recommended clinical dose of prasugrel using, as the index, the safety of prasugrel or clopidogrel administered for 12 weeks to patients with coronary artery disease requiring elective intracoronary stenting, under basal treatment with aspirin (81 or 100 mg/day) (target sample size: 130 subjects/group [100 subjects aged <75 years and weighing >50 kg (ordinary subjects), 30 subjects aged ≥75 years or weighing ≤50 kg (elderly or low body weight subjects)]; 390 subjects in total). In this study, dynamic allocation by type of subjects (ordinary subjects, elderly or low body weight subjects) was adopted. At the beginning of the study, clopidogrel was not approved for the indication related to SA and OMI that are to be managed with PCI in Japan. Therefore, the clopidogrel group was handled as the reference group.

Prasugrel was to be administered orally at 20 mg single loading dose, and then orally once daily after breakfast at the maintenance dose which was 3.75 mg (low dose) or 5 mg (high dose) in ordinary subjects and 2.5 mg (low dose) or 3.75 mg (high dose) in elderly or low body weight subjects. Clopidogrel was to be administered orally at 300 mg single loading dose and then orally once daily at 75 mg after breakfast. PCI was to be performed within the period from 6 hours after the initial dose of prasugrel or clopidogrel to 4 days after the initial dose.

The main inclusion criteria were patients with coronary artery disease scheduled to undergo elective intracoronary stenting because of SA, OMI, etc., in whom coronary stenosis has been confirmed by coronary angiography (CAG) or by coronary computed tomography, and who weigh ≥40 kg which allows the patients to receive the study drugs concomitantly with aspirin (81 or 100 mg/day) as the basal treatment from the start until the end of study drug treatment. The main exclusion criteria were as follows: patients with acute myocardial infarction (ST segment elevation myocardial infarction [STEMI]), non ST segment elevation myocardial infarction [NSTEMI], or unstable angina [UA] of Braunwald class III); patients with current or past history of intracranial haemorrhage; patients with current or past history of cerebral infarction (except asymptomatic cerebral infarction detectable only by diagnostic imaging, etc.) or transient ischemic attack (TIA); or patients with poorly controlled hypertension (blood pressure at rest in the sitting position ≥160 mmHg [systolic] or ≥100 mmHg [diastolic]).

Of 422 randomized subjects, 421 subjects (104 subjects in the low dose group [prasugrel 20 + 3.75 mg], 103 subjects in the high dose group [prasugrel 20 + 5 mg], and 104 subjects in the clopidogrel group in ordinary subjects; 37 subjects in the low dose group [prasugrel 20 + 2.5 mg], 37 subjects in the high dose group [prasugrel 20 + 3.75 mg], and 36 subjects in the clopidogrel group in elderly or low body weight subjects), who received at least 1 dose of the study drug, were included in the safety analysis set. Of these 421 subjects, 412 subjects (101 subjects, 100 subjects, and 101 subjects in ordinary subjects; 37 subjects, 37 subjects, and 36 subjects in elderly or low body weight subjects), excluding 9 subjects who did not undergo PCI (3 subjects, 3 subjects, and 3 subjects in ordinary subjects), were included in the full analysis set (FAS) and as the primary efficacy analysis set. One subject who had been assigned to the high dose group (prasugrel 20 + 5 mg) received clopidogrel by mistake (included in the safety analysis set), and 1 subject who had been assigned to the clopidogrel group received prasugrel 20 + 5 mg by mistake (included in the safety analysis set and FAS). In safety evaluation, they were handled as subjects in the group of the study drug they actually received and, in efficacy evaluation, they were handled as subjects in the originally assigned treatment group.

The primary safety endpoint was the incidence of major or minor bleeding (in Thrombolysis in Myocardial Infarction [TIMI] score) unrelated to coronary artery bypass grafting (CABG) during the period of study drug administration. The secondary endpoints were the incidence of (a) major bleeding, (b) minor bleeding, (c) clinically significant bleeding, (d) other bleeding, (e) bleeding event leading to treatment discontinuation, (f) composite events of major, minor, or clinically significant bleeding, and (g) all bleeding events. The results of the reevaluation and classification by the independent safety event assessment committee were regarded as the final evaluation of each bleeding event. Table 15 shows the incidence of non-CABG-related bleeding events during the period of study drug administration.

Table 15. Incidence of non-CABG-related bleeding events by type of bleeding during the study drug treatment; Safety analysis set (Adapted from submitted data)

	Ordinary subjects			Elderly or low body weight subjects		
	Prasugrel 20 + 3.75 mg (N = 104) n (%)	Prasugrel 20 + 5 mg (N = 103) n (%)	Clopidogrel (N = 104) n (%)	Prasugrel 20 + 2.5 mg (N = 37) n (%)	Prasugrel 20 + 3.75 mg (N = 37) n (%)	Clopidogrel (N = 36) n (%)
Major or minor bleeding	4 (3.8)	0 (0)	3 (2.9)	0 (0)	1 (2.7)	1 (2.8)
All bleeding events	29 (27.9)	37 (35.9)	33 (31.7)	8 (21.6)	15 (40.5)	10 (27.8)
Major bleeding	0 (0)	0 (0)	2 (1.9)	0 (0)	0 (0)	0 (0)
Minor bleeding	4 (3.8)	0 (0)	1 (1.0)	0 (0)	1 (2.7)	1 (2.8)
Clinically significant bleeding	2 (1.9)	5 (4.9)	3 (2.9)	1 (2.7)	0 (0)	0 (0)
Other bleeding	25 (24.0)	34 (33.0)	28 (26.9)	7 (18.9)	14 (37.8)	9 (25.0)
Bleeding event leading to treatment discontinuation	2 (1.9)	0 (0)	3 (2.9)	0 (0)	0 (0)	0 (0)
Major, minor, or clinically significant bleeding	6 (5.8)	5 (4.9)	6 (5.8)	1 (2.7)	1 (2.7)	1 (2.8)

The bleeding events included the following. Major bleeding events were gastrointestinal haemorrhage and lower gastrointestinal haemorrhage in 1 subject each in ordinary subjects in the clopidogrel group. Minor bleeding events were vessel puncture site haematoma, cardiac tamponade, haematoma, and duodenal ulcer haemorrhage in 1 of ordinary subject each in the prasugrel 20 + 3.75 mg group and cardiac tamponade in 1 ordinary subject in the clopidogrel group; and among elderly or low body weight subjects, subcutaneous haematoma in 1 subject in the prasugrel 20 + 3.75 mg group and pericardial haemorrhage in 1 subject in the clopidogrel group. Clinically significant bleeding events were, among ordinary subjects, rectal haemorrhage and vitreous haemorrhage in 1 subject each in the prasugrel 20 + 3.75 mg group, haematuria in 2 subjects, and retinal haemorrhage, diabetic retinopathy, and epistaxis in 1 subject each in the prasugrel 20 + 5 mg group, and haematuria in 2 subjects and lower gastrointestinal haemorrhage in 1 subject in the clopidogrel group; and, among elderly or low body weight subjects, retinal haemorrhage in 1 subject in the prasugrel 20 + 2.5 mg group. Bleeding events leading to treatment discontinuation were cardiac tamponade and duodenal ulcer haemorrhage in 1 subject each in the prasugrel 20 + 3.75 mg group and cardiac tamponade, gastrointestinal haemorrhage, and lower gastrointestinal haemorrhage in 1 subject each in the clopidogrel group, all among ordinary subjects.

The incidence of adverse events was, among ordinary subjects, 74.0% (77 of 104 subjects) in the prasugrel 20 + 3.75 mg group, 68.0% (70 of 103 subjects) in the prasugrel 20 + 5 mg group, and 73.1% (76 of 104 subjects) in the clopidogrel group; and, among elderly or low body weight subjects, 75.7% (28 of 37 subjects) in the prasugrel 20 + 2.5 mg group, 81.1% (30 of 37 subjects) in the prasugrel 20 + 3.75 mg group, and 77.8% (28 of 36 subjects) in the clopidogrel group. Table 16 shows adverse events reported by ≥5% of subjects in any group.

Table 16. Adverse events reported by ≥5% of subjects in any group; Safety analysis set (Adapted from submitted data)

System organ class, preferred term (PT) (MedDRA/J Ver.12.0)	Ordinary subjects			Elderly or low body weight subjects		
	Prasugrel 20 + 3.75 mg (N = 104) n (%)	Prasugrel 20 + 5 mg (N = 103) n (%)	Clopidogrel (N = 104) n (%)	Prasugrel 20 + 2.5 mg (N = 37) n (%)	Prasugrel 20 + 3.75 mg (N = 37) n (%)	Clopidogrel (N = 36) n (%)
Cardiac disorders						
Acute myocardial infarction	0 (0)	6 (5.8)	3 (2.9)	0 (0)	2 (5.4)	2 (5.6)
Myocardial infarction	5 (4.8)	6 (5.8)	2 (1.9)	3 (8.1)	4 (10.8)	2 (5.6)
Gastrointestinal disorders						
Abdominal pain upper	1 (1.0)	1 (1.0)	3 (2.9)	0 (0)	0 (0)	2 (5.6)
Constipation	3 (2.9)	3 (2.9)	3 (2.9)	2 (5.4)	2 (5.4)	3 (8.3)
Diarrhoea	2 (1.9)	2 (1.9)	3 (2.9)	2 (5.4)	0 (0)	2 (5.6)
Haemorrhoidal haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	2 (5.4)	0 (0)
General disorders and administration site conditions						
Chest discomfort	2 (1.9)	2 (1.9)	1 (1.0)	2 (5.4)	2 (5.4)	2 (5.6)
Chest pain	1 (1.0)	2 (1.9)	0 (0)	2 (5.4)	0 (0)	0 (0)
Hepatobiliary disorders						
Hepatic function abnormal	0 (0)	6 (5.8)	5 (4.8)	1 (2.7)	2 (5.4)	2 (5.6)
Infections and infestations						
Cystitis	0 (0)	0 (0)	0 (0)	1 (2.7)	0 (0)	2 (5.6)
Nasopharyngitis	12 (11.5)	13 (12.6)	13 (12.5)	2 (5.4)	4 (10.8)	3 (8.3)
Injury, poisoning and procedural complications						
Subcutaneous haematoma	3 (2.9)	5 (4.9)	1 (1.0)	0 (0)	2 (5.4)	0 (0)
Investigations						
ALT increased	1 (1.0)	2 (1.9)	3 (2.9)	1 (2.7)	1 (2.7)	2 (5.6)
AST increased	1 (1.0)	2 (1.9)	2 (1.9)	1 (2.7)	1 (2.7)	2 (5.6)
Gamma-glutamyltransferase increased	1 (1.0)	1 (1.0)	1 (1.0)	0 (0)	4 (10.8)	1 (2.8)
Blood urine present	2 (1.9)	3 (2.9)	4 (3.8)	1 (2.7)	2 (5.4)	1 (2.8)
Blood ALP increased	1 (1.0)	1 (1.0)	2 (1.9)	2 (5.4)	1 (2.7)	4 (11.1)
Nervous system disorders						
Headache	1 (1.0)	4 (3.9)	4 (3.8)	0 (0)	2 (5.4)	2 (5.6)
Renal and urinary disorders						
Haematuria	2 (1.9)	4 (3.9)	3 (2.9)	0 (0)	2 (5.4)	0 (0)
Respiratory, thoracic and mediastinal disorders						
Epistaxis	5 (4.8)	8 (7.8)	7 (6.7)	1 (2.7)	0 (0)	2 (5.6)
Skin and subcutaneous tissue disorders						
Haemorrhage subcutaneous	11 (10.6)	18 (17.5)	12 (11.5)	0 (0)	6 (16.2)	4 (11.1)
Vascular disorders						
Hypertension	4 (3.8)	3 (2.9)	3 (2.9)	3 (8.1)	2 (5.4)	2 (5.6)

Death occurred in 2 ordinary subjects in the prasugrel 20 + 3.75 mg group (cause of death, ventricular tachycardia and pneumonia aspiration in 1 subject each). The death was considered to be causally related to the study drug in the subject with ventricular tachycardia and not related in the subject with pneumonia aspiration.

The incidence of serious adverse events was, among ordinary subjects, 8.7% (9 of 104 subjects) in the prasugrel 20 + 3.75 mg group, 10.7% (11 of 103 subjects) in the prasugrel 20 + 5 mg group, and 8.7% (9 of 104 subjects) in the clopidogrel group; and, among elderly or low body weight subjects, 8.1% (3 of 37 subjects) in the prasugrel 20 + 2.5 mg group, 10.8% (4 of 37 subjects) in the prasugrel 20 + 3.75 mg group, and 13.9% (5 of 36 subjects) in the clopidogrel group. Serious adverse events among ordinary

subjects included myocardial infarction/cardiac tamponade/pneumonia aspiration, arteriovenous fistula, cardiac tamponade/memory impairment, coronary artery stenosis, haematoma, ventricular tachycardia, vitreous haemorrhage, vertigo, and duodenal ulcer haemorrhage in 1 subject each in the prasugrel 20 + 3.75 mg group; myocardial infarction, acute myocardial infarction, angina pectoris, and subcutaneous haematoma in 2 subjects each and acute myocardial infarction/synostosis, cardiac failure, and chest pain in 1 subject each in the prasugrel 20 + 5 mg group; and lower gastrointestinal haemorrhage in 2 subjects, cardiac neurosis, coronary artery perforation/cardiac tamponade/myocardial infarction, gastrointestinal haemorrhage, gastric cancer/gastric haemorrhage, abdominal pain upper, angina unstable/cardiac failure congestive, and calculus ureteric in 1 subject each in the clopidogrel group. Serious adverse events among elderly or low body weight subjects included chest discomfort, coronary artery bypass/operative haemorrhage, and glaucoma in 1 subject each in the prasugrel 20 + 2.5 mg group; cardiac failure congestive, chest discomfort, prinzmetal angina, and subcutaneous haematoma in 1 subject each in the prasugrel 20 + 3.75 mg group; and acute myocardial infarction, atrial tachycardia, respiratory arrest, myocardial infarction, C-reactive protein increased/chest discomfort in 1 subject each in the clopidogrel group.

Treatment discontinuation due to adverse events reported, among ordinary subjects, by 5 subjects in the prasugrel 20 + 3.75 mg group (myocardial infarction, cardiac tamponade, ventricular tachycardia, drug eruption, and duodenal ulcer haemorrhage in 1 subject each), in 1 subject in the prasugrel 20 + 5 mg group (hypertension), and 4 subjects in the clopidogrel group (cardiac tamponade, gastrointestinal haemorrhage, urticaria, and lower gastrointestinal haemorrhage in 1 subject each); and, among elderly or low body weight subjects, by 1 subject in the prasugrel 20 + 2.5 mg group (anaemia), 2 subjects in the prasugrel 20 + 3.75 mg group (hepatic function abnormal and lip swelling in 1 subject each), and 1 subject in the clopidogrel group (blood pressure increased).

The incidence of major adverse cardiovascular events (MACE) 1 (all-cause death, nonfatal myocardial infarction, nonfatal stroke, myocardial ischaemia or revascularization procedure requiring readmission) during study drug treatment, the efficacy endpoint, was, among ordinary subjects, 4.0% (4 of 101 subjects) in the prasugrel 20 + 3.75 mg group, 13.0% (13 of 100 subjects) in the prasugrel 20 + 5 mg group, and 4.0% (4 of 101 subjects) in the clopidogrel group; and among elderly or low body weight subjects, 5.4% (2 of 37 subjects) in the prasugrel 20 + 2.5 mg group, 10.8% (4 of 37 subjects) in the prasugrel 20 + 3.75 mg group, and 11.1% (4 of 36 subjects) in the clopidogrel group. MACE1 among ordinary subjects included all-cause death in 1 subject and nonfatal myocardial infarction in 3 subjects in the prasugrel 20 + 3.75 mg group, nonfatal myocardial infarction in 13 subjects in the prasugrel 20 + 5 mg group, and nonfatal myocardial infarction in 4 subjects in the clopidogrel group; and, among elderly or low body weight subjects, nonfatal myocardial infarction in 2 subjects in the prasugrel 20 + 2.5 mg group, nonfatal myocardial infarction in 3 subjects and myocardial ischaemia requiring readmission in 1 subject in the prasugrel 20 + 3.75 mg group, and nonfatal myocardial infarction in 4 subjects in the clopidogrel group. Nonfatal myocardial infarction included PCI-associated myocardial infarction (occurring within 48 hours after PCI) except for a case that occurred spontaneously at ≥48 hours after PCI in 1 ordinary subject in the prasugrel 20 + 5 mg group. Neither nonfatal stroke nor revascularization procedure occurred in any treatment group.

4.(iii).A.(3) Phase III studies

4.(iii).A.(3).1) Japanese phase III study in subjects with ACS-PCI (Study CS0747S-B-J301, Attached document 5.3.5.1-2, Study period [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind, parallel group, comparative study was conducted at 162 centers in Japan to evaluate the efficacy and safety of prasugrel or clopidogrel administered for 24 to 48 weeks to patients with ACS scheduled to undergo PCI, under basal treatment with aspirin (target sample size: 600 subjects/group, 1200 subjects in total).

Aspirin as the basal treatment was to be concomitantly administered from the start until the end of study drug treatment. It was administered orally at 81 to 330 mg single loading doseand then orally once daily at 81 to 100 mg. Prasugrel was to be administered orally at 20 mg single loading dose before PCI as a general rule, and then orally once daily at 3.75 mg maintenance dose (after breakfast as a rule). The comparator clopidogrel was to be administered orally at 300 mg single loading dose before PCI as a general rule, and then orally once daily at 75 mg maintenance dose (after breakfast as a general rule). If,

after 24 weeks, no further administration of thienopyridine derivative was deemed necessary for any reason, the study drug administration could be terminated even if the subject did not meet any of the discontinuation criteria. PCI was to be performed within 4 days after the loading dose of prasugrel or clopidogrel.

The main inclusion criteria were ≥20-year old ACS patients with chest discomfort or ischemic symptoms persisting at least 10 minutes at rest within 72 hours before the start of study drug treatment, scheduled to undergo PCI, and who met one or more of the following conditions within 72 hours before the study drug administration: (a) new or presumably new ST elevation or depression of ≥1 mm (0.1 mV) in 1 or more leads of the standard 12-lead ECG; (b) new or presumably new T-wave inversion of ≥3 mm (0.3 mV) in 1 or more leads of the standard 12-lead ECG; and (c) at least one of creatine kinase-MB fraction (CK-MB), troponin T, and troponin I exceeding the upper limit of the normal range (or creatine kinase exceeding twice the upper limit of the reference range if CK-MB or troponin data unavailable). It was recommended to enroll patients with TIMI risk score of ≥3. The main exclusion criteria were patients with current or a history of intracranial haemorrhage (except asymptomatic microbleeding detectable only by magnetic resonance imaging); patients with current or a history of cerebral infarction (except asymptomatic cerebral infarction detectable only by diagnostic imaging, etc.) or TIA; patients with poorly controlled hypertension; patients with current or a history of severe hepatic impairment (fulminant hepatitis, hepatic cirrhosis, liver tumor); or patients with chronic dialysis or with concurrent severe renal impairment (nephrotic syndrome, acute renal failure, chronic renal failure, uremia, hydronephrosis, nonextrinsic gross haematuria). Also, those patients were excluded who used, on the first day of study drug treatment, drugs that have platelet antiaggregating or anticoagulating effect and possibly enhance bleeding (e.g., warfarin, dabigatran) or who required using such drugs after the start of treatment.

Of 1385 subjects randomized (697 subjects in the prasugrel group, 688 subjects in the clopidogrel group), 1363 subjects (685 subjects, 678 subjects) were included in the safety analysis set excluding 22 subjects (12 subjects, 10 subjects) who did not receive even one dose of the study drug. All subjects in the safety analysis set were included in the FAS and in the primary efficacy analysis set. Treatment discontinuation occurred in 395 subjects (195 subjects, 200 subjects), with the main reasons being adverse events (53 subjects, 59 subjects), stent not implanted (50 subjects, 60 subjects), use of prohibited concomitant drugs (35 subjects, 33 subjects), consent withdrawal (24 subjects, 21 subjects), and violation of inclusion or exclusion criteria (13 subjects, 15 subjects). One subject assigned to the clopidogrel group who first received clopidogrel at the loading dose and subsequently received one dose of 3.75 mg of prasugrel by mistake just once (included in the safety analysis set and FAS) was handled as a subject in the clopidogrel group in the data analysis.

The duration (mean ± SD) of study drug treatment was 213.5 ± 121.21 days in the prasugrel group and 207.5 ± 122.81 days in the clopidogrel group.

The primary efficacy endpoint was the incidence of major adverse cardiovascular events 1 (MACE1: composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke) observed during the first 24 weeks of study drug treatment. The results of the reevaluation and classification based on the case reports etc., by the efficacy event assessment committee, blinded to subject assignment, were regarded as the final evaluation of each efficacy event. The incidence of MACE1 during the first 24 weeks of study drug treatment was 9.3% (64 of 685 subjects) in the prasugrel group and 11.8% (80 of 678 subjects) in the clopidogrel group; the hazard ratio [95% CI] calculated by Cox regression analysis[2] was 0.773 [0.557-1.074]. The change over time in the cumulative incidence of MACE1 was as shown in the Kaplan-Meier curve in Figure 3.

[2] The Cox regression model using age (≥75 years, <75 years) and the number of lesions treated by the initial PCI (multiple lesions, 1 lesion, no initial PCI) as covariates

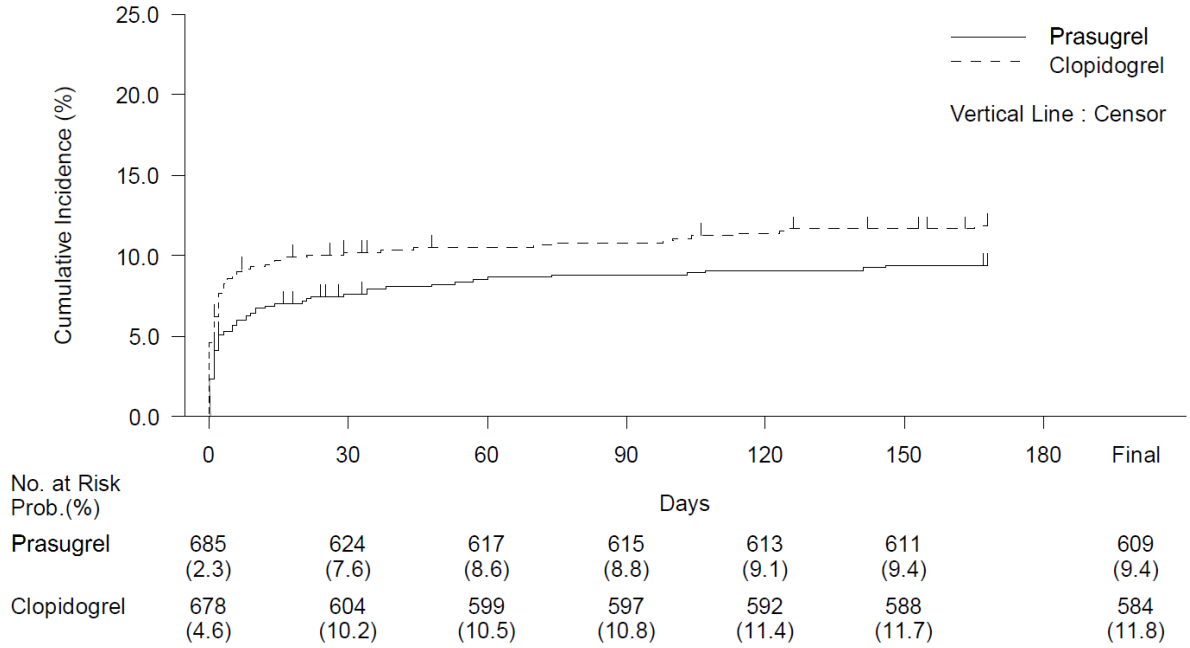


Figure 3. Cumulative incidence of MACE1 during the first 24 weeks of study drug treatment; FAS (Adapted from submitted data)

Table 17 shows the results of the secondary efficacy endpoints, i.e., the incidences of MACE1 from the start of study drug teatment up to the end of follow-up, up to 14 days after treatment completion/discontinuation, and up to 30 and 90 days after the start of study drug treatment.

Table 17. Incidence of MACE1 by observation period; FAS (Adapted from submitted data)

Period	Prasugrel group (N = 685)	Clopidogrel group (N = 678)	Hazard ratio[a] [95% CI]
From the start of study drug treatment up to the end of follow-up	74 (10.8)	84 (12.4)	0.849 [0.621-1.161]
From the start of study drug treatment up to 14 days after treatment completion/discontinuation	67 (9.8)	78 (11.5)	0.826 [0.596-1.145]
From the start of study drug treatment up to 30 days after	52 (7.6)	69 (10.2)	0.732 [0.510-1.049]
From the start of study drug treatment up to 90 days after	60 (8.8)	73 (10.8)	0.796 [0.566-1.121]

n (%); a, Calculated by the Cox regression model using age (≥75 years, <75 years) and the number of lesions treated by the initial PCI (multiple lesions, 1 lesion, no initial PCI) as covariates

Table 18 shows the incidences of the secondary efficacy endpoints, which are composite endpoints of efficacy events ([a] MACE2 [cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, readmission due to angina pectoris, revascularization procedure], [b] cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, [c] cardiovascular death, nonfatal myocardial infarction, revascularization procedure, [d] all-cause death, nonfatal myocardial infarction, revascularization procedure, [e] stent thrombosis, [f] cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, stent thrombosis), as well as each major efficacy event, during the first 24 weeks of study drug treatment.

Table 18. Incidences of each composite endpoint and of each efficacy event that constitute the composite endpoints during the first 24 weeks of study drug treatment; FAS (Adapted from submitted data)

	Prasugrel group (N = 685)	Clopidogrel group (N = 678)
MACE2	87 (12.7)	97 (14.3)
Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke	64 (9.3)	81 (11.9)
Cardiovascular death, nonfatal myocardial infarction, revascularization procedure	82 (12.0)	90 (13.3)
All-cause death, nonfatal myocardial infarction, revascularization procedure	82 (12.0)	92 (13.6)
Stent thrombosis	3 (0.4)	5 (0.7)
Cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, stent thrombosis	67 (9.8)	80 (11.8)
All-cause death	9 (1.3)	8 (1.2)
Cardiovascular death	9 (1.3)	6 (0.9)
Noncardiovascular death	0 (0.0)	2 (0.3)
Nonfatal myocardial infarction	52 (7.6)	68 (10.0)
Nonfatal stroke	3 (0.4)	8 (1.2)
Nonfatal ischemic stroke	3 (0.4)	7 (1.0)
Nonfatal nonischemic stroke	0 (0.0)	1 (0.1)
Readmission due to angina pectoris	5 (0.7)	0 (0.0)
Revascularization procedure	31 (4.5)	32 (4.7)

n (%)

As regards safety, the endpoints related to bleeding events were the incidences of non-CABG-related bleeding events ([a] major bleeding [major in TIMI bleeding classification], [b] major or minor bleeding [minor in TIMI bleeding classification], [c] major, minor, or clinically significant bleeding, [d] bleeding event leading to treatment discontinuation, [e] all bleeding events [major, minor, clinically significant, other bleeding]) that occurred from the start of study drug treatment up to 14 days after treatment completion or discontinuation. The results of the reevaluation and classification based on the case reports etc., by the safety event assessment committee, blinded to subject assignment, were adopted as the final evaluation of each bleeding event. Table 19 shows the incidences of non-CABG-related bleeding events from the start of study drug treatment up to 14 days after treatment completion or discontinuation.

Table 19. Incidences of non-CABG-related bleeding events by type of bleeding from the start of study drug treatment up to 14 days after treatment completion or discontinuation; Safety analysis set (Adapted from submitted data)

	Prasugrel group (N = 685)	Clopidogrel group (N = 678)
Major bleeding	13 (1.9)	15 (2.2)
Life-threatening bleeding	4 (0.6)	7 (1.0)
Fatal bleeding	2 (0.3)	1 (0.1)
Minor bleeding	27 (3.9)	15 (2.2)
Clinically significant bleeding	29 (4.2)	39 (5.8)
Major or minor bleeding	39 (5.7)	29 (4.3)
Major, minor, or clinically significant bleeding	66 (9.6)	65 (9.6)
Bleeding events leading to treatment discontinuation	16 (2.3)	20 (2.9)
All bleeding events	341 (49.8)	247 (36.4)

n (%)

Among the bleeding adverse events, major bleeding events (including duplicate counting) included, in the prasugrel group, operative haemorrhage (5 subjects), vessel puncture site haematoma (3 subjects), subarachnoid haemorrhage (2 subjects), haematuria, haematoma, melaena, brain stem haemorrhage, lower gastrointestinal haemorrhage, pericardial haemorrhage, upper gastrointestinal haemorrhage, forearm fracture, liver injury, and renal injury (1 subject each); and, in the clopidogrel group, operative haemorrhage (4 subjects), vessel puncture site haematoma (3 subjects), puncture site haemorrhage (2 subjects), vascular pseudoaneurysm, haemorrhagic anaemia, duodenal ulcer haemorrhage,

haemorrhoidal haemorrhage, cerebral haemorrhage, pericardial haemorrhage, haematoma, shock haemorrhagic, diverticulitis intestinal haemorrhagic, retroperitoneal haematoma, and subdural haematoma (1 subject each). Minor bleeding events (including duplicate counting) included, in the prasugrel group, vessel puncture site haematoma (6 subjects), subcutaneous haematoma (4 subjects), haemorrhage subcutaneous, upper gastrointestinal haemorrhage, and haematoma (2 subjects each), puncture site haemorrhage, gastrointestinal haemorrhage, vessel puncture site haemorrhage, traumatic haemorrhage, pericardial haemorrhage, retroperitoneal haematoma, haematochezia, diverticulum intestinal haemorrhagic, melaena, epistaxis, operative haemorrhage, myocardial rupture, and cardiac tamponade (1 subject each); and, in the clopidogrel group, retroperitoneal haematoma and subcutaneous haematoma (2 subjects each), diverticulitis, tumour haemorrhage, pericardial haemorrhage, haematoma, haemorrhage, pulmonary haemorrhage, gastric ulcer haemorrhage, haemorrhage subcutaneous, vessel puncture site haematoma, puncture site haemorrhage, and vessel puncture site haemorrhage (1 subject each). Clinically significant bleeding events included, in the prasugrel group, haematuria and retinal haemorrhage (5 subjects each), gastrointestinal haemorrhage (3 subjects), and epistaxis (2 subjects); and, in the clopidogrel group, haematuria, retinal haemorrhage, and epistaxis (7 subjects each), vitreous haemorrhage (3 subjects), gastrointestinal haemorrhage, haemorrhage subcutaneous, and haematochezia (2 subjects each). Bleeding events leading to treatment discontinuation included, in the prasugrel group, subarachnoid haemorrhage and vessel puncture site haematoma in 2 subjects each; and, in the clopidogrel group, vessel puncture site haematoma in 2 subjects.

The incidence of adverse events from the start of study drug treatment until the end of the follow-up period was 89.8% (615 of 685 subjects) in the prasugrel group and 88.5% (600 of 678 subjects) in the clopidogrel group. Table 20 shows adverse events reported by ≥5% of subjects in either group.

Table 20. Adverse events reported by ≥5% of subjects in either group; Safety analysis set (Adapted from submitted data)

System organ class, preferred term (PT) (MedDRA/J Ver.14.1)	Prasugrel group (N = 685)	Clopidogrel group (N = 678)
Infections and infestations		
Nasopharyngitis	100 (14.6)	116 (17.1)
Psychiatric disorders		
Insomnia	30 (4.4)	37 (5.5)
Nervous system disorders		
Headache	42 (6.1)	41 (6.0)
Cardiac disorders		
Myocardial infarction	86 (12.6)	67 (9.9)
Respiratory, thoracic and mediastinal disorders		
Epistaxis	56 (8.2)	40 (5.9)
Gastrointestinal disorders		
Constipation	68 (9.9)	54 (8.0)
Diarrhoea	36 (5.3)	28 (4.1)
Hepatobiliary disorders		
Hepatic function abnormal	39 (5.7)	33 (4.9)
Skin and subcutaneous tissue disorders		
Haemorrhage subcutaneous	67 (9.8)	57 (8.4)
Musculoskeletal and connective tissue disorders		
Back pain	57 (8.3)	46 (6.8)
Renal and urinary disorders		
Haematuria	74 (10.8)	54 (8.0)
General disorders and administration site conditions		
Pyrexia	35 (5.1)	36 (5.3)
Vessel puncture site haematoma	38 (5.5)	22 (3.2)
Investigations		
Blood CK-MB increased	40 (5.8)	40 (5.9)
Injury, poisoning and procedural complications		
In-stent coronary artery restenosis	39 (5.7)	38 (5.6)

n (%)

Death occurred in 8 subjects in the prasugrel group (myocardial rupture in 2 subjects, cardiac failure/mitral valve incompetence, cardiac failure/arrhythmia, myocardial rupture/pericardial haemorrhage, cardiogenic shock, pneumonia, and brain stem haemorrhage in 1 subject each) and in 7 subjects in the clopidogrel group (ventricle rupture/pericardial haemorrhage, myocardial rupture/pericardial haemorrhage, cerebral infarction, thrombosis in device, ventricular fibrillation, cardiogenic shock, and cardiac failure in 1 subject each). A causal relationship to the study drug could not be ruled out for brain stem haemorrhage and pericardial haemorrhage (1 subject each) in the prasugrel group and for pericardial haemorrhage (2 subjects) and ventricular fibrillation (1 subject) in the clopidogrel group.

The incidence of serious adverse events was 27.4% (188 of 685 subjects) in the prasugrel group and 25.4% (172 of 678 subjects) in the clopidogrel group. Serious adverse events reported by ≥1% of subjects in either group were in-stent coronary artery restenosis (5.3% in the prasugrel group, 5.0% in the clopidogrel group), coronary artery stenosis (3.9%, 3.8%), unstable angina (UA) (1.5%, 0.9%), coronary artery restenosis (0.7%, 1.5%), angina pectoris (1.3%, 0.6%), cardiac failure (1.2%, 1.0%), and cerebral infarction (1.0%, 0.7%).

The incidence of adverse events leading to treatment discontinuation was 7.9% (54 of 685 subjects) in the prasugrel group and 9.0% (61 of 678 subjects) in the clopidogrel group. Adverse events reported by ≥2 subjects in either group were anaemia (2 subjects, 2 subjects), iron deficiency anaemia (2 subjects, 0 subjects), cerebral infarction (5 subjects, 5 subjects), subarachnoid haemorrhage (2 subjects, 0 subjects), cardiac failure (2 subjects, 3 subjects), hepatic function abnormal (3 subjects, 1 subject), drug eruption (3 subjects, 5 subjects), rash (2 subjects, 2 subjects), vessel puncture site haematoma (2 subjects, 2 subjects), thrombosis in device (0 subjects, 2 subjects), and platelet count decreased (2 subjects, 1 subject).

4.(iii).A.(3).2) Japanese phase III study in patients with elective PCI (Study CS0747S-B-J302, Attached document 5.3.5.1-3, Study period [redacted] 20[redacted] to [redacted] 20[redacted])

A randomized, double-blind, parallel group comparative study was conducted at 100 centers in Japan to evaluate the efficacy and safety of prasugrel or clopidogrel administered for 24 to 48 weeks together with aspirin as the basal treatment in patients with coronary artery disease requiring elective intracoronary stenting (target sample size: 300 subjects/group, 600 subjects in total). At the beginning of the study, clopidogrel was not approved for the indication related to SA and OMI that were to be managed with PCI in Japan. Therefore, the clopidogrel group was handled as the reference group.

Aspirin as the basal treatment was to be concomitantly administered from the start until the end of study drug treatment, and was administered orally once daily at the dose of 81 to 100 mg. When using loading dose, prasugrel was to be administered orally at 20 mg single loading dose and then orally once daily (after breakfast as a rule) at 3.75 mg maintenance dose; and clopidogrel was to be administered orally at 300 mg single loading dose, and then orally once daily (after breakfast as a rule) at 75 mg maintenance dose. When not using loading dose, prasugrel 3.75 mg or clopidogrel 75 mg was to be administered orally once daily (after breakfast as a rule) as the maintenance dose. If, at 24 weeks after the start of treatment or later, no further administration of thienopyridine derivative was deemed necessary for any reason, the study drug administration could be terminated even if the subject did not meet any of the discontinuation criteria. PCI was performed from 6 to 96 hours after the loading dose, or from 14 to 21 days after the start of treatment at the maintenance dose when not using loading dose.

The main inclusion criteria were patients with coronary artery disease scheduled to undergo elective intracoronary stenting because of SA, OMI, etc., in whom coronary stenosis was confirmed by CAG or by coronary computed tomography. The main exclusion criteria were patients with current or a history of intracranial haemorrhage (except asymptomatic microbleeding detectable only by diagnostic imaging), patients with current or a history of cerebral infarction (except asymptomatic cerebral infarction detectable only by diagnostic imaging), patients with poorly controlled hypertension, patients with current or a history of severe hepatic impairment (fulminant hepatitis, hepatic cirrhosis, liver tumor), and patients with chronic dialysis or with concurrent severe renal impairment (nephrotic syndrome, acute renal failure, chronic renal failure, uremia, hydronephrosis).

Of 751 subjects randomized (377 subjects in the prasugrel group, 374 subjects in the clopidogrel group), 742 subjects (370 subjects, 372 subjects) were included in the safety analysis set excluding 9 subjects (7 subjects, 2 subjects) who did not receive even 1 dose of the study drug. All subjects in the safety analysis set were included in FAS and in the primary efficacy analysis set. Treatment discontinuation occurred in 135 subjects (57 subjects, 78 subjects), with the main reasons being adverse events (18 subjects, 20 subjects) and consent withdrawal (9 subjects, 10 subjects).

The treatment duration with the study drug (mean ± SD) was 242.8 ± 94.04 days in 269 subjects with the loading dose and 233.4 ± 92.48 days in 101 subjects without the loading dose in the prasugrel group; and 222.1 ± 105.46 days in 266 subjects with the loading dose and 220.7 ± 101.80 days in 106 subjects without the loading dose in the clopidogrel group.

The primary efficacy endpoint was the incidences of major adverse cardiovascular events (MACE: composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal ischemic stroke) observed during the first 24 weeks of study drug treatment. The results of the reevaluation and classification based on the case reports etc., by the efficacy assessment committee, blinded to subject assignment, were adopted as the final assessment of efficacy events. The incidence [95% CI] of MACE during the first 24 weeks of study drug treatment was 4.1% (15 of 370 subjects) with 95% CI of [2.3-6.6] in the prasugrel group and 6.7% (25 of 372 subjects) with 95% CI of [4.4-9.8] in the clopidogrel group. The change over time in the cumulative incidence of MACE was as shown in the Kaplan-Meier curve in Figure 4.

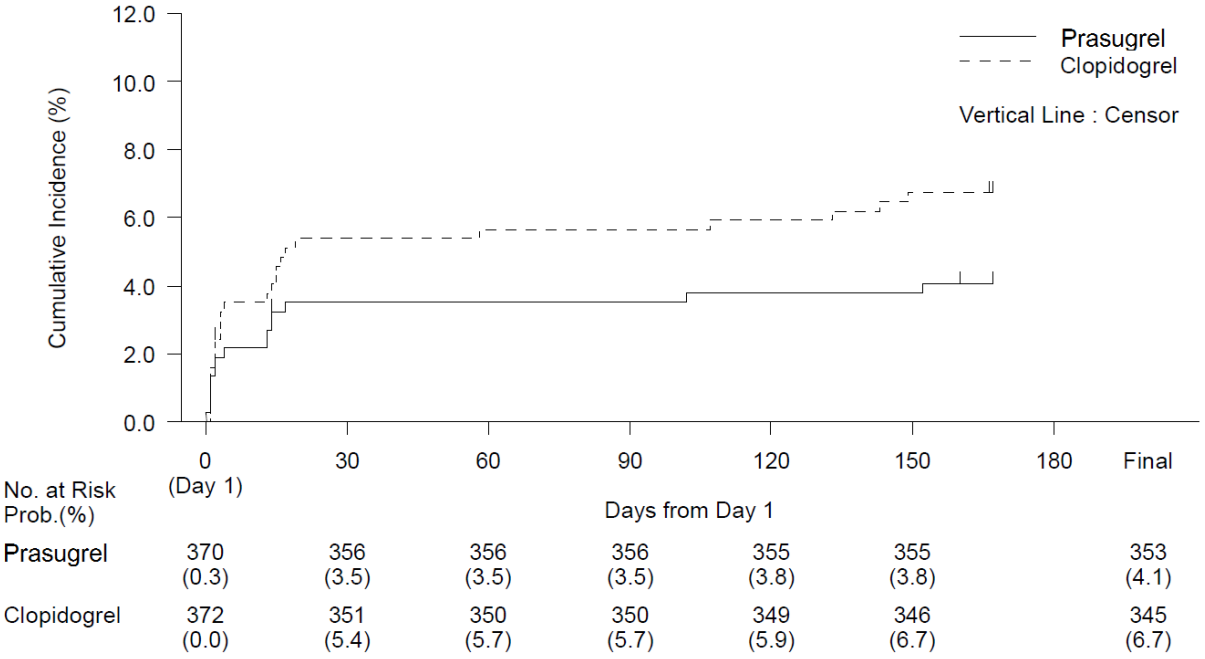


Figure 4. Cumulative incidence of MACE during the first 24 weeks of study drug treatment; FAS (Adapted from submitted data)

Table 21 shows the results of the secondary efficacy endpoints, i.e., the incidences of MACE from the start of study drug treatment up to the end of follow-up, 14 days after treatment completion/discontinuation, and up to 30 and 90 days after PCI.

Table 21. Incidence of MACE by observation period; FAS (Adapted from submitted data)

Period	Prasugrel group	Clopidogrel group
From the start of study drug treatment up to the end of follow-up	17/370 (4.6)	28/372 (7.5)
From the start of study drug treatment up to 14 days after treatment completion/discontinuation	16/370 (4.3)	28/372 (7.5)
From the start of study drug treatment up to 30 days after PCI	13/361 (3.6)	20/349 (5.7)
From the start of study drug treatment up to 90 days after PCI	13/361 (3.6)	21/349 (6.0)

n/N (%)

Table 22 shows the incidences of the secondary efficacy endpoints, which are composite endpoints of efficacy events ([a] cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, [b] cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, readmission due to angina pectoris, revascularization procedure, [c] cardiovascular death, nonfatal myocardial infarction, revascularization procedure, [d] all-cause death, nonfatal myocardial infarction, revascularization procedure, [e] stent thrombosis, [f] cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, stent thrombosis), as well as each major efficacy event, during the first 24 weeks of study drug treatment.

Table 22. Incidence of each composite endpoint and of each efficacy event that constitutes the composite endpoints during the first 24 weeks of study drug treatment; FAS (Adapted from submitted data)

	Prasugrel group (N = 370)	Clopidogrel group (N = 372)
Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke	15 (4.1)	26 (7.0)
Cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, readmission due to angina pectoris, revascularization procedure	22 (5.9)	3 2 (8.6)
Cardiovascular death, nonfatal myocardial infarction, revascularization procedure	19 (5.1)	31 (8.3)
All-cause death, nonfatal myocardial infarction, revascularization procedure	19 (5.1)	31 (8.3)
Stent thrombosis	0 (0.0)	1 (0.3)
Cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke, stent thrombosis	15 (4.1)	25 (6.7)
All-cause death	0 (0.0)	0 (0.0)
Cardiovascular death	0 (0.0)	0 (0.0)
Noncardiovascular death	0 (0.0)	0 (0.0)
Nonfatal myocardial infarction	12 (3.2)	24 (6.5)
Nonfatal stroke	3 (0.8)	2 (0.5)
Nonfatal ischemic stroke	3 (0.8)	1 (0.3)
Nonfatal nonischemic stroke	0 (0.0)	1 (0.3)
Readmission due to angina pectoris	0 (0.0)	1 (0.3)
Revascularization procedure	8 (2.2)	9 (2.4)

n (%)

As regards safety, the endpoints related to bleeding events were the incidences of non-CABG-related bleeding events ([a] major bleeding [major in TIMI bleeding classification], [b] major or minor bleeding [minor in TIMI bleeding classification], [c] major, minor, or clinically significant bleeding, [d] bleeding event leading to treatment discontinuation, [e] all bleeding events [major, minor, clinically significant, other bleeding]) that occurred from the start of study drug treatment up to 14 days after treatment completion or discontinuation. The results of the reevaluation and classification of bleeding events based on the case reports etc., by the safety assessment committee, blinded to subject assignment, were adopted as the final assessment of each bleeding event. Table 23 shows the incidences of non-CABG-related bleeding events from the start of study drug treatment up to 14 days after treatment completion or discontinuation.

Table 23. Incidences of non-CABG-related bleeding events by type of bleeding, from the start of study drug treatment up to 14 days after treatment completion or discontinuation; Safety analysis set (Adapted from submitted data)

	Prasugrel group (N = 370)	Clopidogrel group (N = 372)
Major bleeding	0 (0.0)	8 (2.2)
Life-threatening bleeding	0 (0.0)	3 (0.8)
Fatal bleeding	0 (0.0)	0 (0.0)
Minor bleeding	6 (1.6)	3 (0.8)
Clinically significant bleeding	14 (3.8)	12 (3.2)
Major or minor bleeding	6 (1.6)	11 (3.0)
Major, minor, or clinically significant bleeding	20 (5.4)	23 (6.2)
Bleeding events leading to treatment discontinuation	9 (2.4)	9 (2.4)
All bleeding events	141 (38.1)	128 (34.4)

n (%)

Among the bleeding adverse events, major bleeding events (including duplicate counting) included, in the prasugrel group, procedural haemorrhage and coronary artery bypass (1 subject each); and, in the clopidogrel group, tumour haemorrhage, thalamus haemorrhage, cardiac tamponade, diverticulum intestinal haemorrhagic, gastrointestinal haemorrhage, upper gastrointestinal haemorrhage, haematuria, procedural haemorrhage, subdural haematoma, and brain contusion (1 subject each). Minor bleeding events included, in the prasugrel group, gastrointestinal haemorrhage, upper gastrointestinal haemorrhage, haemorrhage subcutaneous, puncture site haemorrhage, procedural haemorrhage, subcutaneous haematoma, and vascular pseudoaneurysm (1 subject each); and, in the clopidogrel group, haematochezia, vessel puncture site haemorrhage, and urethral injury (1 subject each). Clinically significant bleeding events included, in the prasugrel group, epistaxis and haematuria (3 subjects each), vitreous haemorrhage and haemorrhage subcutaneous (2 subjects each), retinal haemorrhage, gastrointestinal haemorrhage, gingival bleeding, and procedural haemorrhage (1 subject each); and, in the clopidogrel group, retinal haemorrhage, epistaxis, and haematuria (2 subjects each), haematoma, colitis ischaemic, faeces discoloured, haemorrhage subcutaneous, prostatic haemorrhage, and occult blood positive (1 subject each).

The incidence of adverse events that occurred from the start of study drug treatment up to the end of the follow-up period was 82.2% (304 of 370 subjects) in the prasugrel group and 78.5% (292 of 372 subjects) in the clopidogrel group. Adverse events reported by ≥5% of subjects in either group were nasopharyngitis (19.7% [73 of 370 subjects] in the prasugrel group, 21.5% (80 of 372 subjects) in the clopidogrel group), haemorrhage subcutaneous (13.0% [48 of 370 subjects], 9.4% [35 of 372 subjects]), myocardial infarction (8.4% [31 of 370 subjects], 5.1% [19 of 372 subjects]), coronary artery stenosis (6.2% [23 of 370 subjects], 3.5% [13 of 372 subjects]), epistaxis (5.7% [21 of 370 subjects], 6.2% [23 of 372 subjects]), vessel puncture site haematoma (5.1% [19 of 370 subjects], 4.8% [18 of 372 subjects]), and subcutaneous haematoma (5.1% [19 of 370 subjects], 3.2% [12 of 372 subjects]).

Death occurred in 1 subject in the prasugrel group (acute myocardial infarction) and in 1 subject in the clopidogrel group (pancreatitis acute). A causal relationship to the study drug could not be ruled out for acute pancreatitis in the clopidogrel group.

The incidence of serious adverse events was 20.8% (77 of 370 subjects) in the prasugrel group and 21.0% (78 of 372 subjects) in the clopidogrel group. Serious adverse events reported by ≥1% of subjects in either group were coronary artery stenosis (5.1% in the prasugrel group, 3.2% in the clopidogrel group), coronary artery restenosis (2.4%, 2.7%), angina pectoris (1.4%, 2.4%), cataract (1.1%, 0.3%), and intestinal obstruction (1.1%, 0.0%).

The incidence of adverse events leading to treatment discontinuation was 2.4% (9 of 370 subjects) in the prasugrel group and 2.4% (9 of 372 subjects) in the clopidogrel group. The adverse events included, in the prasugrel group, gastrointestinal haemorrhage and haemorrhage subcutaneous (2 subjects each), vitreous haemorrhage, epistaxis, upper gastrointestinal haemorrhage, puncture site haemorrhage, and subcutaneous haematoma (1 subject each); and, in the clopidogrel group, thalamus haemorrhage, cardiac

tamponade, haematoma, gastrointestinal haemorrhage, upper gastrointestinal haemorrhage, diverticulum intestinal haemorrhagic, haemorrhage subcutaneous, haematuria, and subdural haematoma (1 subject each).

4.(iii).A.(3).3) Foreign ACS phase III study (Study TRITON-TIMI 38, Attached document 5.3.5.1-4, Study period November 2004 to July 2007 [Reference data])

A randomized, double-blind, parallel group comparative study (Foreign study ACS phase III) was conducted at 725 centers in 30 foreign countries including the US and European countries in order to evaluate the superiority of prasugrel in efficacy to clopidogrel and its safety when prasugrel was administered for ≥6 months (up to 15 months) to ACS patients scheduled to undergo PCI, together with aspirin as the basal treatment (target sample size: approximately 13,000 subjects in total, with the upper limit of the number of subjects with STEMI set at 3500 subjects). In this study, subjects were stratified according to subject characteristic ("UA/NSTEMI" or "STEMI") and assigned to treatment groups at each study center.

Aspirin as the basal treatment was administered orally at the dose of 75 to 325 mg or intravenously at 250 to 500 mg within 24 hours before PCI, and, during the study drug treatment period, administered orally at the dose of 75 to 325 mg. Prasugrel was to be administered orally at 60 mg single loading dose before PCI, and then orally once daily at 10 mg maintenance dose. The comparator clopidogrel was to be administered orally at 300 mg single loading dose before PCI, and then orally once daily at 75 mg maintenance dose. PCI was performed immediately after randomization or within 24 hours (up to 28 hours) after the loading dose.

The main inclusion criteria were patients whose condition had been diagnosed as moderate to high risk UA, or as moderate to high risk NSTEMI or STEMI, and who were scheduled to undergo PCI.

The main exclusion criteria were patients who had cardiogenic shock at the randomization and patients who had a history of cerebral haemorrhage, concurrent intracranial neoplasm, arteriovenous malformation, arterial aneurysm, or ischemic stroke within 3 months before the screening.

Of 13,619 subjects randomized (6820 subjects in the prasugrel group, 6799 subjects in the clopidogrel group), 13,608 subjects (6813 subjects, 6795 subjects) were included in the intention to treat (ITT) population and in the primary efficacy analysis set, except for 11 subjects (7 subjects, 4 subjects) who did not provide valid informed consent. Of these subjects, 13,457 subjects (6741 subjects, 6716 subjects) who received at least 1 dose of the study drug were included in the safety analysis set. Study discontinuation occurred in 804 subjects (410 subjects in the prasugrel group, 394 subjects in the clopidogrel group), with the main reasons being consent withdrawal (342 subjects, 323 subjects) and missed visit at the end of the study (53 subjects, 51 subjects). The follow-up period[3] (mean ± SD) was 379.1 ± 120.5 days in the prasugrel group and 380.4 ± 121.2 days in the clopidogrel group among all ACS patients, 363.7 ± 120.0 days and 366.0 ± 120.4 days among UA or NSTEMI patients, and 423.1 ± 111.0 days and 421.5 ± 113.7 days among STEMI patients.

The primary efficacy endpoint was the composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke occurring before the end of the study. The results of the assessment by the independent Clinical Endpoint Committee (CEC), blinded to subject assignment, were regarded as the final evaluation of efficacy events. The incidence of the composite endpoint observed up to the end of the study in the entire population was 9.44% (643 of 6813 subjects) in the prasugrel group and 11.49% (781 of 6795 subjects) in the clopidogrel group, showing a significant difference ($P < 0.001$)[4] between the groups by the Gehan-Wilcoxon test,[5] which was handled as the primary analysis; the hazard ratio [95% CI] calculated by Cox regression analysis,[6] was 0.812 [0.732-0.902]. In UA or NSTEMI population, the incidence of the composite endpoint observed up to the end of the study was 9.30% (469 of 5044 subjects) in the prasugrel group and 11.23% (565 of 5030 subjects) in the clopidogrel group;

[3] Days from randomization to the last visit or 464 days, whichever was shorter

[4] The analysis of UA or NSTEMI population was performed first and, after the superiority ($P = 0.002$) of prasugrel group to clopidogrel group was confirmed, the analysis was performed on all ACS patients including STEMI patients.

[5] The Gehan-Wilcoxon test using subject characteristics (UA or NSTEMI, STEMI) as the stratification factor

[6] The Cox regression model using subject characteristics (UA/NSTEMI, STEMI) as the stratification factor

the hazard ratio [95% CI] calculated by Cox regression analysis was 0.820 [0.726-0.927]. In the STEMI population, the incidence of the composite endpoint observed up to the end of the study was 9.84% (174 of 1769 subjects) in the prasugrel group and 12.24% (216 of 1765 subjects) in the clopidogrel group; the hazard ratio [95% CI] calculated by Cox regression analysis was 0.793 [0.649-0.968]. The change over time in the cumulative incidence in the entire population was as shown in the Kaplan-Meier curve in Figure 5.

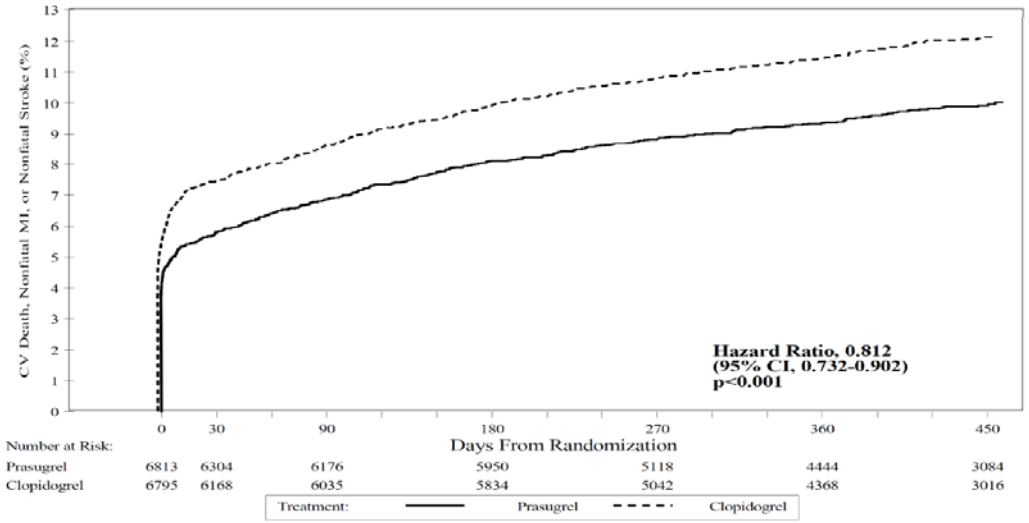


Figure 5. Cumulative incidence of the composite endpoint in the entire population up to the end of the study; ITT (Adapted from submitted data)

Table 24 shows the incidences of the secondary efficacy endpoints, which are composite endpoints of efficacy events ([a] cardiovascular death, nonfatal myocardial infarction, nonfatal stroke [incidence up to 90 or 30 days after randomization], [b] cardiovascular death, nonfatal myocardial infarction, revascularization procedure [incidence up to 90 or 30 days after randomization], [c] stent thrombosis, [d] other individual efficacy events [all-cause death, cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, myocardial ischaemia requiring readmission, revascularization procedure]).

Table 24. Incidence of each composite endpoint and of each efficacy event that constitutes the composite endpoints; ITT (Adapted from submitted data)

	Prasugrel group (N = 6813)	Clopidogrel group (N = 6795)
Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke (up to 90 days after randomization)	462 (6.78)	573 (8.43)
Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke (up to 30 days after randomization)	389 (5.71)	502 (7.39)
Cardiovascular death, nonfatal myocardial infarction, revascularization procedure (up to the end of the study)	652 (9.57)	798 (11.74)
Cardiovascular death, nonfatal myocardial infarction, revascularization procedure (up to 90 days after randomization)	472 (6.93)	588 (8.65)
Cardiovascular death, nonfatal myocardial infarction, revascularization procedure (up to 30 days after randomization)	399 (5.86)	504 (7.42)
Stent thrombosis[a] (up to the end of the study)	58 (0.90)	120 (1.87)
All-cause death (up to the end of the study)	188 (2.76)	197 (2.90)
Cardiovascular death (up to the end of the study)	133 (1.95)	150 (2.21)
Nonfatal myocardial infarction (up to the end of the study)	475 (6.97)	620 (9.12)
Nonfatal stroke (up to the end of the study)	61 (0.90)	60 (0.88)
Myocardial ischaemia requiring readmission (up to the end of the study)	184 (2.70)	203 (2.99)
Revascularization procedure (up to the end of the study)	156 (2.29)	233 (3.43)

n (%); a, N (number of subjects evaluated) = 6422 both in the prasugrel group and in the clopidogrel group

As regards safety, the endpoints related to bleeding events were (a) non-CABG-related major bleeding (major in TIMI bleeding classification), (b) non-CABG-related life-threatening bleeding (life-threatening in TIMI bleeding classification), (c) non-CABG-related minor bleeding (minor in TIMI bleeding classification), and (d) non-CABG-related minimal bleeding (minimal in TIMI bleeding classification). The results of the assessment by CEC, blinded to assignment group, were adopted as the final evaluation of each bleeding event. Table 25 shows the incidences of non-CABG-related bleeding events.

Table 25. Incidences of non-CABG-related bleeding events by type of bleeding, Safety analysis set (Adapted from submitted data)

	Prasugrel group (N = 6741)	Clopidogrel group (N = 6716)
Major bleeding	146 (2.17)	111 (1.65)
Life-threatening bleeding	85 (1.26)	56 (0.83)
Fatal bleeding	21 (0.31)	5 (0.07)
Bleeding accompanied by blood pressure decrease requiring pressure increase by intravenous injection of cardiotonic agent	21 (0.31)	8 (0.12)
Bleeding that necessitated surgical treatment	19 (0.28)	19 (0.28)
Bleeding requiring transfusion of ≥4 units of blood	45 (0.67)	30 (0.45)
Symptomatic intracranial haemorrhage	19 (0.28)	17 (0.25)
Minor bleeding	164 (2.43)	125 (1.86)
Minimal bleeding	460 (6.82)	314 (4.68)
Major or minor bleeding	303 (4.49)	231 (3.44)
Major, minor, or minimal bleeding	732 (10.86)	528 (7.86)

n (%)

The incidence of adverse events was 80.34% (5416 of 6741 subjects) in the prasugrel group and 80.02% (5374 of 6716 subjects) in the clopidogrel group. Adverse events reported by ≥5% of subjects in either group were chest pain (11.30% [762 of 6741 subjects] in the prasugrel group, 10.41% [699 of 6716 subjects] in the clopidogrel group), percutaneous intervention (9.92% [669 of 6741], 10.27% [690 of 6716 subjects]), hypertension (7.46% [503 of 6741 subjects], 7.09% [476 of 6716 subjects]), contusion (6.94% [468 of 6741 subjects], 3.90% [262 of 6716 subjects]), haematoma (6.54% [441 of 6741 subjects], 5.57% [374 of 6716 subjects]), epistaxis (6.16% [415 of 6741 subjects], 3.26% [219 of 6716 subjects]), angina pectoris (5.61% [378 of 6741 subjects], 6.06% [407 of 6716 subjects]), headache (5.52% [372 of 6741 subjects], 5.29% [355 of 6716 subjects]), back pain (5.04% [340 of 6741 subjects], 4.54% [305 of 6716 subjects]), and coronary revascularization (4.64% [313 of 6741 subjects], 5.81% [390 of 6716 subjects]).

Death occurred in 2.76% (188 of 6813 subjects) of the prasugrel group and in 2.90% (197 of 6795 subjects) of the clopidogrel group. Of these fatal cases, cardiovascular death occurred in 1.95% (133 of 6813 subjects) of the prasugrel group and in 2.21% (150 of 6795 subjects) of the clopidogrel group, and non-cardiovascular death occurred in 0.81% (55 of 6813 subjects) of the prasugrel group and in 0.69% (47 of 6795 subjects) of the clopidogrel group. The cardiovascular death included sudden death or unwitnessed death (0.53% [36 of 6813 subjects] in the prasugrel group, 0.62% [42 of 6795 subjects] in the clopidogrel group), cardiac failure congestive or cardiogenic shock (0.46% [31 of 6813 subjects], 0.44% [30 of 6795 subjects]), myocardial infarction (0.35% [24 of 6813 subjects], 0.53% [36 of 6795 subjects]), and events directly caused by revascularization procedure (CABG or PCI) (0.22% [15 of 6813 subjects], 0.24% [16 of 6795 subjects]). The non-cardiovascular death included cancer (0.31% [21 of 6813 subjects], 0.25% [17 of 6795 subjects]), infection (0.16% [11 of 6813 subjects], 0.15% [10 of 6795 subjects]), and non-intracranial haemorrhage (0.13% [9 of 6813 subjects], 0.01% [1 of 6795 subjects]).

The incidence of serious adverse events was 24.70% (1665 of 6741 subjects) in the prasugrel group and 24.26% (1629 of 6716 subjects) in the clopidogrel group. Serious adverse events reported by ≥1% of subjects in either group were gastrointestinal haemorrhage (1.32% in the prasugrel group, 0.82% in the clopidogrel group), coronary artery restenosis (1.59%, 1.65%), angina pectoris (1.26%, 1.28%), non-cardiac chest pain (2.03%, 2.49%), and chest pain (1.35%, 1.09%).

The incidence of adverse events leading to treatment discontinuation was 6.85% (462 of 6741 subjects) in the prasugrel group and 5.81% (390 of 6716 subjects) in the clopidogrel group. The adverse events included gastrointestinal haemorrhage (0.49%, 0.31%), epistaxis (0.31%, 0.12%), haematuria (0.18%, 0.06%), contusion (0.16%, 0.10%), atrial fibrillation (0.30%, 0.49%), intracardiac thrombus (0.18%, 0.04%), atrial flutter (0.10%, 0.06%), rash (0.28%, 0.42%), coronary artery bypass (0.27%, 0.22%), and deep vein thrombosis (0.13%, 0.09%).

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Clinical positioning of prasugrel in ischemic heart disease to be managed with PCI

PMDA asked the applicant to explain the clinical positioning of prasugrel in patients with ischemic heart disease (UA, NSTEMI, STEMI, SA, OMI) who are to be managed with PCI in Japan, based on the results of Japanese and foreign clinical studies.

The applicant responded as follows:
For patients with ischemic heart disease (UA, NSTEMI, STEMI, SA, OMI) who are to be managed with PCI in Japan, mainly antiplatelet therapy is recommended to prevent post-PCI reinfarction by the "Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease (JCS 2009)" (The Japanese Circulation Society), and antiplatelet agents such as aspirin, ticlopidine, and clopidogrel are used. Particularly in patients with an indwelling stent, concomitant use of aspirin and a thienopyridine drug is the basic treatment method, with the combination of aspirin and ticlopidine or clopidogrel recommended as the class I treatment (evidence supports that treatment is useful and effective and there is general agreement that the treatment is indicated for the conditions). Both ticlopidine and clopidogrel are drugs that are in the same class as prasugrel, but since ticlopidine is known to cause serious adverse drug reactions such as thrombotic thrombocytopenic purpura, agranulocytosis, and serious hepatic impairment, clopidogrel is widely used currently in clinical practice

in the US, Europe, and Japan. However, clopidogrel also has problems, as shown below. It takes a long time before clopidogrel exhibits its antiplatelet effect after administration, and, because of this delayed onset of action, it is reported that the risk of early cardiovascular event is higher if clopidogrel is administered <6 hours before PCI compared with the risk when administered ≥6 hours before PCI (Steinhubl SR et al., *JAMA.* 2002;288:2411-21). It is unrealistic to start administration of an antiplatelet drug from ≥6 hours before PCI in patients with ACS. In foreign countries, it is often the case that an antagonist of platelet glycoprotein GPIIb/IIIa receptor (GPIIb/IIIa receptor blocker) is used before PCI and then clopidogrel is administered. However, in Japan, where no GPIIb/IIIa receptor blocker is approved as yet, clopidogrel is administered without concomitant use of a GPIIb/IIIa receptor blocker, regardless of the time to PCI. It is also reported that there are patients who do not respond sufficiently to clopidogrel (poor responders) (Snoep JD et al., *Am Heart J.* 2007;154:221-31), and the risk of cerebro-cardiovascular event is higher in these poor responders (Wiviott SD et al., *Circulation.* 2004;109:3064-7, Matetzky S et al., *Circulation.* 2004;109:3171-5, Barragan P et al., *Catheter Cardiovasc Interv.* 2003;59:295-302, Muller I et al., *Thromb Haemost.* 2003;89:783-7). The definition of poor responders varies from report to report. If poor responders are defined as patients with IPA of <20% after drug administration, poor responders to clopidogrel account for 17% to 25% of patients according to a meta-analysis out of Japan (Snoep JD et al., *Am Heart J.* 2007;154:221-31.). It has been shown that genetic polymorphism of CYP2C19 is the main cause for the poor response to clopidogrel, and there is a report that the percentage of CYP2C19 poor metabolizers (PM) is higher in Japanese than in Caucasians (Furuta T et al., *Drug Metab Pharmacokinet.* 2005;20:153-167.).

The results of Japanese and foreign clinical studies of prasugrel are as shown below. In the foreign ACS phase III study, the incidence of the primary efficacy endpoint, i.e., composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, was significantly lower in the prasugrel group (9.4%, 643 of 6813 subjects) than in the clopidogrel group (11.5%, 781 of 6795 subjects) (hazard ratio [95% CI], 0.812 [0.732-0.902]), demonstrating the superiority of prasugrel to clopidogrel. The incidence of non-CABG-related major bleeding events was significantly higher in the prasugrel group (2.2%, 146 of 6741 subjects) than in the clopidogrel group (1.7%, 111 of 6716 subjects) (hazard ratio [95% CI], 1.315 [1.028-1.683]).

In the Japanese phase III study in patients with ACS-PCI, patients with ACS who are to be managed with PCI, the disease population similar to that investigated in the foreign ACS phase III study, the incidence of the primary efficacy endpoint, i.e., MACE1 during the first 24 weeks of the study drug treatment, was lower in the prasugrel group compared with the clopidogrel group, with the point estimate of the hazard ratio adjusted for covariates being less than 1. The incidence of the secondary endpoint, i.e., MACE1 within 3 days after administration, was 5.3% (36 of 685 subjects) in the prasugrel group and 8.3% (56 of 678 subjects) in the clopidogrel group (hazard ratio [95% CI], 0.626 [0.412-0.951]), confirming a more potent event-suppressive effect during the early stage of treatment in the prasugrel group than in the clopidogrel group. These results, coupled with the results of the foreign ACS phase III study, have demonstrated that prasugrel is sufficiently effective in Japanese patients as well. As regards safety, the incidence of non-CABG-related major bleeding events was similar between the prasugrel group and the clopidogrel group. PRU in the prasugrel group decreased from 2 to 4 hours after the loading dose compared with the baseline level, whereas PRU in the clopidogrel group showed little or no decrease at 2 to 4 hours after the loading dose. Also, PRU was lower in the prasugrel group than in the clopidogrel group at all time points during the period from 2 to 4 hours, and from 5 to 12 hours, after the loading dose, demonstrating the more rapid onset of the efficacy of prasugrel compared with clopidogrel. Furthermore, both in the prasugrel group and in the clopidogrel group, PRU remained almost at a constant level at all time points of 4, 12, 24, 36, and 48 weeks after the start of treatment, persisting at a lower level in the prasugrel group than in the clopidogrel group. As regards the quantitative trait locus for each phenotype of CYP2C19, PRU at 4 weeks after the start of treatment in the prasugrel group was similar regardless of the phenotype of CYP2C19, i.e., regardless of whether the patient was an extensive metabolizer (EM), intermediate metabolizer (IM), or PM. In contrast, PRU at 4 weeks after the start of treatment in the clopidogrel group was lowest in EM, followed in the increasing order by IM and PM. In the Japanese phase III study in patients with elective PCI, the patients requiring elective PCI because of SA or OMI, the incidence of MACE1 observedduring the first 24 weeks of the study drug treatment, the primary endpoint, was 4.1% (15 of 370 subjects) in the prasugrel group and 6.7% (25 of 372 subjects) in the clopidogrel group. The incidence of non-CABG-related major bleeding

events from the start of study drug treatment up to 14 days after the study completion or discontinuation was 0.0% (0 of 370 subjects) in the prasugrel group and 2.2% (8 of 372 subjects) in the clopidogrel group.

Based on the above results of the Japanese and foreign clinical studies, the applicant considers that prasugrel has the following characteristic features when compared with clopidogrel, which is widely used currently: (i) prasugrel exhibits an antiplatelet effect more rapidly in patients with ischemic heart disease who are to be managed with PCI (UA, NSTEMI, STEMI, SA, OMI), and it has a definite inhibitory effect against platelet aggregation at the time of PCI; (ii) there are few poor responders; and (iii) the incidence of adverse drug reactions is comparable to that observed with clopidogrel. Also, the results of clinical studies in Japanese patients suggest that the preventive effect against cardiovascular events at the early stage of treatment is greater compared with clopidogrel, and that the preventive effect is constantly maintained throughout the treatment period. Thus, the applicant considers that, with a favorable benefit-risk balance compared with the current standard treatment, prasugrel provides a superior treatment to patients with ischemic heart disease who are to be managed with PCI, compared with clopidogrel.

PMDA considers the clinical positioning of prasugrel as follows:
Because of the feasibility problem, the applicant did not conduct the Japanese phase III study in patients with ACS-PCI using a sufficient number of patients for efficacy assessment. Therefore, there is a limitation to the comparison of the efficacy between clopidogrel and prasugrel based on the results of this study. The results of the foreign ACS phase III study showed the superiority in efficacy of prasugrel to clopidogrel, but the dose levels employed in this study were different from those in the Japanese phase III study in patients with ACS-PCI. Therefore, the rank order of efficacy between prasugrel and clopidogrel demonstrated in the foreign ACS phase III study does not necessarily remain the same in Japanese patients. Thus, it cannot be concluded that prasugrel is more potent than clopidogrel in preventing cardiovascular events in Japanese patients. The applicant further asserts that prasugrel exhibits its effect more rapidly than clopidogrel, resulting in definite inhibition of platelet aggregation at the time of PCI. However, there is no evidence to support that clinical efficacy of prasugrel, such as prevention of cardiovascular events, can be estimated from the platelet aggregation parameters such as PRU. Thus, there is a limitation to such an estimation. Based on the incidence of MACE1 within 3 days after administration (the secondary endpoint) in the Japanese phase III study in patients with ACS-PCI, the applicant discussed that prasugrel exhibits a more potent event-preventing effect during the early period of treatment compared with clopidogrel. However, firstly, this study was not designed to allow sufficient statistical power to verify the superiority in efficacy of prasugrel to clopidogrel, and, secondly, the above estimation was based on the results of the analysis of the secondary endpoint, i.e., events within 3 days. Thus, the available data do not provide sufficient evidence to claim the clinical usefulness of prasugrel compared to clopidogrel in clinical use in Japan. Regarding the fewer poor responders to prasugrel than to clopidogrel, which is alleged to be one of the advantages of prasugrel to clopidogrel, although it is theoretically understandable, whether or not such a difference actually translates to any clinically significant difference in ACS patients has not been shown in any of the clinical studies conducted so far.

Taking account of the above, together with the similar tendencies observed in Japanese and foreign clinical studies of the efficacy of prasugrel, and with the results of the Japanese and foreign clinical studies of clopidogrel, a similar drug, and its use conditions in Japan and elsewhere, prasugrel is expected to be as similarly effective as clopidogrel and is also estimated to have a similar level of safety to clopidogrel in patients with ACS (UA, NSTEMI, STEMI) who are to be managed with PCI in Japan as an antiplatelet therapy to be concomitantly administered with aspirin. However, it is difficult to decide which is more effective and safer between prasugrel and clopidogrel. Also, taking account of the results of the Japanese phase III study in patients with elective PCI, PMDA considers that, under the current conditions, prasugrel is an option worth being made available in clinical settings as an antiplatelet therapy of equal clinical significance to clopidogrel for patients with ischemic heart disease, including SA and OMI, who are to be managed with PCI.

4.(iii).B.(2) Efficacy and indication of prasugrel

4.(iii).B.(2).1) Effectiveness and background of having selected the approved dosage and administration of prasugrel and its efficacy in foreign countries

PMDA asked the applicant to explain the background leading to having selected the following approved dosage regimen of prasugrel for ACS patients undergoing PCI in foreign countries and its rationale: 60 mg loading dose followed by 10 mg maintenance dose.

The applicant responded as follows:
The selection of dose in the foreign ACS phase III study is justified as shown below. In the clinical pharmacology study in patients with stable atherosclerosis (Study H7T-EW-TAAD), IPA (induced by 20 μM ADP) at 4 hours post-dose on Day 1 of treatment was 68.4% in the groups receiving the 60 mg loading dose of prasugrel (60 + 10 mg group, 60 + 15 mg group), which was significantly higher than 30.0% in the clopidogrel group receiving the 300 mg loading dose. Also, IPA on Day 28 was 57.5% in the prasugrel 60 + 10 mg group, which was significantly higher than 31.2% observed in the clopidogrel group (maintenance dose 75 mg). In the dose-finding study in patients with elective or urgent PCI (Study H7T-MC-TAAH), the incidence of major cardiovascular events within 30 days after the start of the study drug treatment was 7.5% (15 of 200 subjects) in the prasugrel 60 + 10 mg group and 6.8% (17 of 251 subjects) in the 60 + 15 mg group, both of which tended to be lower compared with 9.4% (24 of 254 subjects) in the clopidogrel 300 + 75 mg group. The incidence of non-CABG-related "major or minor bleeding" (by TIMI bleeding classification) within 30 days of treatment was 2.0% (4 of 200 subjects) in the prasugrel 60 + 10 mg group and 1.6% (4 of 251 subjects) in the 60 + 15 mg group, showing no significant increase compared with 1.2% (3 of 254 subjects) in the clopidogrel 300 + 75 mg group. Based on the above results, a loading dose of 60 mg and a maintenance dose of 10 mg were selected as the dosage regimen of prasugrel for the foreign ACS phase III study.

The results of the foreign ACS phase III study were as shown below. The incidence of the primary efficacy endpoint, i.e., the composite endpoint of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, was significantly lower in the prasugrel group compared with the clopidogrel group (hazard ratio [95% CI], 0.812 [0.732-0.902]), and the incidence of the safety endpoint, i.e., non-CABG-related major bleeding events, was significantly higher in the prasugrel group compared with the clopidogrel group (hazard ratio [95% CI], 1.315 [1.028-1.683]). The incidence of events related to clinical usefulness (composite endpoint of all-cause death, nonfatal myocardial infarction, nonfatal stroke, and non-CABG-related major bleeding) was significantly lower in the prasugrel group compared with the clopidogrel group (hazard ratio [95% CI], 0.87 [0.79-0.95]). In a post-hoc analysis, the composite endpoints for efficacy and safety were subjected to subpopulation analysis by patient background characteristics. The results showed that "past history of stroke or TIA," "≥75 years of age," and "body weight <60 kg" were risk factors for decreased clinical usefulness of prasugrel (Stephen D. Wiviott et al., *N Engl J Med.* 2007;357:2001-15.). Based on the above results, prasugrel was approved in the US and Europe with the dosage regimen of 60-mg loading dose and 10-mg maintenance dose despite concerns about a higher bleeding risk in the prasugrel group.

PMDA asked the applicant to explain the background and the rationale that led to the approval in foreign countries for using prasugrel in patients weighing <60 kg under the conditions to give consideration to administering a maintenance dose of 5 mg.

The applicant responded as follows:
Table 26 shows the incidence of non-CARB-related bleeding events in the foreign ACS phase III study. All bleeding events showed a higher incidence in the prasugrel group than in the clopidogrel group.

Table 26. Incidence of non-CABG-related bleeding events in foreign ACS phase III study (Adapted from submitted data)

Bleeding events (non-CABG-related)	Prasugrel group (N = 6741) n (%)	Clopidogrel group (N = 6716) n (%)	Hazard ratio [95% CI]
Major bleeding	146 (2.17)	111 (1.65)	1.315 [1.028-1.683]
Life-threatening bleeding	85 (1.26)	56 (0.83)	1.517 [1.083-2.126]
Minor bleeding	164 (2.43)	125 (1.86)	1.313 [1.040-1.656]
Major or minor bleeding	303 (4.49)	231 (3.44)	1.314 [1.107-1.559]
Minimal bleeding	460 (6.82)	314 (4.68)	1.475 [1.278-1.702]

Major bleeding events on and after Day 3, which are considered to reflect the effect of 10-mg maintenance dose, were subjected to univariate and multivariate analyses. The results suggested an increased bleeding risk in low body weight patients and in elderly patients. A further analysis with a classification and regression tree (CART) showed higher incidences of major or minor bleeding events in subjects weighing <60 kg. In the foreign ACS phase III study, plasma concentration of the active metabolite of prasugrel was higher in subjects weighing <60 kg compared with ordinary subjects. When the maintenance dose in subjects weighing <60 kg was reduced from 10 mg to 5 mg, the range of the exposure to the active metabolite roughly overlapped with that observed in ordinary subjects receiving 10-mg maintenance dose, which suggested that the 5-mg dose decreases the bleeding risk while maintaining the efficacy. Thus, the foreign ACS phase III study showed that, in subjects weighing <60 kg, the incidence of non-CABG-related bleeding events was higher than in ordinary subjects, and suggested that the higher incidence was partly due to the increased exposure to the active metabolite of prasugrel. Therefore, in foreign countries, prasugrel was approved with the conditions to give consideration to administering 5-mg maintenance dose in patients weighing <60 kg.

PMDA considers the dosage and administration of prasugrel in foreign countries as follows:
Given the low incidence of cardiovascular events in ACS patients undergoing PCI, it was appropriate, in the development of prasugrel in foreign countries, that the dose in the ACS phase III study was determined using IPA as the index and taking account of the comparison with clopidogrel, and the loading dose and maintenance dose determined are understandable. The results of the foreign ACS phase III study are interpreted as showing the superior effect of prasugrel in preventing cardiovascular events compared with clopidogrel in ACS patients undergoing PCI. However, the usefulness of prasugrel should be determined with consideration to safety concerns, i.e., the higher risk of bleeding events compared to clopidogrel. The dose adjustment of prasugrel in Japanese patients with lower body weight will be discussed in the "4.(iii).B.(4).2) Administration in patients with body weight of ≤50 kg" section.

4.(iii).B.(2).2) Use of the data of foreign ACS phase III study for application in Japan
PMDA asked the applicant to compare the patient characteristics (an underlying disease such as UA), study design, and efficacy data (e.g., primary endpoint, the details of each cardiovascular event, time of onset) between the Japanese phase III study in patients with ACS-PCI and the foreign ACS phase III study, and to explain whether it was possible to conclude that the results of these studies were similar to each other.

The applicant responded as follows:
Noteworthy differences in patient characteristics between the FAS in the Japanese phase III study in patients with ACS-PCI and the ITT population in the foreign ACS phase III study were as shown below. Regarding disease type, STEMI accounted for 50% of patients, UA for 20%, and NSTEMI for 30% in the Japanese phase III study, and STEMI accounted for 26% of patients and sum of UA and NSTEMI for 74% in the foreign phase III study. The morbidity of diabetes mellitus, dyslipidaemia, and hypertension was 10% to 20% higher in the Japanese phase III study. As regards the initial number of lesions treated, one-vessel lesion was treated in 95% of patients in the foreign phase III study, whereas multi-vessel lesions were present in 26% of patients in the Japanese phase III study. The percentage of elderly, low body weight patients appeared to be higher in the Japanese phase III study. Although the above differences in patient characteristics were observed between the two studies, the patient characteristics in the Japanese phase III study are close to those of current Japanese ACS patients, demonstrating the appropriateness of evaluating the efficacy of prasugrel in Japanese ACS patients

based on the results of this study. Also, since the dosage regimen of the comparator clopidogrel were the same as those used in the foreign phase III study, it is appropriate to compare the efficacy and safety of prasugrel with those of clopidogrel by referring to the data of the foreign phase III study.

There are mainly the following differences in the study design and the efficacy evaluation between the Japanese phase III study in patients with ACS-PCI and the foreign ACS phase III study. The loading dose and the maintenance dose of prasugrel were 20 and 3.75 mg, respectively, in the Japanese phase III study and 60 and 10 mg, respectively, in the foreign phase III study. Regarding nonfatal stroke, a parameter in the composite primary endpoint, only ischemic stroke was evaluated in the Japanese phase III study, whereas both ischemic and non-ischemic stroke were evaluated in the foreign phase III study. The follow-up period for the primary endpoint was 24 weeks in the Japanese phase III study and 14.5 months (median) in the foreign phase III study.

In the Japanese phase III study in patients with ACS-PCI, the incidence of the primary efficacy endpoint, i.e., MACE1 up to 24 weeks of treatment with the study drug, was lower in the prasugrel group than in the clopidogrel group, with the covariate-adjusted point estimate of the hazard ratio being <1. The incidence of the composite endpoint (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke [including non-ischemic stroke]) up to 24 weeks of treatment with the study drug, the same endpoint as used in the foreign phase III study, was similar to that of the primary endpoint. Therefore, the applicant considered that the difference in endpoints constituting the primary endpoint between the two studies did not affect the comparison of the data of these studies. As for individual cardiovascular events, the incidence of nonfatal myocardial infarction was the highest in both studies, and the incidences of cardiovascular death and nonfatal stroke were similar between these studies. In both studies, events included in the primary endpoint occurred mostly within 3 days of the study drug treatment, and the incidence was lower in the prasugrel group than in the clopidogrel group. The incidence of the primary endpoint over 180 days in the foreign phase III study was 8.0% in the prasugrel group and 9.7% in the clopidogrel group, which was similar to the incidence of MACE1 over 24 weeks of treatment in the Japanese phase III study. In both studies, the between-group difference remained unchanged until the end of the study. These results suggested that the incidences of efficacy events over the same time window were also similar between the two groups.

Based on the above, the applicant considers that the efficacy results are similar between the Japanese phase III study in patients with ACS-PCI and the foreign ACS phase III study despite some differences in patient characteristics and study design.

PMDA considers as follows:
In the development of prasugrel in Japan targeted at ACS patients undergoing PCI, it is a basic requirement that the dosage regimen be appropriately selected for Japanese patients and the efficacy and safety of the drug used according to the pertinent dosage regimen be verified. However, given the low frequency of cardiovascular events in ACS patients eligible for PCI in Japan, it is difficult to verify the effect of prasugrel to prevent cardiovascular events solely based on the data in Japan. In the development of prasugrel in Japan, a pharmacodynamic marker related to the antiplatelet effect was used as the index for selecting the dose of prasugrel and, as a result, the loading dose and the maintenance dose different from those approved in foreign countries were selected by also taking account of the results of the comparison with clopidogrel. Consequently it was inevitable that the study design in the confirmatory study in Japanese patients did not allow a comparison of the efficacy between prasugrel and clopidogrel in a statistically valid manner. Therefore, in evaluating the efficacy of prasugrel, it is necessary to use the data of foreign clinical studies, which confirmed the efficacy. Comparison of the Japanese phase III study in patients with ACS-PCI and the foreign ACS phase III study shows the differences in the loading dose and the maintenance dose, study design, and the efficacy endpoint between the two studies, allowing only a limited comparison between the studies. It is thus difficult to assert that the results of the foreign ACS phase III study are reproducible in Japan. Consequently, it cannot be concluded that efficacy was shown for prasugrel to a similar extent in the two studies. However, from the comparison of the incidences of MACE1 and each cardiovascular event and the timing of onset of these events in the prasugrel group with those observed in the group treated with clopidogrel, the standard drug used in ACS patients eligible for PCI both in Japan and foreign countries, it can be concluded that prasugrel and clopidogrel showed a similar tendency of efficacy between the two studies. Based on the above, PMDA

considers that currently prasugrel is expected to exhibit efficacy at least equal to that of clopidogrel in antiplatelet treatment in Japanese patients with ACS who are to be managed with PCI, as judged from the results of the Japanese phase III study in patients with ACS-PCI and the foreign ACS phase III study. However, given the safety results (e.g. bleeding risk) in Japanese and foreign clinical studies, it is inappropriate to use the data of the foreign ACS phase III study by assuming that the efficacy-safety balance of prasugrel observed in foreign clinical studies is similarly maintained in Japanese patients. The following review was performed taking account of this point also.

4.(iii).B.(2).3) Efficacy of prasugrel in Japanese patients with ACS who are to be managed with PCI and in Japanese patients with SA or OMI

PMDA asked the applicant to explain the efficacy of prasugrel in Japanese patients with ACS who are to be managed with PCI and in Japanese patients with SA or OMI, including the comparison with clopidogrel.

The applicant responded as follows:

The results of the primary endpoint, occurrences of each cardiovascular event, and the timing of onset of each cardiovascular event in the Japanese phase III study in patients with ACS-PCI showed similar tendencies to those observed in the foreign ACS phase III study and, despite the differences in patient characteristics and the study design, the efficacy results in the two studies are similar to each other. In the Japanese phase III study in patients with ACS-PCI, the incidence of MACE1 by disease type was 10.9% (17 of 156 patients) for UA, 9.1% (17 of 187 patients) for NSTEMI, and 8.8% (30 of 340 patients) for STEMI in the prasugrel group; and 14.5% (18 of 124 patients) for UA, 15.5% (33 of 213 patients) for NSTEMI, and 8.5% (29 of 341 patients) for STEMI in the clopidogrel group.

In the Japanese phase III study in patients with elective PCI, the incidence of MACE, the primary endpoint, was 4.1% (15 of 370 patients) in the prasugrel group and 6.7% (25 of 372 patients) in the clopidogrel group, which suggested that the difference in the incidence in the two groups and the change over time in the occurrences were similar to those observed with the primary endpoint in the Japanese phase III study in patients with ACS-PCI. The incidence of MACE by disease type was 4.0% (11 of 277 patients) for SA, 4.8% (1 of 21 patients) for OMI, 3.3% (1 of 30 patients) for UA, and 4.9% (2 of 41 patients) for asymptomatic myocardial ischaemia in the prasugrel group; and 7.0% (20 of 284 patients) for SA, 6.3% (1 of 16 patients) for OMI, 2.9% (1 of 35 patients) for UA, and 9.1% (3 of 33 patients) for asymptomatic myocardial ischaemia in the clopidogrel group. Thus, the results suggested that prasugrel exhibits sufficient efficacy regardless of disease type. It was therefore inferred that prasugrel would prevent cardiovascular events in patients with SA or OMI who are to be managed with PCI in a similar manner as observed in patients with ACS who are to be managed with PCI.

Both in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, a statistically valid test for the primary endpoint cannot be performed because of the limited number of subjects. However, a higher antiplatelet effect was observed in the prasugrel group than in the clopidogrel group throughout the treatment period in both studies.

From the above findings, prasugrel 20 + 3.75 mg is expected to exhibit a higher antiplatelet effect than clopidogrel, resulting in the inhibition of ischemic events throughout the treatment period in Japanese patients with ischemic heart disease who are to be managed with PCI. Therefore, it is inferred that prasugrel 20 + 3.75 mg is equally or more effective than clopidogrel in these patients.

PMDA considers as follows:

The Japanese phase III study in patients with ACS-PCI was conducted in a limited number of subjects insufficient to provide adequate power for a statistically valid comparison of the efficacy between prasugrel and clopidogrel. It is therefore inappropriate to claim the superior efficacy of prasugrel compared to clopidogrel. However, as discussed in the "4.(iii).B.(2).2) Use of the data of foreign ACS phase III study for application in Japan" section, it is appropriate to conclude that the efficacy of prasugrel demonstrated in the Japanese phase III study in patients with ACS-PCI and the foreign ACS phase III study shows a similar tendency in both studies, as judged by the comparison of relative efficacy with clopidogrel. Thus, based on the results of both studies, prasugrel is expected to be at least as effective as clopidogrel also in Japanese patients with ACS who are to be managed with PCI. Similarly,

the sample size of the Japanese phase III study in patients with elective PCI was not sufficiently large to allow a statistically valid comparison, precluding the accurate comparison of the efficacy between prasugrel and clopidogrel. Nevertheless, the data are interpretable as showing the efficacy at least equal to clopidogrel as an antiplatelet therapy for Japanese patients with SA or OMI who are to be managed with PCI, as is the case with patients with ACS who are to be managed with PCI.

4.(iii).B.(2).4) Target patients and indication of prasugrel

PMDA considers as follows:

The efficacy of prasugrel was suggested in Japanese patients investigated in the Japanese phase III study in patients with ACS-PCI and the Japanese phase III study in patients with elective PCI. Therefore, the target patients in both studies, i.e., patients with ACS (UA, NSTEMI, STEMI), SA, or OMI who are to be managed with PCI, are the appropriate patient population for treatment with prasugrel. Also, since prasugrel has the same clinical positioning as clopidogrel, the indication should be "the following ischemic heart disease to be managed with percutaneous coronary intervention (PCI): acute coronary syndrome (unstable angina, non ST segment elevation myocardial infarction, ST segment elevation myocardial infarction), stable angina pectoris, and old myocardial infarction," as is the case with clopidogrel.

4.(iii).B.(3) Dosage and administration of prasugrel

4.(iii).B.(3).1) Doses investigated in Japanese phase II dose-finding study

PMDA asked the applicant to explain the rationale for selecting 20 + 3.75 mg and 20 + 5 mg as the doses to be investigated in ordinary subjects in the Japanese phase II dose-finding study (Study CS0747S-B-J202).

The applicant responded as follows:

First, the study doses in the Japanese clinical pharmacology study in patients with coronary disease requiring elective intracoronary stenting (Study CS0747S-B-J107, Japanese clinical pharmacology study in patients with elective PCI) were set at 10 + 2.5 mg, 15 + 3.75 mg, and 20 + 5 mg, by taking account of the results of comparison of IPA in the foreign clinical pharmacology study in patients with atherosclerotic disease during the stable stage (Study H7T-EW-TAAD) and Japanese and foreign clinical studies in healthy adult subjects, as well as bleeding risks observed in the foreign ACS phase III study. As a result, IPA at 4 hours after the loading dose was 12.3% at prasugrel 10 mg, 20.9% at 15 mg, and 29.8% at 20 mg; and 8.43% at clopidogrel 300 mg (loading dose). IPA on Day 28 of treatment was 21.5% at prasugrel 2.5 mg, 32.1% at 3.75 mg, and 37.7% at 5 mg; and 21.7% at clopidogrel 75 mg (maintenance dose). Bleeding events classified as major bleeding or "clinically significant bleeding" was not observed in any of the groups. The only severe bleeding event observed was pericardial haemorrhage due to coronary artery perforation associated with PCI, which occurred in 1 patient (15 + 3.75 mg group) within 3 days of the study drug treatment. The incidence of haemorrhagic adverse events in any prasugrel groups was similar to that in the clopidogrel group. In Study H7T-EW-TAAD, IPA with concomitant use of prasugrel 60 + 10 mg with aspirin was 68.4% at 4 hours after prasugrel 60 mg administration and 62.2% on Day 7 of prasugrel 10 mg administration, showing higher levels than observed at the maximum dose (20 + 5 mg) in the Japanese clinical pharmacology study in patients with elective PCI. Based on the above results, the dosage regimen for ordinary subjects in the Japanese phase II dose-finding study was determined to be 20 + 3.75 mg and 20 + 5 mg, which were lower than the dosage levels approved in foreign countries, so as to allow prompt and sufficient reactivity as judged by the antiplatelet effect as the index, to expect a superior suppressive effect against cardiovascular events compared with clopidogrel, and to give consideration to the balance of benefits of treatment against bleeding risk.

PMDA considers as follows:

In the development of prasugrel for the treatment of ACS in Japan, no surrogate marker for the true efficacy endpoint, including IPA, has been established. However, given the difficulty of conducting clinical studies that evaluate the true endpoint, it is understandable that currently the dosage regimen has to be selected based on the pharmacodynamic markers that evaluate the antiplatelet effect. Therefore, the applicant's decision to select 20 + 3.75 mg and 20 + 5 mg, which are lower than the dose levels approved in foreign countries, as the dosage regimen for ordinary subjects in the Japanese phase II dose-finding study is acceptable because these dosage regimens, using IPA after administration of prasugrel

or clopidogrel in Japanese patients as the index, are expected to exhibit a more potent antiplatelet effect than clopidogrel with minimal bleeding risk in Japanese patients.

4.(iii).B.(3).2) Doses of prasugrel investigated in elderly patients and low body weight patients in Japanese phase II dose-finding study

PMDA asked the applicant to explain the rationale for selecting the study doses separately for elderly patients and low body weight patients in the Japanese phase II dose-finding study, the cut-off level of ≥75 years for elderly subjects and ≤50 kg for low body weight subjects.

The applicant responded as follows:
The results of clinical studies of clopidogrel, a similar drug, and of foreign clinical studies of prasugrel suggested a higher bleeding risk in elderly or low body weight subjects. In order to investigate the necessity for dose reduction in these patient groups, dose levels different from those in ordinary subjects were employed.

The cut off level for "elderly subjects" and for "low body weight subjects" were determined based on the following circumstances and findings.

- At the time when the Japanese clinical pharmacology study was conducted in patients with elective PCI, the comparator clopidogrel was not approved in Japan for coronary artery disease requiring elective intracoronary stenting. Therefore, a reference was made to the patient population for whom reduced dose of clopidogrel was indicated to suppress recurrent ischemic cerebrovascular disorder.

- According to the review report on clopidogrel relating to the suppression of recurrent ischemic cerebrovascular disorder (excluding cardioembolic stroke), bleeding events occurred with a high frequency in elderly patients aged ≥75 years and low body weight patients weighing ≤50 kg receiving clopidogrel 75 mg. Therefore, for prasugrel as well, in the Japanese clinical pharmacology study in patients with elective PCI, elderly patients aged ≥75 years and low body weight patients weighing ≤50 kg were excluded for safety. Also, prior to the conduct of the Japanese phase II dose-finding study, subjects in these patient groups had not been enrolled in Japanese clinical studies of prasugrel.

- In the foreign ACS phase III study, bleeding events were observed more frequently in the prasugrel group than in the clopidogrel among subjects aged ≥75 years (odds ratio [95% CI] of major bleeding in TIMI classification, 1.805 [1.205-2.704]).

- PPK analysis using the drug concentration data gathered in the foreign ACS phase III study showed that body weight had the greatest effect among subject characteristics on the pharmacokinetics of R-138727, the active metabolite of prasugrel, suggesting the increased blood R-138727 concentration in low body weight subjects. Also, age was found to affect the pharmacokinetics of R-138727, albeit to a lesser extent compared with body weight.

- In the foreign ACS phase III study, subjects weighing <60 kg showed a high bleeding risk, whereas, in the Japanese clinical pharmacology study in patients with elective PCI, there were no safety problems in subjects weighing >50 kg and <60 kg.

Based on the above, the cut-off levels were set at 75 years for age and 50 kg for body weight.

PMDA considers as follows:
Given the results of foreign clinical studies of prasugrel and information on clopidogrel suggesting an increased bleeding risk in elderly subjects and in low body weight subjects, it is appropriate that lower doses were investigated in elderly subjects and low body weight subjects, who are populations with high bleeding risk, in the Japanese phase II dose-finding study. Also, the cut-off levels for age and body weight were appropriately selected based on the information available at the start of the study. The cut-off level for body weight in the Japanese population was set at 50 kg instead of 60 kg, the cut-off level for dose reduction in the analysis of foreign clinical studies and in the approved dosage regimen in foreign countries, by taking account of the difference in physique between Japanese and foreign populations. PMDA also considers that this setting was appropriate.

PMDA asked the applicant to explain the reason for selecting 20 + 3.75 mg and 20 + 2.5 mg as the doses to be investigated in elderly or low body weight subjects in the Japanese phase II dose-finding study.

The applicant responded as follows:
The loading dose was determined based on the following findings and reasoning. In the Japanese clinical pharmacology study in patients with elective PCI, no clinically significant events were observed at any one of the investigated doses of 10 + 2.5 mg, 15 + 3.75 mg, and 20 + 5 mg. In the foreign ACS phase III study, although conducted using a loading dose (60 mg) different from that in the Japanese phase II dose-finding study, the incidence of bleeding events within 3 days post-dose was independent of the plasma concentration of the active metabolite R-138727. The loading dose is administered only once as the first dose and should be set at the dose that is expected to exhibit an appropriate suppressive effect against ischemic events. By taking account of the above, the loading dose was set at 20 mg for elderly or low body weight subjects as was the case with ordinary subjects. The maintenance dose was selected with the aim of maintaining more potent antiplatelet activity than clopidogrel while ensuring safety. Thus, in elderly or low body weight subjects, the high dose was set at 3.75 mg, is the same dose as the low dose for ordinary subjects, and the low dose was set at 2.5 mg, the dose that exhibited antiplatelet activity comparable to that of clopidogrel in the Japanese clinical pharmacology study in patients with elective PCI.

PMDA considers that the applicant appropriately selected the loading dose of 20 mg and the maintenance doses of 3.75 and 2.5 mg for elderly or low body weight subjects in the Japanese phase II dose-finding study.

4.(iii).B.(3).3) Safety of prasugrel in Japanese phase II dose-finding study and dosage regimens of prasugrel studied in Japanese phase III study in patients with ACS-PCI and in Japanese phase III study in patients with elective PCI

The applicant explained the safety of prasugrel in the Japanese phase II dose-finding study as follows:
In the prasugrel group, there were no major bleeding events or haemorrhagic adverse events leading to study discontinuation either in the ordinary subjects or in the elderly or low body weight subjects. Also, no clear difference in the incidence of minor bleeding events was observed among the prasugrel groups of different doses in ordinary subjects or in elderly or low body weight subjects. The incidence of all haemorrhagic adverse events (major, minor, "clinically significant," or "other bleeding") was higher in the high dose groups (20 + 5 mg in ordinary subjects, 20 + 3.75 mg in elderly or low body weight subjects) than in the low dose groups (20 + 3.75 mg in ordinary subjects, 20 + 2.5 mg in elderly or low body weight subjects) in any of the patient groups. However, the events that showed a tendency of increase in the number of affected subjects in the high dose groups were haemorrhage subcutaneous, epistaxis, blood urine present (urinary occult blood positive), haematuria, and subcutaneous haematoma, with no other events showing any tendency of increase in the number of affected subjects with the increase of prasugrel dose. Based on the above, the applicant determined that prasugrel was tolerated at 20 + 3.75 mg and 20 + 5 mg in ordinary subjects and at 20 + 2.5 mg and 20 + 3.75 mg in elderly or low body weight subjects.

PMDA considers the safety of the dosage regimens investigated for prasugrel in the Japanese phase II dose-finding study as follows:
Because of the small number of patients investigated, only limitated evaluation is possible for the occurrence of haemorrhagic adverse events in the Japanese phase II dose-finding study. Nevertheless, as far as the results of this clinical study is concerned, increased bleeding risk was not suggested in any of the prasugrel groups compared with the clopidogrel for any of the endpoints of haemorrhagic adverse events including all haemorrhagic adverse events and major, minor, and clinically significant bleeding. Thus, from the view point of safety, all dosage regimens investigated in the Japanese phase II dose-finding study are acceptable as those investigated in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI.

4.(iii).B.(3).4) Efficacy of prasugrel in Japanese phase II dose-finding study and dosage regimens for prasugrel in Japanese phase III study in patients with ACS-PCI and in Japanese phase III study in patients with elective PCI

PMDA asked the applicant to explain the reason why nonfatal myocardial infarction, an efficacy event, occurred in greater number of ordinary subjects in the prasugrel 20 + 5 mg group (13 subjects) than in the 20 + 3.75 mg group (3 subjects) in the Japanese phase II dose-finding study, taking into account the timing of onset of nonfatal myocardial infarction, etc.

The applicant responded as follows:

In the Japanese phase II dose-finding study, efficacy events in the prasugrel group included, among ordinary subjects, all-cause death (cardiovascular death due to ventricular tachycardia) in 1 subject and nonfatal myocardial infarction in 3 subjects in the 20 + 3.75 mg group, and all-cause death in 0 subjects and nonfatal myocardial infarction in 13 subjects in the 20 + 5 mg group; and, among elderly or low body weight subjects, all-cause death in none and nonfatal myocardial infarction in 2 subjects in the 20 + 2.5 mg group, and all-cause death in none, nonfatal myocardial infarction in 3 subjects, and myocardial ischaemia requiring readmission in 1 subject in the 20 + 3.75 mg group. Thus, nonfatal myocardial infarction accounted for the majority of efficacy events. An exploratory investigation was conducted by classifying the cases of nonfatal myocardial infarction according to the timing of onset within 48 hours after PCI (PCI-related myocardial infarction) and >48 hours after PCI (spontaneous myocardial infarction). The results showed that, among ordinary subjects, myocardial infarction occurred > 48 hours after PCI (Day 10 of treatment) only in 1 subject in the 20 + 5 mg group, and in all other cases, including 12 subjects in the 20 + 5 mg group and 3 subjects in the 20 + 3.75 mg group, myocardial infarction occurred within 48 hours after PCI. Nonfatal myocardial infarction observed in elderly or low body weight subjects was also related to PCI. From these results, the applicant considers that the occurrence of nonfatal myocardial infarction did not depend on the dose of prasugrel.

PMDA asked the applicant to explain the relationship between prasugrel-induced change in IPA and the preventive effect of prasugrel against cardiovascular events, taking account of the fact that IPA was used as the pharmacodynamic marker in selecting the dose of prasugrel. PMDA also asked the applicant to explain how the dosage regimens were selected in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI.

The applicant responded as follows:

It is reported that clopidogrel has poor prognosis in patients with ischemic heart disease having low pharmacodynamic response (Matetzky S et al., *Circ.* 2004;109:3171-5, Wiviott SD et al., *Circ.* 2004;109:3064-7; Barragan P et al., *Catheter Cardiovasc Interv.* 2003;59:295-302), suggesting that PRI obtained by measuring pharmacodynamic markers IPA and vasodilator-stimulated phosphoprotein (VASP) has a certain correlation with the occurrence of cardiovascular events. In the foreign ACS phase III study, the dose of prasugrel was set at a level to achieve a greater IPA than clopidogrel and, as a result, prasugrel was shown to be superior to clopidogrel in decreasing the incidence of cerebro-cardiovascular events. From this result, the applicant considers that there is a certain correlation between the change in IPA and the preventive effect of prasugrel against cardiovascular events, as was observed for clopidogrel.

In the Japanese phase II dose-finding study, the platelet-aggregation parameters (PRU and % inhibition measured using the VerifyNow system, PRI obtained by measuring VASP) investigated as pharmacodynamic markers were lower in the high dose group (20 + 5 mg in ordinary subjects, 20 + 3.75 mg in elderly or low body weight subjects) than in the low dose group (20 + 3.75 mg in ordinary subjects, 20 + 2.5 mg in elderly or low body weight subjects) both at 4 and 12 weeks post-dose and both in ordinary and in elderly or low body weight subjects. Also, compared with the clopidogrel groups, the parameter levels were lower in the 20 + 5 mg and 20 + 3.75 mg groups in ordinary subjects and in the 20 + 3.75 mg group in elderly or low body weight subjects, both at 4 and 12 weeks post-dose. Based on the above, the applicant considered that prasugrel 20 + 3.75 mg was sufficiently effective in inhibiting platelet aggregation compared with clopidogrel both in ordinary subjects and in elderly or low body weight subjects. In the Japanese clinical pharmacology study in patients with elective PCI, prasugrel 20 mg exhibited a more potent antiplatelet activity than clopidogrel 300 mg at 4 and 6 hours, and 1 day after the loading dose.

The Japanese phase II dose-finding study was a small-scale study insufficient for evaluating the relationship between cardiovascular events and pharmacodynamic markers. Nevertheless, changes in pharmacodynamic marker levels showed a correlation with prasugrel both in ordinary subjects and in elderly or low body weight subjects, and prasugrel at each maintenance dose exhibited antiplatelet activity exceeding that of clopidogrel 75 mg. Thus, taking account of the presence of a certain relationship between pharmacodynamic markers and cardiovascular events, the applicant decided to use pharmacodynamic markers as indices to assist the selection of the doses in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI.

Based on the above results, the applicant considered that, in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, the loading dose of 20 mg and the maintenance doses of 3.75 and 5 mg could be selected for ordinary subjects from the view point of efficacy. However, because of the sufficient antiplatelet effect observed in the 20 + 3.75 mg group as well as a higher incidence of other bleeding events in the 20 + 5 mg group, the applicant selected 20 + 3.75 mg by taking into consideration the target disease and the treatment duration in these phase III studies.

PMDA considers as follows:
The main objective of the Japanese phase II dose-finding study was to evaluate the safety of prasugrel, and the study was not conducted using a sufficiently large sample size to allow the evaluation of the preventive effect of prasugrel against cardiovascular event. However, among ordinary subjects in the study, nonfatal myocardial infarction, an efficacy event, occurred in 13 subjects of the prasugrel 20 + 5 mg group and in 3 subjects of the 20 + 3.75 mg group and, among them, 12 subjects in the 20 + 5 mg group and 3 subjects in the 20 + 3.75 mg group developed myocardial infarction ≤48 hours after PCI, indicating that the event was related to PCI, which suggests the possibility that prasugrel was not sufficiently effective at that time point. Therefore, whether or not the loading dose of 20 mg is appropriate as the approved dose in Japan should be carefully evaluated based on the results of the Japanese phase III study in patients with ACS-PCI and the Japanese phase III study in patients with elective PCI [see "4.(iii).B.(3).7) Loading dose"]. Although there are some concerns as discussed above, the incidences of cardiovascular events in the Japanese phase II dose-finding study did not suggest the possibility of markedly inferior efficacy of prasugrel compared with clopidogrel. Therefore, from the view point of efficacy, it is understandable that the applicant selected a loading dose of 20 mg and a maintenance dose of 3.75 mg as the doses investigated in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI.

As regards the antiplatelet effect assessed using pharmacodynamic markers as the indices, the correlation with the life expectancy, the true endpoint, is not completely clear. In particular, it remains unknown how much the antiplatelet effect is required to achieve the full preventive effect of prasugrel against cardiovascular events. Thus, the antiplatelet effect has to be positioned not as the main ground but as just a reference for the evaluation of the effectiveness of prasugrel. However, PMDA understands the applicant's opinion that it is desirable to treat ordinary subjects with a loading dose of 20 mg and a maintenance dose of 3.75 mg, including the comparison of antiplatelet activity with that of clopidogrel. Based on the above, PMDA considers it appropriate that the applicant selected a loading dose of 20 mg and a maintenance dose of 3.75 mg as the doses of prasugrel to be investigated in ordinary subjects in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, based on the results of clinical studies, etc., available at the time of planning the studies.

4.(iii).B.(3).5) Setting of the dose of prasugrel investigated in elderly or low body weight subjects in Japanese phase III study in patients with ACS-PCI and in Japanese phase III study in patients with elective PCI

Among elderly or lower body weight subjects in the Japanese phase II dose-finding study, there were a greater number of subjects with any haemorrhagic adverse events in the prasugrel 20 + 3.75 mg group (15 subjects) than in the clopidogrel group (10 subjects). Despite this fact, in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, the doses of prasugrel investigated in elderly or low body weight subjects were set at the same doses

investigated in ordinary subjects without any rule for dose reduction. PMDA asked the applicant to explain the reason for such settings.

The applicant responded as follows:
In the Japanese phase II dose-finding study, there were no major bleeding or haemorrhagic adverse events leading to study discontinuation in elderly or low body weight subjects receiving prasugrel, and no clear difference in the incidence of minor bleeding was observed between different doses of prasugrel. Among elderly or low body weight subjects, the number of subjects with "other bleeding events" was greater in the prasugrel group than in the clopidogrel group, whereas there were no events leading to study discontinuation, with all events being mild, non-serious, and reversible. Haemorrhagic adverse events that tended to increase in the number of affected subjects in the 20 + 3.75 mg group compared with the 20 + 2.5 mg were haemorrhage subcutaneous, epistaxis, blood urine present (urinary occult blood positive), haematuria, and subcutaneous haematoma, none of which were likely to pose any particular problems. Therefore, the applicant considered that the haemorrhagic adverse events observed in elderly or low body weight subjects receiving 20 + 3.75 mg were acceptable in the clinical use of prasugrel. From the investigation using pharmacodynamic markers as the indices in the Japanese phase II dose-finding study, prasugrel was shown to have a dose-dependent effect against platelet aggregation in both subject strata, and in elderly or low body weight subjects, the antiplatelet effect of 20 + 2.5 mg was similar to that observed with clopidogrel, and the effect of 20 + 3.75 mg was more potent than that of clopidogrel. As regards pharmacokinetics, there was no major difference in the plasma concentration of R-138727 (the active metabolite) after administration of prasugrel 3.75 mg between ordinary subjects and elderly or low body weight subjects.

Taking account of the above and of the seriousness of the target disease for which an occurrence of cardiovascular event may be fatal, the applicant determined that it was desirable to select 20 + 3.75 mg, the same dosage regimen investigated in ordinary subjects, as the dosage regimen investigated in elderly or low body weight subjects in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI.

PMDA considers as follows:
Due attention should be paid to the effect on occurrence of haemorrhagic adverse events in elderly or low body weight subjects, populations with higher risks for bleeding. The incidence of haemorrhagic adverse events in elderly or low body weight subjects observed in the Japanese phase II dose-finding study does not suggest any increase in clinically significant bleeding risk in the prasugrel groups studied compared with the clopidogrel group. Also, although there is a limitation to the dose setting using the antiplatelet effect as the index, it is justified that the applicant selected 20 + 3.75 mg as the dose expected to exhibit sufficient antiplatelet activity, based on the comparison with clopidogrel from the view point of the antiplatelet effect.

4.(iii).B.(3).6) Maintenance dose
PMDA asked the applicant to explain the appropriateness of the prasugrel maintenance dose of 3.75 mg in Japanese patients with ischemic heart disease who are to be managed with PCI, based on the results of efficacy and safety in the prasugrel group compared with the clopidogrel group in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI.

The applicant responded as follows:
In the Japanese phase III study in patients with ACS-PCI, the incidence of MACE1 from 4 days after the start of study drug treatment up to Week 24 of the treatment was 4.1% (28 of 680 subjects) in the prasugrel group and 3.7% (25 of 674 subjects) in the clopidogrel group (hazard ratio [95% CI], 1.12 [0.65-1.92]). Also, the incidence of MACE1 from 4 days after the start of study drug treatment up to Week 24 of the treatment (or up to 14 days after the completion or discontinuation of study drugtreatment if the treatment was completed or discontinued before Week 24) was 3.2% (22 of 680 subjects) and 3.1% (21 of 674 subjects), respectively, (hazard ratio [95% CI], 1.04 [0.57-1.90]). Furthermore, the incidence of major bleeding from 4 days after the start of study drug treatment up to 14 days after the study completion or discontinuation was 1.3% (9 of 680 subjects) and 0.9% (6 of 674 subjects), respectively, and the incidence of "major, minor, or clinically significant bleeding" during the same period was 5.6% (38 of 680 subjects) and 6.8% (46 of 674 subjects), respectively; the incidences in the

prasugrel group were not markedly higher than in the clopidogrel group. Thus, the applicant considers that the efficacy and safety of prasugrel 3.75 mg were comparable to those of clopidogrel in the Japanese phase III study in patients with ACS-PCI.

In the Japanese phase III study in patients with elective PCI, the incidence of MACE from 4 days after PCI up to Week 24 of study drug treatment was 0.8% (3 of 361 subjects) in the prasugrel group and 2.0% (7 of 348 subjects) in the clopidogrel group. The incidence of major bleeding from 4 days after PCI up to 14 days after the study completion or discontinuation was 0.0% (0 of 360 subjects) and 2.0% (7 of 348 subjects), respectively, and the incidence of "major, minor, or clinically significant bleeding" during the same period was 5.0% (18 of 360 subjects) and 5.2% (18 of 348 subjects), respectively; the incidence of bleeding in the prasugrel group was not markedly higher than in the clopidogrel group. Therefore, the applicant considers that the efficacy and safety of prasugrel 3.75 mg were at least comparable to those of clopidogrel in the Japanese phase III study in patients with elective PCI.

Because of the limited number of subjects investigated both in the Japanese phase III studies in patients with ACS-PCI and in patients with elective PCI, valid statistical evaluation based on the results on the primary endpoint is not be feasible . However, changes over time in platelet aggregating activity in both studies showed a higher antiplatelet effect in the prasugrel group than in the clopidogrel group at and after 4 weeks after the start of study drug treatment.

Based on the above, prasugrel 3.75 mg is expected to prevent ischemic events by a antiplatelet effect more potent than achieved by clopidogrel while maintaining a similar bleeding risk observed with clopidogrel, in Japanese patients with ischemic heart disease who are to be managed with PCI. Therefore, the applicant considers that it is appropriate to set the maintenance dose of prasugrel at 3.75 mg.

PMDA considers as follows:
Regarding the maintenance dose defined in the dosage regimen of prasugrel, 3.75 mg is appropriate since the results of the Japanese phase III study in patients with ACS-PCI, the Japanese phase III study in patients with elective PCI, and of the foreign ACS phase III study suggest clinically acceptable efficacy of prasugrel similar to that of clopidogrel. In the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, a greater antiplatelet effect was observed in the prasugrel group than in the clopidogrel group 4 weeks after the start of study drug treatment. However, it is unknown to what extent this difference is reflected clinically, namely, in the prevention of cardiovascular events, precluding the assertion of clinical significance from the difference in the antiplatelet effect.

4.(iii).B.(3).7) Loading dose
In the Japanese phase III study in patients with ACS-PCI, bleeding events, particularly those caused by external factors such as a complication of PCI, occurred more frequently within 3 days after the start of the study drug treatment in the prasugrel group than in the clopidogrel group. PMDA asked the applicant to explain the cause of the increased incidence and the possibility of overdosage of prasugrel (loading dose of 20 mg in particular).

The applicant responded as follows:
In the Japanese phase III study in patients with ACS-PCI, the occurrences of bleeding events within 3 days from the start of study drug treatment were as follows: the incidence of non-CABG-related major bleeding events was 0.6% (4 of 685 subjects) in the prasugrel group and 1.3% (9 of 678 subjects) in the clopidogrel group; the incidence of "clinically significant bleeding" was 0.7% (5 of 685 subjects) and 0.6% (4 of 678 subjects); the incidence of minor bleeding was 2.9% (20 of 685 subjects) and 1.2% (8 of 678 subjects); and the incidence of "other bleeding" was 21.5% (147 of 685 subjects) and 13.4% (91 of 678 subjects). Minor bleeding events and "other bleeding" events were mainly caused by extrinsic factors, with a tendency of higher incidences of PCI-induced bleeding events in particular (0.4% [3 of 685 subjects] and 0.9% [6 of 678 subjects] for major bleeding, 2.2% [15 of 685 subjects] and 0.6% [4 of 678 subjects] for minor bleeding, 0.1% [1 of 685 subjects] and 0.0% [0 of 678 subjects] for "clinically significant bleeding," 0.6% [4 of 685 subjects] and 0.6% [4 of 678 subjects] for "bleeding requiring study drug discontinuation," 8.0% [55 of 685 subjects] and 4.1% [28 of 678 subjects] for "other bleeding").

In subjects who received the loading dose in the Japanese phase III study in patients with elective PCI (269 subjects in the prasugrel group, 266 subjects in the clopidogrel group), the incidence of "other bleeding" events occurring from the loading dose up to 3 days after the start of study drug treatment was higher in the prasugrel group than in the clopidogrel group, with a majority of the events being associated with PCI, whereas the incidences of major bleeding, minor bleeding, "clinically significant bleeding," and "bleeding requiring study drug discontinuation" were similarly low in the prasugrel group and in the clopidogrel group.

Comparison of the puncture rate by blood vessel region during the initial revascularization procedure showed a higher rate of femoral artery puncture in patients with ACS (Japanese phase III study in patients with ACS-PCI) than in patients with elective PCI (Japanese phase III study in patients with elective PCI). In the Japanese phase III study in patients with ACS-PCI, which showed a higher incidence of PCI-associated bleeding events, bleeding events caused by puncturing the femoral artery tended to occur with a higher incidence than those caused by puncturing the radial artery with a smaller diameter both in the prasugrel group and the clopidogrel group, and the incidences of minor bleeding events and "other bleeding" events tended to be higher in the prasugrel group than the clopidogrel group when the femoral artery was punctured. These results suggested that the higher incidences of minor bleeding events and "other bleeding" events caused by extrinsic factors such as PCI within 3 days after the start of study drug treatment was partly due to the puncture of the blood vessel with a larger diameter because of a clinical emergency.

In the Japanese phase III study in patients with ACS-PCI, distribution of bleeding events was plotted to analyze the relationship of the events and the antiplatelet effect from 5 to 12 hours after the initial loading dose, using PRU as the index. The results did not show any consistent tendency between the extent of the antiplatelet effect and the onset of bleeding events.

Thus, a more potent preventive effect on efficacy events was observed in the prasugrel group than in the clopidogrel group in the Japanese phase III study in patients with ACS-PCI, from which the applicant considered that the 20-mg loading dose of prasugrel was not an overdosage, by taking account of the balance between benefits and clinical risk.

PMDA asked the applicant to justify the 20-mg loading dose of prasugrel in Japanese patients, by taking account of the above explanation of the applicant; the efficacy data in the prasugrel group compared with the clopidogrel group in the Japanese phase III study in patients with ACS-PCI; and the efficacy and safety results in the prasugrel group compared with the clopidogrel group in the Japanese phase III study in patients with elective PCI.

The applicant responded as follows:
In the Japanese phase III study in patients with ACS-PCI, the incidence of MACE1 ≤3 days after the start of the study drug treatment was lower in the prasugrel group (5.3%, 36 of 685 subjects) than in the comparator clopidogrel group (8.3%, 56 of 678 subjects); the hazard ratio [95% CI] was 0.626 [0.412-0.951]. In subjects receiving the 20-mg loading dose in the Japanese phase III study in patients with elective PCI, the incidence of MACE occurring ≤3 days after the start of study drug treatment was 2.6% (7 of 269 subjects) in the prasugrel group and 4.5% (12 of 266 subjects) in the clopidogrel group, suggesting efficacy similar to that observed in the Japanese phase III study in patients with ACS-PCI study. As regards the safety, the applicant considers that the safety comparable to that of clopidogrel is ensured for prasugrel when haemostatic measures are used appropriately at the time of PCI, as discussed above, according to the results of both the Japanese phase III study in patients with ACS-PCI and the Japanese phase III study in patients with elective PCI. Based on the above, the applicant considers that the loading dose of 20 mg was appropriate both for the Japanese phase III study in patients with ACS-PCI and for the Japanese phase III study in patients with elective PCI, taking account of the balance between clinical benefits and risks.

PMDA considers as follows:
The incidence of haemorrhagic adverse events is higher in the puncture of the femoral artery with a larger diameter than in the puncture of the radial artery with a smaller diameter. This is an invariant fact

regardless of the type of antithrombotic treatment used. Therefore, the following findings should be taken seriously: (i) in the Japanese phase III study in patients with ACS-PCI, the incidence of bleeding events within 3 days after the start of study drug treatment tended to be higher in the prasugrel group than in the clopidogrel group; and (ii) also in the Japanese phase III study in patients with elective PCI, the incidence of bleeding events within 3 days after the start of study drug treatment was higher in the prasugrel group than in the clopidogrel group, with bleeding caused by extrinsic factors such as that caused by PCI being higher in particular. These are important findings that should be provided as information requiring special caution in supplying prasugrel to clinical settings. However, in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, no significant difference was observed between the prasugrel group and the clopidogrel group in the incidence of either major bleeding or "clinically significant bleeding" within 3 days after the start of study drug treatment. From these results, the data have provided the evidence to support the clinical acceptability of prasugrel 20 mg as the loading dose from the view point of safety. Also, regarding the efficacy, the results of the Japanese phase III study in patients with ACS-PCI conducted using prasugrel hydrochloride 20 mg as the loading dose suggested that prasugrel was at least as effective as clopidogrel in Japanese patients with ACS who are to be managed with PCI. Consequently, the loading dose of 20 mg is clinically acceptable. Furthermore, the results of the Japanese phase III study in patients with elective PCI also suggested that prasugrel was at least as effective as clopidogrel and that the safety profile of prasugrel relative to that of clopidogrel is similar to that observed in the Japanese phase III study in patients with ACS-PCI. Therefore, PMDA considers that it is appropriate to set the loading dose of prasugrel at 20 mg in Japanese patients undergoing elective PCI.

4.(iii).B.(3).8) Timing of the loading dose administration

PMDA asked the applicant to explain the background of the revision of the Company Core Data Sheet (CCDS) and of the application for partial changes (revision of the labeling) in the approval in the US and Europe regarding the timing of loading dose administration, based on the efficacy and safety results of the foreign ACS phase III study and the foreign post-marketing clinical study investigating the relationship between the timing of the loading dose and the efficacy in NSTEMI patients scheduled to undergo CAG and PCI (Foreign Study ACCOAST).

The applicant responded as follows:

The measures taken in relation to the safety data in the Foreign Study ACCOAST were triggered by the recommendation to close the study to further enrollment by the independent data monitoring committee of the study in November 2012. The outline of the results of the Foreign Study ACCOAST was as shown below.

- The primary endpoint, incidence of the efficacy events (composite endpoint of cardiovascular death, myocardial infarction, cerebral infarction, emergency revascularization, and rescue treatment with a GPIIb/IIIa receptor antagonist) within 7 days after randomized assignment, was 10.0% (203 of 2037 subjects) in the group orally given prasugrel 30 mg both before CAG and at the time of PCI (pre-administration group) and 9.8% (195 of 1996 subjects) in the group orally given prasugrel 60 mg at the time of PCI only (non-pre-administration group) (hazard ratio [95% CI], 1.02 [0.84-1.25]), showing no significant difference between the treatment groups ($P = 0.812$, log-rank test).

- The secondary endpoint, incidence of the efficacy events (composite endpoint of cardiovascular death, myocardial infarction, and cerebral infarction) occurring ≤7 days after randomized assignment, was 6.4% (130 of 2037 subjects) in the pre-administration group and 6.4% (127 of 1996 subjects) in the non-pre-administration group (hazard ratio [95% CI], 1.00 [0.84-1.25]).

- The incidence of non-CABG-related major bleeding within 7 days after the start of study drug treatment was significantly higher in the pre-administration group (1.3%, 27 of 2037 subjects) than in the non-pre-administration group (0.5%, 9 of 1996 subjects) (hazard ratio [95% CI], 2.96 [1.39-6.28]; $P = 0.003$, log-rank test).

- The incidence of non-CABG-related major bleeding within 30 days after the start of study drug treatment was significantly higher in the pre-administration group (1.6%, 32 of 2037 subjects) than

in the non-pre-administration group (0.6%, 11 of 1996 subjects) (hazard ratio [95% CI], 2.86 [1.44-5.68]; $P = 0.002$, log-rank test).

- Among haemorrhagic adverse events occurring within 7 days after the start of study drug treatment, the incidence of fatal bleeding was 0.1% (1 of 2037 subjects) in the pre-administration group and 0.1% (1 of 1996 subjects) in the non-pre-administration group. The incidence of serious haemorrhagic adverse events was significantly higher in the pre-administration group (2.8%, 56 of 2037 subjects) than in the non-pre-administration group (1.0%, 20 of 1996 subjects) ($P < 0.001$, chi-square test).

- Among haemorrhagic adverse events occurring within 7 days after the start of study drug treatment in the sub-cohort who underwent PCI only, the incidence of major bleeding tended to be higher in the pre-administration group than in the non-pre-administration group as observed in the entire patient population, regardless of the use or non-use of a GPIIb/IIIa receptor antagonist or an antithrombin agent.[7] A similar tendency was observed in the subgroup with a dose of ≥100 mg of aspirin,[8] whereas in the subgroup with a dose of <100 mg of aspirin, the incidence was similar in the pre-administration group and in the non-pre-administration group.

In the Foreign Study ACCOAST, the bleeding risk was higher in the pre-administration group than in the non-pre-administration group. The incidence of major bleeding regardless of the relationship with CABG was 2.6% (52 of 2037 subjects) in the pre-administration group and 1.4% (27 of 1996 subjects) in the non-pre-administration group, and most of the major bleeding events observed were related to the procedure of PCI or CABG. Among major bleeding events, the incidence of vessel puncture site haemorrhage was the highest, being 0.4% (9 of 2037 subjects) in the pre-administration group and 0.1% (2 of 1996 subjects) in the non-pre-administration group. In patients who underwent PCI, bleeding events were observed during the early stage of the treatment, most of them occurring within 48 to 72 hours post-dose. Major bleeding occurred during the early stage of treatment with the study drug. The difference in incidence between the pre-administration group and the non-pre-administration group became evident within 48 hours post-dose, with the difference being maintained thereafter until 7 days post-dose.

Bleeding events within 30 days after the start of study drug treatment were compared between patients undergoing PCI in the Foreign Study ACCOAST and patients with UA or NSTEMI in the foreign ACS phase III study. The results showed that the incidence of haemorrhagic adverse events in the non-pre-administration group in the Foreign Study ACCOAST was consistently lower than in patients with UA or NSTEMI in the foreign ACS phase III study, although the comparison of the two studies were only possible to limited extent because of the study design difference.

Based on the above results, the applicant considered that the increased bleeding risk associated with prasugrel administration before CAG should be taken into account in determining the timing of administration, and therefore revised the CCDS and submitted the application for partial changes in the approval (revision of the labeling) in the US and Europe. The revision of the labeling is now in progress in both regions, and in Europe, will be completed before the end of December 2013.

PMDA asked the applicant to explain the effect of the timing of the loading dose on the efficacy and safety of prasugrel, based on the results in the prasugrel group and in the clopidogrel group by the timing of the loading dose (before, during, or after PCI), in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI.

The applicant responded as follows:
As regards the efficacy, the incidence of MACE1 from the start of study drug treatment up to Week 24 by the timing of the loading dose in the prasugrel group and in the clopidogrel group in the Japanese phase III study in patients with ACS-PCI was 10.6% (42 of 395 subjects) and 12.3% (48 of 390 subjects), respectively, before PCI; 3.9% (2 of 51 subjects) and 9.3% (5 of 54 subjects), respectively, during PCI;

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7 Before and during PCI, use of a GPIIb/IIIa receptor antagonist was allowed and an antithrombin agent was used as the standard treatment.

8 Aspirin was concomitantly administered with prasugrel from the loading dose.

and 7.8% (16 of 205 subjects) and 12.4% (24 of 193 subjects), respectively, after PCI. An additional analysis was performed on the incidence of MACE1 from the start of study drug treatment up to 3 days after, the period when the loading dose had a significant effect. The results showed that the timing of the loading dose did not cause any significant difference in the incidence.

In subjects who received the loading dose (before PCI) in the Japanese phase III study in patients with elective PCI, the incidence of MACE from the start of study drug treatment up to 24 weeks later was 4.1% (11 of 269 subjects) in the prasugrel group and 6.8% (18 of 266 subjects) in the clopidogrel group. An additional analysis on the incidence of MACE from the start of study drug treatment up to 3 days later did not show any significant difference either.

As regards the safety, the incidence of non-CABG-related major bleeding from the start of study drug treatment up to 14 days after the study completion or discontinuation in the prasugrel group and in the clopidogrel group in the Japanese phase III study in patients with ACS-PCI was 2.5% (10 of 395 subjects) and 2.6% (10 of 390 subjects), respectively, before PCI; 2.0% (1 of 51 subjects) and 5.6% (3 of 54 subjects), respectively, during PCI; and 1.0% (2 of 205 subjects) and 1.0% (2 of 193 subjects), respectively, after PCI, showing no significant difference. In contrast, the incidence of non-CABG-related "major, minor, and clinically significant bleeding" was 12.2% (48 of 395 subjects) and 12.1% (47 of 390 subjects), respectively, before PCI; 2.0% (1 of 51 subjects) and 13.0% (7 of 54 subjects), respectively, during PCI; and 8.3% (17 of 205 subjects) and 5.2% (10 of 193 subjects), respectively, after PCI, showing a higher tendency when the loading dose was administered before PCI than after PCI.

Among non-CABG-related major bleeding events and "major, minor, or clinically significant bleeding" events within 3 days after the start of study drug treatment, the incidence of bleeding events without extrinsic factors was not significantly different regardless of the timing of administering the loading dose either in the prasugrel group or in the clopidogrel group, and the incidence was comparable between the two treatment groups. The incidence of major bleeding events and "major, minor, and clinically significant bleeding" with extrinsic factors was higher when the loading dose was administered before PCI than during or after PCI, and higher in the prasugrel group than in the clopidogrel group. However, almost all of the "major, minor, or clinically significant bleeding" events are associated with the PCI procedure and can be alleviated by appropriate haemostatic treatment.

In the Japanese phase III study in patients with elective PCI, the incidence of non-CABG-related major bleeding from the start of study drug treatment up to 14 days after the study completion or discontinuation in subjects given the loading dose was 0% in the prasugrel group and 2.3% (6 of 266 subjects) in the clopidogrel group. The incidence of non-CABG-related "major, minor, or clinically significant bleeding" was 5.6% (15 of 269 subjects) in the prasugrel group and 4.9% (13 of 266 subjects) in the clopidogrel group, showing no significant difference.

PMDA asked the applicant to explain the reason for providing caution in the package insert draft in Japan regarding the timing of the loading dose of prasugrel in patients with ischemic heart disease eligible for PCI.

The applicant responded as follows:
Based on the results of the Japanese phase III studies, the loading dose in Japanese patients may be administered at any timing (before, during, or after PCI), depending on the clinical conditions of patients. In the Foreign Study ACCOAST, the pre-administration group received the loading dose of 60 mg in 2 divided doses of 30 mg each before and after CAG. Although this dosage regimen is different from the dosage regimen proposed in the application in Japan, the applicant considers it necessary to provide information in the package insert regarding the increased bleeding risk when the loading dose was administered before CAG.

Based on the above, the "Important Precaution" section includes the statement "When the loading dose is administered before coronary angiography, due caution should be paid to bleeding, particularly from the puncture site, because PCI-associated bleeding risk increases due to the antiplatelet effect of the product" to raise caution, together with the following rationale: "In a foreign clinical study in NSTEMI patients (the ACCOAST Study), a split loading dose of prasusgrel 30 mg given on average 4 hours prior

to coronary angiography followed by 30 mg at the time of PCI resulted in an increased risk of major peri-procedural bleeding with no additional benefit, compared to a standard loading dose of 60 mg given at the time of PCI."

PMDA considers as follows:
In the Foreign Study ACCOAST, the incidence of non-CABG-related haemorrhagic adverse events including major bleeding at 7 and 30 days after the start of sstudy drug treatment was higher in the pre-administration group than in the non-pre-administration group, whereas there was no difference in the efficacy between the two groups. This is important in evaluating the timing of the loading dose of prasugrel. Based on the results, it is not recommendable from the view point of both safety and efficacy to administer 30 mg of prasugrel before CAG and then another 30 mg at the time of PCI, as attempted in the Foreign Study ACCOAST. In Japan, however, both the loading dose and the maintenance dose are lower than those used in foreign countries, precluding the conclusion that similar efficacy and safety as observed in the Foreign Study ACCOAST would be achieved in Japanese patients as well. Also, the PCI-related clinical environment differs between Japan and foreign countries. Thus, in the Study ACCOAST, administration of a GPIIb/IIIa receptor antagonist, which is not approved in Japan, before or at the time of PCI may have affected the study results.

The Japanese phase III study in patients with ACS-PCI was not intended to compare the efficacy and safety of prasugrel among subjects receiving prasugrel at different timings, and the results by different administration timings were obtained from the subpopulation analysis on a small number of patients, which requires attention be paid to only a limited interpretation of the results being possible. Regarding the efficacy, however, a comparison with the clopidogrel group suggested that clinically acceptable efficacy was achieved regardless of the timing of the loading dose of prasugrel. Regarding the safety as well, no bleeding risk exceeding that of the clopidogrel group was shown at any timing of the loading dose. Based on the above, PMDA concludes that, as the timing of the loading dose of prasugrel in Japan, administration before, during, and after PCI is equally clinically acceptable. Also, the results of the Japanese phase III study in patients with elective PCI, albeit as reference data, showed that subjects receiving the loading dose did not show marked increasing trend of difference in the efficacy or safety compared with the clopidogrel group, supporting the acceptability of prasugrel administration before PCI.

Thus, the results of the Japanese phase III study in patients with ACS-PCI, although not conducted in a sufficiently large sample size, suggested clinically acceptable efficacy and safety regardless of whether the loading dose was administered before, during, or after PCI. As for clopidogrel, its loading dose is most commonly administered before PCI currently. Taking account of the above, together with the fact that prasugrel is a product administered in expectation of its antiplatelet effect as is the case with clopidogrel, PMDA considers that it is acceptable to determine the timing of the loading dose depending on the conditions of the patient at the clinical settings as is the case for clopidogrel, and that the timing of administration may be before, during, or after PCI as appropriate. However, it should be noted that, both in the prasugrel group and in the clopidogrel group, the incidence of "major, minor, or clinically significant bleeding" from the start of study drug treatment up to 14 days after the study completion or discontinuation was higher when the loading dose was administered before PCI than during or after PCI. This information should be provided in the package insert to raise caution, and information on the occurrence of haemorrhagic adverse events by the timing of starting prasugrel treatment should be collected via post-marketing surveillance. Also, it is a clinically important information that most of the bleeding events within 3 days after the start of study drug treatment were bleeding associated with extrinsic factors in patients receiving the loading dose before PCI. This information should be provided in the package insert to raise caution.

Furthermore, although it is not a report on prasugrel, there is a foreign report of a meta-analysis on clopidogrel, a drug used with the expectation of efficacy by the same mechanism of action as that of prasugrel, which states that there is little merit in administering the loading dose before PCI (Bellemain-Appaix A et al., *JAMA.* 2012;308:2507-16). It should be noted that active debate is ongoing internationally on the timing of loading dose of antiplatelet drugs such as prasugrel and clopidogrel in patients undergoing PCI, and it cannot be excluded that a more appropriate timing for prasugrel administration may possibly become clear in the future. Therefore, PMDA considers that it is necessary

to collect information after the market launch in Japan and to take appropriate measures also taking account of the international trend.

The necessity for setting the timing of prasugrel loading dose, the details of the caution statement in the package insert, and the details of collecting information related to safety by timing of the prasugrel administration via post-marketing surveillance will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(3).9) Cases in which the loading dose is unnecessary

Regarding the description in the package insert draft "the loading dose is not mandatory if prasugrel 3.75 mg has been administered for at least 3 days before PCI" in the "Precautions for Dosage and Administration" section of the proposed package insert, PMDA considers as follows:

Even when PCI is performed after administration of several maintenance doses instead of the loading dose, the antiplatelet effect available at the timing of PCI should be comparable to that achieved by the loading dose. The duration of the maintenance dose of prasugrel before PCI should be determined based on the pharmacokinetics and the pharmacodynamics of prasugrel, and it is not appropriate to determine, as proposed by the applicant, the duration of the maintenance dose before PCI as ≥3 days when PCI is performed without the loading dose, simply based on the platelet aggregation rate achieved by clopidogrel under a steady state. PMDA asked the applicant to explain the appropriateness of the above description in the package insert taking account of the foregoing discussion and the following: (i) in the Japanese phase III study in patients with elective PCI, it was required to administer prasugrel for 14 days before PCI if the loading dose was not administered; and (ii) the applicant explained that "if the antiplatelet effect has reached a steady state by the maintenance doses, the antiplatelet effect comparable to that achieved by the loading dose is available," but actually, the antiplatelet effect of prasugrel is considered to reach a steady state not on Day 3, but on Day 5 of the maintenance dose administration.

The applicant responded as follows:

In the phase I multiple dose study, the platelet aggregation rate almost reached a steady state on Day 5 of administration of prasugrel at both 2.5 and 5 mg. Therefore, the applicant considers that the platelet aggregation rate has reached a steady state also on Day 5 of administration of the 3.75-mg maintenance dose. In contrast, at the start of Japanese phase III study in patients with elective PCI, the time required for the antiplatelet effect of clopidogrel, the reference drug, to achieve steady state was unknown. In the Japanese clinical pharmacology study in patients with elective PCI, the antiplatelet effect of clopidogrel was similar between Day 14 and Day 28 of administration, when the loading dose had little or no effect anymore. From this, the applicant considered that the antiplatelet effect of clopidogrel reached a steady state on Day 14 at the latest regardless of the presence or absence of the loading dose. Therefore, in the Japanese phase III study in patients with elective PCI, if administration of prasugrel was started with the maintenance dose, PCI was to be performed after ≥14 days of treatment at the maintenance dose in line with the observation obtained with clopidogrel administration. The results of the comparison of efficacy between the cohort receiving the maintenance dose from the start of treatment and the cohort receiving the loading dose in the Japanese phase III study in patients with elective PCI were as follows: The incidence of MACE was 4.0% (4 of 101 subjects) in the prasugrel group and 6.6% (7 of 106 subjects) in the clopidogrel group in the cohort who started with the maintenance dose, and 4.1% (11 of 269 subjects) and 6.8% (18 of 266 subjects), respectively in the cohort receiving the loading dose, showing the results identical to that observed in the entire population, 4.1% (15 of 370 subjects) and 6.7% (25 of 372 subjects), respectively.

Changes over time in MPA and IPA following daily administration of the 3.75-mg maintenance dose (in combination with aspirin after a meal) in Japanese patients with coronary artery disease were simulated using a PPK/PD model. The results showed that 5-day administration was required for the antiplatelet effect to almost reach a steady state. However, it was predicted that if the maintenance dose had already been administered for 3 days, IPA exceeded roughly 80% of the pre-dose level under a steady state (after 14-day maintenance dose) at 2 hours after administration of the maintenance dose on Day 4, and that the level did not decrease below 70% of the pre-dose level under a steady state until before administration on Day 5. The treatment with prasugrel is assumed to start with the maintenance dose mostly in patients undergoing elective PCI, and it appears easy to achieve the minimum antiplatelet effect by taking prasugrel before the scheduled PCI. Since the antiplatelet effect reached the level close

to a steady state after administration of prasugrel 3.75 mg for at least 3 days, the applicant considered that the efficacy of prasugrel was unlikely to decrease if PCI was performed after 3 days of administration. Based on the above, the applicant determined that the description in the proposed package insert that "the loading dose is not mandatory if the product 3.75 mg has been administered for at least 3 days before PCI" was appropriate.

PMDA considers as follows:
To patients with ACS (UA, NSTEMI, STEMI), who mostly undergo PCI as soon as possible after the onset, it is appropriate to give the loading dose to promptly obtain the antiplatelet effect of prasugrel. In contrast, in patients with SA or OMI, PCI is performed in a planned manner and, consequently, it is possible to administer prasugrel for a longer duration from the disease onset to PCI than in patients with ACS. Therefore, treatment without the loading dose is a feasible option as a method for prasugrel treatment in patients with SA or OMI who are to be managed with PCI, and it is of significance to provide information in the package insert on the method to start prasugrel treatment with the maintenance dose. As described above, the duration of prasugrel treatment before PCI should be sufficiently long so that the antiplatelet effect available at the time of PCI is comparable to that achieved by the loading dose. In patients for whom the loading dose is deemed unnecessary, the clinical conditions do not require prompt PCI. Therefore, it is not necessarily important to shorten the duration of the maintenance dose of prasugrel before PCI. Rather, it is more important that PCI be performed at the time when the antiplatelet effect of prasugrel has reached a steady state by administration of the maintenance dose, i.e., when a sufficient antiplatelet effect is available. On the other hand, it is unnecessary to require 14-day duration of the maintenance dose as was the case in the Japanese phase III study in patients with elective PCI in which the duration was determined based on the rough information on the platelet aggregation rate in clopidogrel administration. It is more appropriate to determine the duration of the maintenance dose by referring to the results of the pharmacokinetics and pharmacodynamics of prasugrel. However, the antiplatelet effect of prasugrel after 3-day administration of the maintenance dose has not reached a steady state, precluding the assurance of sufficient efficacy. Therefore, PMDA considers that it is appropriate to set the duration of the maintenance dose in a conservative manner at 5 days during which the antiplatelet effect of prasugrel is expected to reach a steady state, as judged from the results of the phase I multiple dose study. The details of the information to be provided regarding the administration method when the loading dose is not administered in patients with SA or OMI who are to be managed with PCI will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4) Safety of prasugrel

4.(iii).B.(4).1) Bleeding risk

PMDA asked the applicant to explain the risk factors for bleeding in prasugrel administration, based on the incidences of haemorrhagic adverse events in the Japanese phase III studies.

The applicant responded as follows:
Tables 27 and 28 show the results of the incidences of bleeding events by presence/absence of extrinsic factors in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI.

Table 27. Incidences of bleeding events by presence/absence of extrinsic factors; Japanese phase III study in patients with ACS-PCI (Adapted from submitted data)

Bleeding events		Prasugrel group N = 685 n (%)	Clopidogrel group N = 678 n (%)
All bleeding events	Regardless of relation to CABG [a]	347 (50.7)	253 (37.3)
	Without extrinsic factors	115 (16.8)	103 (15.2)
Major bleeding	Regardless of relation to CABG [a]	20 (2.9)	21 (3.1)
	Without extrinsic factors	4 (0.6)	6 (0.9)
Major or minor bleeding	Regardless of relation to CABG [a]	48 (7.0)	36 (5.3)
	Without extrinsic factors	11 (1.6)	12 (1.8)
Minor bleeding	Regardless of relation to CABG [a]	29 (4.2)	16 (2.4)
	Without extrinsic factors	7 (1.0)	6 (0.9)
Major, minor, or clinically significant bleeding	Regardless of relation to CABG [a]	75 (10.9)	72 (10.6)
	Without extrinsic factors	34 (5.0)	45 (6.6)
Clinically significant bleeding	Regardless of relation to CABG [a]	29 (4.2)	39 (5.8)
	Without extrinsic factors	24 (3.5)	35 (5.2)
Bleeding leading to treatment discontinuation	Regardless of relation to CABG [a]	16 (2.3)	21 (3.1)
	Without extrinsic factors	9 (1.3)	12 (1.8)
Life-threatening bleeding	Regardless of relation to CABG [a]	7 (1.0)	11 (1.6)
	Without extrinsic factors	1 (0.1)	4 (0.6)
Fatal bleeding	Regardless of relation to CABG [a]	2 (0.3)	1 (0.1)
	Without extrinsic factors	1 (0.1)	1 (0.1)

a, Extrinsically caused bleeding events regardless of the relation to CABG

Table 28. Incidences of bleeding events by presence/absence of extrinsic factors; Japanese phase III study in patients with elective PCI (Adapted from submitted data)

Bleeding events		Prasugrel group N = 370 n (%)	Clopidogrel group N = 372 n (%)
All bleeding events	Regardless of relation to CABG [a]	143 (38.6)	129 (34.7)
	Without extrinsic factors	58 (15.7)	55 (14.8)
Major bleeding	Regardless of relation to CABG [a]	2 (0.5)	9 (2.4)
	Without extrinsic factors	0 (0.0)	6 (1.6)
Major or minor bleeding	Regardless of relation to CABG [a]	9 (2.4)	12 (3.2)
	Without extrinsic factors	2 (0.5)	7 (1.9)
Minor bleeding	Regardless of relation to CABG [a]	7 (1.9)	3 (0.8)
	Without extrinsic factors	2 (0.5)	1 (0.3)
Major, minor, or clinically significant bleeding	Regardless of relation to CABG [a]	23 (6.2)	24 (6.5)
	Without extrinsic factors	15 (4.1)	18 (4.8)
Clinically significant bleeding	Regardless of relation to CABG [a]	14 (3.8)	12 (3.2)
	Without extrinsic factors	13 (3.5)	11 (3.0)
Bleeding leading to treatment discontinuation	Regardless of relation to CABG [a]	9 (2.4)	9 (2.4)
	Without extrinsic factors	7 (1.9)	6 (1.6)

a, Extrinsically caused bleeding events regardless of the relation to CABG

In the Japanese phase III study in patients with ACS-PCI, there was no clear difference in the incidence of spontaneous bleeding events between the prasugrel group and the clopidogrel group, with the incidence in the prasugrel group tending to be comparable to or slightly lower than that in the clopidogrel group. As regards extrinsically caused bleeding events, the incidence of minor bleeding was higher in the prasugrel group compared with the clopidogrel group, and the incidence of the composite endpoint including minor bleeding events also tended to be higher in the prasugrel group than in the clopidogrel group.

In the Japanese phase III study in patients with elective PCI, there was no difference in the incidence of all bleeding events that occurred spontaneously without any extrinsic factors involved between the two treatment groups. Of the bleeding events caused by extrinsic factors, the incidence of minor bleeding

was slightly higher in the prasugrel group than in the clopidogrel group, whereas no clear difference was observed in the incidence of other bleeding events between the groups.

Based on the above, the applicant considered that, in patients with elective PCI, the incidence of bleeding events in the prasugrel group was comparable to that in the clopidogrel group regardless of presence or absence of extrinsic factors.

In the Japanese phase III study in patients with ACS-PCI, minor bleeding events with extrinsic factors occurred more frequently in the prasugrel group than in the clopidogrel group. Detailed examination of the occurrence showed that extrinsic factors causing minor bleeding included complications of CABG in 0.3% (2 of 685 of subjects), complications of PCI in 2.2% (15 of 685 subjects), and other in 0.7% (5 of 685 subjects); most of the minor bleeding events occurred during the perioperative period. In contrast, the incidence of bleeding events leading to treatment discontinuation was similar between the two groups (2.3% [16 of 685 subjects] in the prasugrel group, 3.1% [21 of 678 subjects] in the clopidogrel group). These results suggest that PCI-related bleeding events may increase with prasugrel, but continued administration is considered possible provided that sufficient measures such as appropriate haemostatic treatment are taken. Because of the higher incidence of PCI-related bleeding events, the incidence of bleeding events within 3 days after the start of study drug treatment by the site of puncture for PCI were investigated. The results showed that, in the Japanese phase III study in patients with ACS-PCI, the incidence of bleeding events in both groups was higher when the femoral artery (a blood vessel with a large diameter) was punctured than when the radial artery (a blood vessel with a small diameter) was punctured, and the incidences of minor bleeding and of "other bleedings" were higher in the prasugrel group than in the clopidogrel group when the puncture was performed in the femoral artery. In ACS patients, the puncture in the femoral artery was more frequent than in patients with elective PCI.

Based on the above, the applicant considered that the higher incidences of minor bleeding events and "other bleeding" events caused by extrinsic factors such as complications of PCI within 3 days after the start of study drug treatment was partly due to the puncture of the blood vessel with a larger diameter because of a clinical emergency.

Table 29 shows the incidences of "major or minor bleeding" events with and without extrinsic factors by major characteristics closely associated with subjects with "major or minor bleeding" in the prasugrel group.

Table 29. Odds ratio of non-CABG-related major or minor bleeding and of bleeding with extrinsic factors by patient characteristics (Adapted from submitted data)

Background risk factor	N_1	Non-CABG-related major or minor bleeding			
		All bleedings		Bleeding with extrinsic factors	
		N (%)	Odds ratio[a]	N (%)	Odds ratio[a]
All subjects	685	39 (5.7)	-	28 (4.1)	-
Concurrent hypertension	495	31 (6.3)	1.49	22 (4.4)	1.41
STEMI	340	25 (7.4)	1.80	17 (5.0)	1.56
Chest pain lasting ≥20 min	567	35 (6.2)	1.82	26 (4.6)	2.71
Pre-PCI administration	395	29 (7.3)	1.88	24 (6.1)	3.89
eGFR[b] <60	136	13 (9.6)	2.02	9 (6.6)	1.70
Female	149	15 (10.1)	2.35	13 (8.7)	3.12
≥65 years	347	28 (8.1)	2.48	21 (6.1)	2.92
≥75 years	165	18 (10.9)	2.70	13 (7.9)	2.73
≤50 kg	85	15 (17.6)	4.40	10 (11.8)	3.92

N_1, Number of subjects classified by background risk factor; n, Number of subjects with each bleeding event
a, Odds ratio in comparison with the alternative factor; b, Estimated glomerular filtration rate (mL/min/1.73 m^2)

For all non-CABG-related "major or minor bleeding" events (in 39 subjects), the risk factors with a high incidence of the events were "low body weight (≤50 kg)," "≥75 years of age," "females," and "≥65 years of age." These risk factors also showed a higher odds ratio of the incidence in comparison with the alternative factor, with the odds ratio being particularly high for low body weight (≤50 kg). Many (10 of 15 subjects) of the female subjects with major or minor bleeding had low body weight (≤50 kg).

Based on the above, the applicant considers that due care should be taken to protect against bleeding with extrinsic factors (e.g., appropriate haemostatic treatment) and that careful administration is required in patients with "low body weight" or "elderly," characteristics considered to be bleeding risk factors in prasugrel administration.

PMDA considers as follows:
It should be noted that the incidences of bleeding events in the prasugrel group in the Japanese phase III studies in patients with ACS-PCI and in patients with elective PCI were investigated in the limited number of subjects. However, the data are within the clinically acceptable range when compared with the results in the clopidogrel group. On the other hand, it should not be underestimated that the incidence of PCI-associated bleeding events was higher in the prasugrel group than in the clopidogrel group in the Japanese phase III study in patients with ACS-PCI, inasmuch as most of the bleeding events at the puncture site were clinically manageable. In the Japanese phase III study in patients with ACS-PCI, the clinical conditions required more urgent treatment compared with the Japanese phase III study in patients with elective PCI, which resulted in the more frequent selection of the femoral artery with the larger diameter rather than the brachial artery or the radial artery, as the puncture site. The applicant's explanation that this selection caused a tendency of the higher incidence of bleeding from the puncture site is clinically acceptable. However, even admitting this explanation and the minor extent of the bleeding observed in the clinical studies, the higher incidence of puncture site bleeding in the prasugrel group should be provided to the clinical practice as information suggesting a higher bleeding risk with prasugrel compared with the approved drug, and this should be included in the package insert to raise caution.

Also, in administering prasugrel to patients with low body weight (≤50 kg) or elderly patients (≥75 years), characteristics considered to be bleeding risk factors, it is necessary to thoroughly evaluate the appropriateness of selecting prasugrel as the antiplatelet agent in PCI, to administer prasugrel only to eligible patients, and to pay due attention to haemorrhagic adverse events throughout the treatment period. A caution statement in the package insert regarding the bleeding risk of prasugrel, as well as the appropriateness of administering prasugrel in patients with low body weight or elderly patients, characteristics considered to be bleeding risk factors, and the details of the caution for such patients in the package insert will be finalized, taking account of the comments raised in the Expert Discussion [see also the next section for administration in patients with low body weight].

4.(iii).B.(4).2) Administration in patients with body weight of ≤50 kg
In the Japanese phase III study in patients with ACS-PCI, the incidence of bleeding events without extrinsic factors from 4 days after the start of study drug treatment tended to be higher in the prasugrel group than in the clopidogrel group among subjects weighing ≤50 kg. Also, in the US, it is required to give consideration to administering 5 mg, a half of the usual dose (10 mg), in patients weighing <60 kg. Taking account of the above, PMDA asked the applicant to investigate the necessity of dose adjustment in patients weighing ≤50 kg and the necessity of providing caution in the package insert.

The applicant responded as follows:
In the US, body weight of <60 kg was identified as a factor that increases bleeding events, based on the results of the foreign ACS phase III study using a maintenance dose of 10 mg. In subjects weighing <60 kg, exposure to the active metabolite of prasugrel in blood increases, but when the maintenance dose was reduced from 10 mg to 5 mg, the range of the exposure to the active metabolite roughly overlapped with that observed in ordinary subjects receiving a 10-mg maintenance dose, which led to the requirement to give consideration to administering 5 mg in these patients. In Japan, as a maintenance dose to reduce bleeding risk, 3.75 mg was selected from the dose range of prasugrel expected to exhibit a superior effect to prevent cardiovascular events compared with clopidogrel. Table 30 shows the results of the subgroup evaluation of bleeding events by body weight (≤50 kg, >50 kg) in the Japanese phase III study in patients with ACS-PCI.

Table 30. Incidences of bleeding events by body weight: Japanese phase III study in patients with ACS-PCI (Adapted from submitted data)

Bleeding events		Prasugrel group[a] n/N_1 (%)	Clopidogrel group n/N_1 (%)
Major bleeding	All subjects	13/685 (1.9)	15/678 (2.2)
	≤50 kg	5/85 (5.9)	2/72 (2.8)
	>50 kg	8/599 (1.3)	13/606 (2.1)
Major or minor bleeding	All subjects	39/685 (5.7)	29/678 (4.3)
	≤50 kg	15/85 (17.6)	7/72 (9.7)
	>50 kg	24/599 (4.0)	22/606 (3.6)
Major, minor, or clinically significant bleeding	All subjects	66/685 (9.6)	65/678 (9.6)
	≤50 kg	19/85 (22.4)	13/72 (18.1)
	>50 kg	46/599 (7.7)	52/606 (8.6)

N_1, Number of subjects in each population; n, Number of subjects with each bleeding event; a, Body weight not measured in 1 subject in the prasugrel group

In the ≤50 kg subgroup, the incidence of "major or minor bleeding" was 17.6% (15 of 85 subjects) in the prasugrel group and 9.7% (7 of 72 subjects) in the clopidogrel group, and the incidence of "major, minor, or clinically significant bleeding" was 22.4% (19 of 85 subjects) in the prasugrel group and 18.1% (13 of 72 subjects) in the clopidogrel group, showing a tendency of a higher rate in the prasugrel group compared with the results in the entire population for safety analysis. Table 31 shows the incidence of "major, minor, or clinically significant bleeding," by the presence/absence of extrinsic factors and by the timing, in each patient subpopulation (body weight of ≤50 kg, >50 kg).

Table 31. Incidences of major, minor, or clinically significant bleeding by presence/absence of extrinsic factors and by body weight: Japanese phase III study in patients with ACS-PCI (Adapted from submitted data)

Bleeding events (major, minor, or clinically significant bleeding)		Prasugrel group[a] n/N_1 (%)	Clopidogrel group n/N_1 (%)
All		75/685 (10.9)	72/678 (10.6)
≤3 days, extrinsic	≤50 kg	8/85 (9.4)	4/72 (5.6)
	>50 kg	19/599 (3.2)	12/606 (2.0)
≤3 days, no extrinsic	≤50 kg	2/85 (2.4)	3/72 (4.2)
	>50 kg	3/599 (0.5)	5/606 (0.8)
≥4 days, extrinsic	≤50 kg	3/83 (3.6)	3/71 (4.2)
	>50 kg	11/596 (1.8)	10/603 (1.7)
≥4 days, no extrinsic	≤50 kg	7/83 (8.4)	4/71 (5.6)
	>50 kg	21/596 (3.5)	33/603 (5.5)

N_1, Number of subjects in each population; n, Number of subjects with bleeding event; a, Body weight not measured in 1 subject in prasugrel group

The incidence of bleeding events with extrinsic factors within 3 days after the start of study drug treatment was higher in the prasugrel group than in the clopidogrel group because of the higher incidence of PCI-associated bleeding events in the prasugrel group, whereas the incidence of bleeding events without extrinsic factors was comparable between the prasugrel group and the clopidogrel group. The incidence of bleeding events with extrinsic factors ≥4 days after the start of study drug treatment tended to be lower in the prasugrel group than in the clopidogrel group, whereas the incidence of bleeding events without extrinsic factors tended to be higher in the prasugrel group than in the clopidogrel group.

In the Japanese phase III study in patients with ACS-PCI, evaluation of the antiplatelet effect in subgroups by body weight (≤50 kg, >50 kg) showed that the effect was similar between subjects weighing ≤50 kg and subjects weighing >50 kg, showing no tendency of increase in low body weight subjects. Evaluation of platelet aggregation in subjects who had bleeding events (major, minor, or "clinically significant bleeding") did not show any correlation between the bleeding event and antiplatelet activity.

As a result of evaluation in subgroups by body weight (≤50 kg, >50 kg) in the Japanese phase III study in patients with elective PCI, the incidence of "major, minor, or clinically significant bleeding" was

5.4% (20 of 370 subjects) in the prasugrel group and 6.2% (23 of 372 subjects) in the clopidogrel group in all study subjects; 17.6% (6 of 34 subjects) and 5.0% (2 of 40 subjects), respectively, in subjects weighing ≤50 kg; and 4.2% (14 of 336 subjects) and 6.3% (21 of 332 subjects), respectively, in subjects weighing >50 kg, showing a tendency of a higher incidence in subjects weighing ≤50 kg in the prasugrel group. Among subjects weighing ≤50 kg in the prasugrel group, 2 subjects had minor bleeding and 4 subjects had "clinically significant bleeding."

In the Japanese phase III study in patients with ACS-PCI, the incidence of MACE1 during the first 24 weeks of study drug treatment was 17.6% (15 of 85 subjects) in the prasugrel group and 13.9% (10 of 72 subjects) in the clopidogrel group (hazard ratio [95% CI], 1.153 [0.515-2.581]) in subjects weighing ≤50 kg; and 8.0% (48 of 599 subjects) and 11.6% (70 of 606 subjects), respectively, (hazard ratio, 0.684 [0.474-0.989]) in subjects weighing >50 kg. In the Japanese phase III study in patients with elective PCI, the incidence was 0.0% (0 of 34 subjects) and 12.5% (5 of 40 subjects), respectively, in subjects weighing ≤50 kg; and 4.5% (15 of 336 subjects) and 6.0% (20 of 332 subjects), respectively, in subjects weighing >50 kg.

Based on the above, the applicant determined that prasugrel is useful provided that measures are taken against bleeding events caused by extrinsic factors including PCI since, in the Japanese phase III studies in patients with ACS-PCI and in patients with elective PCI, the incidences of MACE1 and MACE within 24 weeks of the study drug treatment in subjects weighing ≤50 kg were comparable between the prasugrel group and the clopidogrel group; therefore it was hardly necessary to adjust the dose of prasugrel in patients weighing ≤50 kg. However, bleeding events showed a tendency of increase in low body weight patients in the prasugrel group, and the events were considered to be due to extrinsic factors such as PCI performed during the early stage of treatment with prasugrel. Therefore, in administering prasugrel to low body weight patients, it is necessary to provide caution to administer prasugrel with sufficient care, including haemostatic treatment as necessary, to patients during the perioperative period depending on the clinical conditions of individual patients. Therefore, the applicant plans to require careful administration in "low body weight patients" in the package insert.

PMDA considers as follows:
In the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, there were only a very limited number of patients weighing ≤50 kg, precluding the accurate interpretation of the safety and efficacy results in this subpopulation. Notwithstanding this limitation, it is of significance to evaluate the clinical safety of prasugrel because the difference in the safety profile between prasugrel and the approved drug. In subjects weighing ≤50 kg in the Japanese phase III study in patients with ACS-PCI, major and minor bleeding events ≥4 days after the start of study drug treatment were observed only in the prasugrel group, while none of them occurred in the clopidogrel group. Also, among "major, minor, or clinically significant bleeding" events, severe bleeding was observed only in the prasugrel group. In addition, 1 subject with major bleeding in the prasugrel group died of brain stem haemorrhage. These observations should be taken into account in evaluating the bleeding risk associated with the 3.75-mg maintenance dose of prasugrel in patients weighing ≤50 kg. In the Japanese phase III study in patients with elective PCI, the incidence of "major, minor, or clinically significant bleeding" tended to be higher in subjects weighing ≤50 kg in the prasugrel group than in those in the clopidogrel group. This result also suggests the necessity to pay close attention to the possibility of high bleeding risk when prasugrel is administered to patients weighing ≤50 kg.

As regards efficacy, there is a limitation to the interpretation of data because of the small number of subjects in the subgroup. Nevertheless, given the tendency of a higher incidence of MACE1 in the prasugrel group compared with the clopidogrel group in subjects weighing ≤50 kg in the Japanese phase III study in patients with ACS-PCI, the possibility cannot be excluded that, in patients weighing ≤50 kg as compared with patients weighing >50 kg, the benefit-to-risk balance of prasugrel is inferior to that of clopidogrel. Particularly, in patients weighing ≤50 kg, the risk of bleeding events without extrinsic factors ≥4 days after the start of study drug treatment was higher in the prasugrel group than in the clopidogrel group. This raises concerns about the safety of long-term treatment with prasugrel in this patient group, and it cannot be ruled out that the usefulness of the prasugrel in these patients is possibly lower than that observed in other patients.

Taking account of the above conclusion and of the requirement in the US to give consideration to administering 5 mg, a half of the usual dose (10 mg), to patients weighing <60 kg, PMDA considers possible dose reduction in Japanese patients weighing ≤50 kg, as follows:
In the Japanese phase II dose-finding study, the number of subjects with all haemorrhagic adverse events in elderly or low body weight subjects was larger in the prasugrel 20 + 3.75 mg group (15 subjects) than in the clopidogrel group (10 subjects). By considering the seriousness of the target disease, which may possibly result in fatal due to onset of cardiovascular event, 20 + 3.75 mg was selected as a dosage regimen to be investigated in elderly or low body weight subjects in the Japanese phase III studies in patients with ACS-PCI and in patients with elective PCI. However, the incidence of MACE1 in the Japanese phase II dose-finding study was 4.0% (4 of 101 subjects) in the prasugrel 20 + 3.75 mg group, 13.0% (13 of 100 subjects) in the prasugrel 20 + 5 mg group, and 4.0% (4 of 101 subjects) in the clopidogrel group in ordinary subjects; and 5.4% (2 of 37 subjects) in the prasugrel 20 + 2.5 mg group, 10.8% (4 of 37 subjects) in the prasugrel 20 + 3.75 mg group, and 11.1% (4 of 36 subjects) in the clopidogrel group in elderly or low body weight subjects, showing no clear tendency of lower efficacy of 20 + 2.5 mg compared with 20 + 3.75 mg in elderly or low body weight subjects although the data were obtained from a limited number of subjects. Also, in elderly or low body weight subjects, a more potent antiplatelet effect was observed in the 20 + 3.75 mg group compared with the clopidogrel group, whereas the effect in the 20 + 2.5 mg group was comparable to that in the clopidogrel group. In addition, the results of the Japanese phase II dose-finding study suggested that prasugrel 20 + 3.75 mg had a clinically acceptable safety profile in elderly or low body weight subjects. Based on the above, PMDA considers that it is essential to carefully evaluate the appropriateness of using prasugrel as an antiplatelet drug before administering prasugrel to patients weighing ≤50 kg, and that, if prasugrel is selected, it is worthy to give consideration to administering 20 + 2.5 mg, the dose not investigated in the Japanese phase III studies, depending on patients upon comprehensive evaluation of bleeding risk factors such as age and renal function and of the severity of the risk of vascular events. The appropriateness of administering prasugrel to patients weighing ≤50 kg, the appropriateness of dose reduction to 20 + 2.5 mg as one of the treatment options in this patient group, the details of the caution statement including bleeding risk in the package insert, and the details of collecting information on administration in low body weight patients after the market launch will be further investigated taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).3) Administration in patients aged ≥75 years

In both the Japanese phase III study in patients with ACS-PCI and the Japanese phase III study in patients with elective PCI, the incidences of some endpoints related to haemorrhagic adverse events, such as "major, minor, or clinically significant bleeding," tended to be slightly higher in the subgroup ≥75 years of age compared with the subgroup <75 years of age or the entire study population. Also, in foreign countries, it is not recommended to administer prasugrel to patients aged ≥75 years, except for patients with a high risk (past history of diabetes mellitus or myocardial infarction). Based on the above, PMDA asked the applicant to explain the appropriateness of administering prasugrel to patients aged ≥75 years, from the view point of efficacy and safety.

The applicant responded as follows:
In the Japanese phase III study in patients with ACS-PCI, efficacy was evaluated in subgroups by age (<75 years, ≥75 years). The incidence of MACE1, the primary endpoint, was 8.5% (44 of 520 subjects) in the prasugrel group and 11.3% (60 of 530 subjects) in the clopidogrel group in the subpopulation aged <75 years, and 12.1% (20 of 165 subjects) and 13.5% (20 of 148 subjects), respectively, in the subpopulation aged ≥75 years, with the point estimate of a hazard ratio of less than 1 in the subpopulation aged ≥75 years as well, showing a similar tendency as in the entire population. Also, in the Japanese phase III study in patients with elective PCI, the incidence of MACE was 3.2% (9 of 284 subjects) and 6.5% (18 of 279 subjects), respectively, in the subpopulation aged<75 years, and 7.0% (6 of 86 subjects) and 7.5% (7 of 93 subjects), respectively, in the subpopulation aged ≥75 years, showing a similar tendency in the subpopulation aged ≥75 years as in the entire population.

As regards safety, the incidence of non-CABG-related bleeding events in the prasugrel group in the Japanese phase III study in patients with ACS-PCI was as follows: major bleeding, 1.3% (7 of 520 subjects) in subjects aged <75 years and 3.6% (6 of 165 subjects) in subjects aged ≥75 years; "major, minor, or clinically significant bleeding," 7.5% (39 of 520 subjects) and 16.4% (27 of 165 subjects);

"clinically significant bleeding," 3.8% (20 of 520 subjects) and 5.5% (9 of 165 subjects); and "other bleeding," 40.6% (211 of 520 subjects) and 52.7% (87 of 165 subjects) with all bleeding events showing a tendency of increase in subjects aged ≥75 years, and the incidence was comparable to that observed in the same age subgroups in the clopidogrel group.

In the Japanese phase III study in patients with elective PCI, the incidence of bleeding events in the prasugrel group by age group (<75years, ≥75 years) was as follows: major bleeding, none; minor bleeding, 1.4% (4 of 284 subjects) in subjects aged <75 years and 2.3% (2 of 86 subjects) in subjects aged ≥75 years; "major, minor, or clinically significant bleeding," 4.6% (13 of 284 subjects) and 8.1% (7 of 86 subjects); "clinically significant bleeding," 3.2% (9 of 284 subjects) and 5.8% (5 of 86 subjects); and "other bleeding," 31.7% (90 of 284 subjects) and 46.5% (40 of 86 subjects). All bleeding events showing a tendency of increase in subjects aged ≥75 years, and the incidence was comparable to that observed in the same age subgroups in the clopidogrel group.

In the Japanese phase III study in patients with ACS-PCI, bleeding events occurred more frequently within 3 days after the start of study drug treatment in the prasugrel group than in the clopidogrel group. In particular, minor bleeding occurred with a higher incidence, and in subjects aged ≥75 years it also showed a high incidence. Therefore, the incidence of bleeding events within 3 days after the start of study drug treatment by the presence or absence of extrinsic factors was investigated. The incidence of minor bleeding without extrinsic factors was comparable between in the prasugrel group and in the clopidogrel group, both in subjects aged <75 years and in those aged ≥75 years, whereas the incidence of minor bleeding with extrinsic factors tended to be higher in the prasugrel group than in the clopidogrel group in both age subgroups (≥75 years of age; 4.8% [8 of 165 subjects] in the prasugrel group, 0.0% [0 of 148 subjects] in the clopidogrel group). In contrast, the incidence of minor bleeding from 4 days after the start of study drug treatment until 14 days after the study completion or discontinuation was similar between in the prasugrel group and in the clopidogrel group in both subjects aged <75 years and aged ≥75 years irrespective of presence or absence of extrinsic factors.

In the foreign ACS phase III study, the incidence of "major or minor bleeding" was higher in the elderly subjects (≥75 years) of the prasugrel group (8.98% [80 of 891 subjects]) than in the non-elderly subjects (<75 years) of the same group (3.81% [223 of 5850 subjects]). A similar tendency was observed in the clopidogrel group as well (6.94% in subjects aged ≥75 years, 2.90% in subjects aged <75 years), while the hazard ratio of "major or minor bleeding" in the prasugrel group compared with the clopidogrel group was similar between subjects aged <75 years and subjects aged ≥75 years (1.320 and 1.346, respectively). In the subpopulation aged ≥75 years, the hazard ratio of the incidence of individual bleeding events (major bleeding, minor bleeding) in the prasugrel group compared with the clopidogrel group was similar (hazard ratio: 1.359 for major bleeding, 1.385 for minor bleeding). Similarly, in the Japanese phase III study in patients with ACS-PCI, the incidence of "major or minor bleeding" in the prasugrel group was higher in subjects aged ≥75 years than in subjects aged <75 years (10.9% [18 of 165 subjects] in subjects aged ≥75 years, 4.0% [21 of 520 subjects] in subjects aged <75 years). This tendency was observed in the clopidogrel group as well, which was attributable to the higher incidence of minor bleeding in subjects aged ≥75 years in the prasugrel group than in the clopidogrel group, although the incidence of major bleeding was comparable between the two groups. Based on the above, the applicant considers that the dosage regimen of 20 + 3.75 mg for prasugrel used in the Japanese clinical studies is as effective as the regimen used in foreign countries, while reducing the bleeding risks encountered in foreign countries.

The above results suggested the usefulness of prasugrel compared with clopidogrel in subjects aged ≥75 years as well. However, the incidence of minor bleeding with extrinsic factors, PCI-associated minor bleeding in particular, was higher in the prasugrel group than in the clopidogrel group, suggesting the necessity of close monitoring of possible bleeding sites, including the puncture site, in performing PCI in ACS patients. Also, since frequency of bleeding events generally increases in elderly patients, prasugrel should be administered carefully while monitoring the clinical conditions of patients and, if a high bleeding risk is suspected or any abnormalities are observed, discontinuation of the administration should be considered.

PMDA considers as follows:

The Japanese phase III study in patients with ACS-PCI was not designed to allow validation of the superiority of prasugrel in efficacy to clopidogrel. Therefore, the applicant should not claim that prasugrel has a greater usefulness than clopidogrel in Japanese patients based on the results of the study. Nonetheless, in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, the efficacy evaluation by age group shows the possibility that prasugrel is as effective as clopidogrel not only in patients aged <75 years but also in patients aged ≥75 years. However, both studies show that the incidence of bleeding events in patients aged ≥75 years tends to be higher than in patients aged <75 years as was the case in the foreign ACS phase III study, requiring particular caution against bleeding risk caused by prasugrel in patients aged ≥75 years. The results of the Japanese phase III study in patients with ACS-PCI suggest that, in patients aged ≥75 years, the incidence of minor bleeding is higher in the prasugrel group than in the clopidogrel group. Given the higher incidence of minor bleeding with extrinsic factors (PCI-associated minor bleeding in particular) in patients aged ≥75 years, it is necessary to carefully determine whether to use prasugrel in patients aged ≥75 years and to closely monitor for PCI-associated bleeding during and after PCI. Appropriate caution against these points should be provided in the package insert, etc. The appropriateness of administering prasugrel to patients aged ≥75 years and the details of the caution statement in the package insert will be further investigated taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).4) Administration in patients with renal impairment

PMDA asked the applicant to explain the efficacy and safety of prasugrel by renal function (eGFR) in the Japanese phase III studies and to discuss the appropriateness of administering prasugrel to patients with mild to moderate renal impairment, taking account of the results of the foreign ACS phase III study and also the rules stipulated in the labeling in the US. PMDA also asked the applicant to explain the appropriateness of requiring careful administration in patients with severe renal impairment, taking account of non-inclusion of this patient group in the Japanese clinical studies.

The applicant responded as follows:

As regards the efficacy of prasugrel in patients by renal function in the Japanese phase III study in patients with ACS-PCI, the point estimate of the hazard ratio of the primary endpoint was approximately 1 or less in all subgroups by eGFR adjusted for body surface area (mL/min/1.73 m^2), including subgroups with eGFR of ≥90, ≥60 and <90, and ≥30 and <60, except for subgroups with eGFR of ≥15 and <30 who accounted for an extremely small number of the patients studied. These results suggested that prasugrel was similarly effective in each subgroup as in the entire population in the prasugrel group. Similarly, in the Japanese phase III study in patients with elective PCI, there was no subgroup with markedly inferior efficacy, which suggests the efficacy of prasugrel in all subgroups.

In the Japanese phase III study in patients with ACS-PCI, the incidence of bleeding events in subjects of the prasugrel group by renal function (normal [eGFR ≥90], mild impairment [eGFR ≥60 and <90], moderate impairment [eGFR ≥30 and <60], severe impairment [eGFR ≥15 and <30]) was as follows: major bleeding 0.0% (0 of 138 subjects) in subjects with normal function, 2.3% (8 of 349 subjects) in subjects with mild impairment, 3.9% (5 of 128 subjects) in subjects with moderate impairment, and 0.0% (0 of 8 subjects) in subjects with severe impairment; “major or minor bleeding” 3.6% (5 of 138 subjects), 5.2% (18 of 349 subjects), 10.2% (13 of 128 subjects), and 0.0% (0 of 8 subjects); “major, minor, or clinically significant bleeding” 4.3% (6 of 138 subjects), 8.6% (30 of 349 subjects), 20.3% (26 of 128 subjects), and 0.0% (0 of 8 subjects), respectively; minor bleeding 3.6% (5 of 138 subjects), 3.2% (11 of 349 subjects), 6.3% (8 of 128 subjects), and 0.0% (0 of 8 subjects); “clinically significant bleeding” 1.4% (2 of 138 subjects), 3.4% (12 of 349 subjects), 10.2% (13 of 128 subjects), and 0.0% (0 of 8 subjects); and “other bleeding” 40.6% (56 of 138 subjects), 43.6% (152 of 349 subjects), 46.1% (59 of 12 8 subjects), and 50.0% (4 of 8 subjects). In the prasugrel group, the incidence of bleeding events in subjects with mild renal impairment tended to be higher than in subjects with normal renal function. This tendency was similar to that observed in the clopidogrel group. In subjects with moderate renal impairment, the incidence of bleeding events was still higher and tended to be higher than that observed in the clopidogrel group.

In the Japanese phase III study in patients with elective PCI, the incidence of bleeding events in subjects of the prasugrel group by renal function (normal [eGFR ≥90], mild impairment [eGFR ≥60 and <90], moderate impairment [eGFR ≥30 and <60]) was as follows: major bleeding, none; minor bleeding 0.0%

(0 of 38 subjects) in subjects with normal function, 2.1% (4 of 190 subjects) in subjects with mild impairment, and 0.0% (0 of 72 subjects) in subjects with moderate impairment; "major, minor, or clinically significant bleeding" 5.3% (2 of 38 subjects), 6.8% (13 of 190 subjects), and 4.2% (3 of 72 subjects); "clinically significant bleeding" 5.3% (2 of 38 subjects), 4.7% (9 of 190 subjects), and 4.2% (3 of 72 subjects); and "other bleeding" 42.1% (16 of 38 subjects), 34.2% (65 of 190 subjects), and 37.5% (27 of 72 subjects). Thus, the bleeding events in the prasugrel group did not increase with the decrease in renal function, with the incidence being comparable to or lower than that in the clopidogrel group.

eGFR is adjusted for the Japanese subjects with a standard body type and, as a result, subjects with a body type significantly deviating from the standard body type, such as elderly subjects with low muscle content, are classified in the subgroup with more impaired renal function than in reality. Also, low body weight and elderly age are considered to be factors that induce bleeding events, and in the Japanese phase III study in patients with ACS-PCI, a larger number of elderly and low body weight subjects were enrolled in the prasugrel group than in the clopidogrel group or in the Japanese phase III study in patients with elective PCI, causing between-group imbalance. Also, in the Japanese phase III study in patients with ACS-PCI, 80.5% (103 of 128 subjects) of patients with moderate renal impairment were elderly or low body weight subjects, and they accounted for a majority of patients with moderate renal impairment who had bleeding events (major bleeding in 4 of 5 subjects, minor bleeding in 7 of 8 subjects, "clinically significant bleeding" in 9 of 13 subjects).

The frequency of "major or minor bleeding" in patients with renal impairment was evaluated in the foreign ACS phase III study although the dose of prasugrel used in this study was different from that in the Japanese phase III studies. In the subpopulation with creatinine clearance (CL_{CR} [mL/min]) of >60, the incidence of "major or minor bleeding" was similar between the prasugrel group and the clopidogrel group. In the subpopulation with CL_{CR} of ≥30 and ≤60, the incidence was slightly higher in the prasugrel group. The incidence of MACE by renal function, was 8.61% (515 of 5982 subjects) for CL_{CR}>60, 13.81% (92 of 666 subjects) for CL_{CR} ≥30 and ≤60, and 21.57% (11 of 51 subjects) for CL_{CR} <30 in the prasugrel group; and 10.67% (630 of 5907 subjects) for CL_{CR} >60, 14.72% (106 of 720 subjects) for CL_{CR} ≥30 and ≤60, and 38.89% (21 of 54 subjects) for CL_{CR} <30 in the clopidogrel group. In the subpopulation with CL_{CR} of ≥30 and ≤60 or CL_{CR} of <30, the hazard ratio of MACE was <1. The labeling in the US includes patients with moderate and severe renal impairment in the "Warnings and Precautions" as examples of "patients with bleeding tendency," but provides instructions to administer prasugrel without dose adjustment, by taking account of the above benefit-risk balance.

In a foreign clinical pharmacology study (Study H7T-EW-TABW), pharmacokinetic parameters and MPA of prasugrel following a single oral administration in patients with moderate renal impairment (CL_{CR}, ≥30 and ≤50) were similar to those observed in healthy subjects. In another clinical pharmacology study (Study H7T-EW-TACJ), MPA following a single oral administration of prasugrel in patients with end-stage renal impairment (hemodialysis ≥3 months) was similar to that in healthy adult subjects, whereas decreases in AUC_{last} and C_{max} were suspected of being caused by uremia were observed.

Thus, in the prasugrel group in the Japanese phase III study in patients with ACS-PCI, the incidence of efficacy events in patients with mild or moderate renal impairment was comparable to that observed in the entire study population. Similarly, in the Japanese phase III study in patients with elective PCI, there was no subgroup that showed a markedly inferior efficacy. These results suggested that, in both studies, the efficacy in patients with renal impairment is similar to that in the entire study population. In the Japanese phase III study in patients with ACS-PCI, the incidence of bleeding events in patients with moderate renal impairment tended to be higher compared with subjects with normal renal function and subjects in the clopidogrel group. However, since no significant difference was observed in the platelet aggregation and most of the subjects with bleeding events were elderly or had low body weight, moderate renal impairment per se was unlikely to affect the efficacy or safety of prasugrel. Therefore, it is appropriate, from the point of efficacy and safety, to administer prasugrel to Japanese patients with mild to moderate renal impairment.

In addition, when the efficacy and safety in Japanese patients with severe renal impairment are estimated from the data on the safety and efficacy in Japanese patients with moderate renal impairment and the results of the foreign ACS phase III study, the benefits of prasugrel seems to outweigh the risk in Japanese patients with severe renal impairment. However, since patients with severe renal impairment were excluded from clinical studies in the developmental stage, it is necessary to require careful administration in this patient population to ensure safety.

PMDA considers as follows:
In the Japanese phase III study in patients with ACS-PCI, all bleeding risks, i.e., the risks of major, minor, or "clinically significant" bleeding, in patients with eGFR of ≥30 and <60 were higher in the prasugrel group than in the clopidogrel group and in patients with eGFR of ≥60, although the results were obtained by a post-hoc explanatory analysis of data from a limited number of patients. This should not be made light of. As the applicant discussed, it could be that the incidence of bleeding increased because of a higher proportion of patients with advanced age and low body weight, risk factors for bleeding, in the population with low eGFR level. However, it cannot be ruled out that prasugrel hydrochloride administration may increase bleeding risk with reduced renal function. As pointed out by the applicant, the imbalance in the patient characteristics in the Japanese phase III study in patients with ACS-PCI might have affected the between-group comparison of safety. It is considered that, in actual clinical practice in Japan, several patients with ischemic heart disease requiring PCI have 2 or more of the risk factors of advanced age, low body weight,or eGFR level of ≥30 and <60 in combination. For such patients, the appropriateness of administering prasugrel should be evaluated in a comprehensive manner, taking account of the benefit-to-risk balance of each drug in individual cases. Even if it is considered appropriate to administer prasugrel, it should be fully recognized that there is an increased risk of bleeding in such patients. It was observed that platelet aggregation in patients with end-stage renal impairment and in patients with moderate renal impairment after prasugrel administration was similar to that in healthy adult subjects, and that pharmacokinetic parameters were similar between patients with moderate renal impairment and healthy adult subjects. However, these findings do not necessarily mean that the bleeding risk in patients with renal impairment receiving prasugrel is similar to that in healthy adult subjects. In the Japanese phase III study in patients with elective PCI, still fewer patients were enrolled than in Japanese phase III study in patients with ACS-PCI, precluding a discussion on the effect of renal impairment on the bleeding risk of prasugrel from the results of this study.

It should be noted that bleeding risk is known to generally increase with the severity of renal impairment of the patients, and that, in fact in the foreign ACS phase III study, haemorrhagic adverse events occurred more frequently in patients with moderate renal impairment than in patients with normal renal function or mild renal impairment. Although the Japanese phase III study in patients with ACS-PCI was conducted using a dosage regimen different from that in the foreign ACS phase III study, the results obtained from Japanese patients with reduced renal function possibly suggest the increased bleeding risk in prasugrel.

Based on the above, PMDA considers that it is appropriate to administer prasugrel to Japanese patients with mild to moderate renal impairment from the view point of efficacy and safety. However, in the clinical use of, attention should be paid to the possible increase in the bleeding risk depending on the severity of renal impairment, and it is critical to collect post-marketing information on the bleeding risk caused by prasugrel in patients with renal impairment.

Since patients with severe renal impairment were excluded from clinical studies during the developmental stage, safety of prasugrel in this patient group is unclear. However, given the possibility of increased bleeding risk depending on the severity of renal impairment as suggested by Japanese and foreign studies on bleeding risk in patients with different severities of renal impairment, it is inferred that bleeding risk further increases in patients with severe renal impairment. However, the limited information available from Japanese clinical studies does not show any clear tendency of increase in the bleeding risk in patients with renal impairment following the administration of prasugrel compared with clopidogrel. Currently, therefore, PMDA considers that it is appropriate to require careful administration in patients with severe renal impairment as is the case with clopidogrel in Japan. Also, it is necessary to collect post-marketing information on the occurrences of haemorrhagic adverse events in patients with

severe renal impairment. The details of the caution statements for patients with renal impairment in the package insert and the details of post-marketing information collection will be further investigated taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).5) Administration in patients with hepatic impairment

PMDA asked the applicant to explain the efficacy and safety of prasugrel in patients with different severity of hepatic impairment in the Japanese phase III studies and to explain the appropriateness of administering prasugrel to patients with mild to moderate hepatic impairment.

The applicant responded as follows:

In the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, "patients with current or past severe hepatic impairment (fulminant hepatitis, hepatic cirrhosis, liver tumor)" were excluded. Therefore, the incidences of efficacy events and bleeding events were evaluated in subgroups by level of hepatic function parameters AST and ALT using 80 U/L as the reference value for mild or moderate hepatic impairment. Except in the subgroup of AST <80 U/L and ALT ≥80 U/L, which contained only an extremely limited number of patients, the point estimate of the hazard ratio in the incidence of efficacy events in the prasugrel group compared with the clopidogrel group was <1 for all other subgroups by severity of hepatic impairment, which suggests that the efficacy in each subgroup was similar to that in the entire prasugrel group.

In the Japanese phase III study in patients with ACS-PCI, the incidence of bleeding events in the prasugrel group by the severity of hepatic impairment (AST <80 U/L and ALT <80 U/L, AST ≥80 U/L and ALT ≥80 U/L) was as follows: major bleeding, 2.9% (13 of 441 subjects) and 0.0% (0 of 25 subjects), respectively; minor bleeding, 3.6% (16 of 441 subjects) and 0.0% (0 of 25 subjects); "clinically significant bleeding," 4.1% (18 of 441 subjects) and 8.0% (2 of 25 subjects); and "other bleeding," 43.3% (191 of 441 subjects) and 60.0% (15 of 25 subjects). Thus, the incidence showed no clear difference among patients with hepatic impairment of different severity, and was similar to that observed in the clopidogrel group.

In the Japanese phase III study in patients with ACS-PCI, there were 99 subjects with hepatic impairment-associated complication (48 subjects in the prasugrel group, 51 subjects in the clopidogrel group), and the incidence of bleeding events in subjects with complication in the prasugrel group was lower than in subjects without complication in the same treatment group, but similar to that in subjects of the clopidogrel group. In the Japanese phase III study in patients with elective PCI, there were 60 subjects with hepatic impairment-associated complication (33 subjects in the prasugrel group, 27 subjects in the clopidogrel group), and the incidence of bleeding events in subjects with complication in the prasugrel group was higher than in subjects without complication in the same treatment group, but similar to that in subjects of the clopidogrel group.

In the foreign ACS phase III study, the safety in patients with hepatic impairment was evaluated based on Hy's rule (FDA Guidance--Guidance for Industry, Drug-Induced Liver Injury; Premarketing Clinical Evaluation) and on the results of blood tests. As a result, "major or minor bleeding" in patients with hepatic impairment occurred in 2 of 32 subjects in the prasugrel group and in 3 of 37 subjects in the clopidogrel group, showing a similar frequency in both groups, albeit assessed in a limited number of subjects. In a foreign clinical pharmacology study (Study H7T-EW-TAAN), prasugrel 60 mg was administered orally in a single dose to patients with mild to moderate hepatic impairment and, in another foreign clinical pharmacology study (Study H7T-EW-TABV), prasugrel was administered orally to patients with moderate hepatic impairment at 60 mg loading dose, and then for 6 days at 10 mg/day maintenance dose. In both studies, the pharmacokinetic parameters and MPA were similar to those in healthy subjects, and no clinically significant adverse events were observed.

Based on the above, the applicant considered that prasugrel did not affect bleeding events in patients with mild to moderate hepatic impairment.

No clinical studies have been conducted in patients with severe hepatic impairment and the safety of prasugrel in this patient group is unclear. In addition, prasugrel is contraindicated in this patient group

in the labeling of Europe. On these bases, PMDA asked the applicant to explain the appropriateness to require careful administration in patients with severe hepatic impairment in Japan.

The applicant responded as follows:
In the European labeling, not only prasugrel but also clopidogrel is contraindicated in patients with severe hepatic impairment. The US labeling includes patients with severe hepatic impairment as an example of "patients with bleeding tendency" in "Warnings and Precautions," but indicates that prasugrel should be administered to these patients without dose adjustment. The US labeling for clopidogrel also indicates that clopidogrel should be administered to these patients without dose adjustment. In the US, no additional safety measures for these patients have been taken. According to the periodic safety update reports (PSURs) published so far, no particularly high incidence of fatal cases or haemorrhagic adverse events have been observed in patients with hepatic impairment, although the evaluation of post-marketing information available from foreign countries is considered feasible only to some extent.

Thus, taking account of the facts that there is no tendency of an increase in bleeding risk with prasugrel compared with clopidogrel in patients with mild to moderate hepatic impairment and that the proposed dose in Japan is lower than that approved in foreign countries, together with the content of the US labeling and post-marketing conditions in foreign countries, the applicant considers that it is appropriate to require careful administration in patients with severe hepatic impairment.

PMDA considers as follows:
According to the applicant's explanation on the results of the Japanese phase III study in patients with ACS-PCI and the Japanese phase III study in patients with elective PCI, there are no data suggesting markedly inferior efficacy and safety of prasugrel in patients with mild to moderate hepatic impairment than in patients with normal hepatic function. However, given that data on the Japanese phase III study in patients with ACS-PCI were obtained from a subpopulation with only a small number of subjects, and that subjects were stratified according to AST and ALT, not precluding the possibility that merely the effect on parameters AST and ALT immediately after onset of ACS was evaluated, it cannot be concluded that the study method was appropriate for evaluating the efficacy and safety of prasugrel in patients with mild to moderate hepatic impairment and the evaluation has limitations. However, the results of foreign clinical studies did not show any possibility of increased bleeding risk in subjects with mild to moderate hepatic impairment compared with subjects without hepatic impairment. Thus, it is appropriate to indicate prasugrel in these patients without dose adjustment.

As regards patients with severe hepatic impairment, there is no use experience in Japanese or foreign clinical studies and, because of abnormalities in the coagulation system, etc., these patients are generally considered to have an increased bleeding risk compared with patients with mild to moderate hepatic impairment. Taking account of the caution statement in Japan for clopidogrel, which is considered not significantly different from prasugrel in efficacy and safety in Japanese patients, it is unnecessary to contraindicate prasugrel in these patients, but it should be carefully evaluated whether to administer prasugrel with other bleeding risk factors taken into consideration. In addition, PMDA concludes that it is appropriate to require careful administration because due attention should be paid to possible occurrence of haemorrhagic adverse events even if prasugrel administration is considered appropriate.

A caution statement and other measures to be taken in administering prasugrel to patients with hepatic impairment, special requirements for patients with severe hepatic impairment, etc., will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).6) Administration in patients with a history of cerebral infarction or TIA
In foreign countries, prasugrel is contraindicated in patients with a history of cerebral infarction or TIA. Taking account of this fact, PMDA asked the applicant to explain the reason and justification for requiring careful administration in patients with a history of cerebral infarction or TIA in Japan, based on the inclusion/exclusion criteria regarding these patients in the Japanese phase III studies and on the results of efficacy and safety in these patients.

The applicant responded as follows:

In the foreign ACS phase III study, patients with a history of cerebral infarction or TIA accounted for 3.8% (518 of 13,608 patients). The incidence of MACE among patients without a history was 9.1% in the prasugrel group and 11.4% in the clopidogrel group, showing a significantly lower rate in the prasugrel group. Among patients with a history, the incidence was 17.9% in the prasugrel group and 13.7% in the clopidogrel group, showing a tendency of a higher rate in the prasugrel group. The incidence of non-CABG-related "major or minor bleeding" among patients without a history was 4.4% in the prasugrel group and 3.4% in the clopidogrel group, and the incidence among patients with a history was 7.8% in the prasugrel group and 4.0% in the clopidogrel group, showing a tendency for a higher rate in the prasugrel group. In foreign countries, a history of TIA or stroke was identified as a risk factor for decreasing the clinical usefulness based on the results of the post-hoc subgroup analysis of the composite endpoints of efficacy events and bleeding events stratified according to patient characteristics and, as a result, prasugrel was contraindicated in patients with a history of either of these diseases.

In Japan, cerebrovascular disease is the third leading cause of death, and ischemic cerebrovascular disease accounts for a majority of the disease. In REACH Registry, which surveyed in a prospective manner the outcome of atherothrombosis such as cerebral infarction (which accounts for a majority of ischemic cerebrovascular diseases) and myocardial infarction, 68,129 patients were registered from 44 countries around the world, including 5193 patients from Japan (Steg PG et al., *JAMA.* 2007;297:1197-206). The results showed that the incidence of cerebrovascular disease in Japan is higher than that across the world, and further that the relapse risk of cardiovascular events is higher in patients with concurrent cerebrovascular disorder than in patients with coronary disease alone. Thus, because of the higher relapse rate in patients with concurrent cerebral infarction, there is an urgent need to take measures to prevent the relapse in patients with coronary artery disease complicated with cerebrovascular disease, particularly in Japan where the rate of cerebrovascular disease is high.

Prasugrel is now contraindicated in patients with a history of TIA or stroke in foreign labelings. In the Japanese phase III study in patients with ACS-PCI involving ACS patients undergoing PCI, the same patient population as investigated in the foreign ACS phase III study, the exclusion criteria included "patients with a current or past history of cerebral infarction or transient ischemic attack (TIA) (except asymptomatic cerebral infarction detectable only by diagnostic imaging, etc.)" and "patients with a current or past history of intracranial haemorrhage (except asymptomatic microbleeding detectable only by MRI)," as opposed to the foreign ACS phase III study.

In the Japanese phase III study in patients with elective PCI, the applicant considered that the bleeding risk, which was a concern from the results of the foreign ACS phase III study, could be effectively addressed by a lower dose than that used in foreign countries, on ground that the observation that the incidence of bleeding events was not higher than anticipated in the then-ongoing Japanese phase III study in patients with ACS-PCI. As a result, the following exclusion criterion was set: "patients with current or past cerebral infarction* who met any of 1) to 3) below: 1) patients requiring anticoagulant therapy, 2) patients aged ≥75 years, and 3) patients within 6 months after the onset of cerebral infarction (*except asymptomatic cerebral infarction detectable only by diagnostic imaging)."

The efficacy and safety results in these patients in each study were as shown below. In the Japanese phase III study in patients with ACS-PCI, 49 subjects (25 subjects in the prasugrel group, 24 subjects in the clopidogrel group) with asymptomatic cerebral infarction detected by diagnostic imaging only were enrolled. The incidence of MACE1 in the prasugrel group and in the clopidogrel group was 12.0% (3 of 25 subjects) and 25.0% (6 of 24 subjects), respectively, in subjects with a history; and 9.2% (61 of 660 subjects) and 11.3% (74 of 654 subjects), respectively, in subjects without a history, suggesting that MACE1 was prevented by prasugrel even in patients with asymptomatic cerebral infarction, although the results of prasugrel were derived from only 25 subjects with a history. As regards bleeding events, the incidence of "major or minor bleeding" was 8.0% (2 of 25 subjects) and 4.2% (1 of 24 subjects), respectively, in subjects with a history; and 5.6% (37 of 660 subjects) and 4.3% (28 of 654 subjects), respectively, in subjects without a history. The incidence of "major, minor, or clinically significant bleeding" was 12.0% (3 of 25 subjects) and 4.2% (1 of 24 subjects), respectively, in subjects with a history; and 9.5% (63 of 660 subjects) and 9.8% (64 of 654 subjects), respectively, in subjects without a history.

In the Japanese phase III study in patients with elective PCI, the efficacy and safety in patients with a history of cerebral infarction or TIA were investigated, albeit in a limited number of patients. MACE did not occur in subjects with a history of cerebral infarction (14 subjects in the prasugrel group, 9 subjects in the clopidogrel group) or in subjects with a history of TIA (3 subjects, 2 subjects). In both prasugrel group and clopidogrel group, the incidence of MACE was higher in subjects with a history of asymptomatic cerebral infarction (10.0% [2 of 20 subjects], 6.9% [2 of 29 subjects]) than in subjects without a history (3.7% [13 of 350 subjects], 6.7% [23 of 343 subjects]), but obtained data did not suggest the possibility of any marked inferiority of prasugrel to clopidogrel in preventing MACE. As regards bleeding events, "major or minor bleeding" did not occur in subjects with a history of cerebral infarction. The incidence of "major, minor, or clinically significant bleeding" in this patient group was 14.3% (2 of 14 subjects) and 11.1% (1 of 9 subjects). In subjects with a history of TIA, "major, minor, or clinically significant bleeding" did not occur. In subjects with a history of asymptomatic cerebral infarction, the incidence of "major or minor bleeding" was 5.0% (1 of 20 subjects) and 17.2% (5 of 29 subjects), and the incidence of "major, minor, or clinically significant bleeding" was 10.0% (2 of 20 subjects) and 20.7% (6 of 29 subjects). Intracranial haemorrhage, an adverse event of concern in foreign countries, did not occur in the prasugrel group.

In the foreign ACS phase III study, the incidence of bleeding events was higher in the prasugrel group than in the clopidogrel group both in patients with a history of stroke or TIA and in all study patients with ACS. The applicant considered that the higher incidence was due to the selection of the dose of prasugrel (60 + 10 mg), which has a significantly higher antiplatelet activity compared with clopidogrel (300 + 75 mg). In contrast, the efficacy results did not show a similar tendency between patients with a history of stroke or TIA and all study patients, with the incidence of cerebro-cardiovascular events among patients with a history of stroke or TIA being higher in the prasugrel group than in the clopidogrel group. This result was unexpected given the use of the dose of prasugrel with a significantly higher antiplatelet activity than clopidogrel. This efficacy result was considered highly likely to be accidental, since the result was obtained by the post-hoc analysis of a subgroup with only a small number of subjects and since among patients with a history of stroke or TIA in this study, the relapse rate of cerebral infarction in the clopidogrel group was 1.2%, which was extremely low compared with the previously-reported relapse rate of cerebral infarction (≥5%/year) in patients with the same past history who were receiving clopidogrel.

In the Japanese phase III studies, the dose with well-balanced efficacy and safety was used. The results suggested that MACE was suppressed in all patients in the prasugrel group and demonstrated safety similar to that observed in the clopidogrel group. In patients with a history of cerebral infarction, TIA, or asymptomatic cerebral infarction, the data did not suggest any inferiority of prasugrel to clopidogrel in usefulness, albeit derived from a limited number of patients. Given the conditions for the treatment of patients with cerebral infarction in Japan, a new treatment method is required for patients with a history of cerebral infarction or TIA because of a high relapse rate of cardiovascular events in these patients. However, prasugrel is contraindicated in these patients in the US and Europe and the data in the Japanese phase III studies were obtained from a limited number of subjects, although the data obtained indicated no problems in using prasugrel in these patients. Therefore, the applicant considered that it is necessary to require careful administration in patients with a history of cerebral infarction or TIA to raise caution.

PMDA considers as follow:
In the Japanese phase III study in patients with ACS-PCI, patients with a history of cerebral infarction or TIA were excluded and, in the Japanese phase III study in patients with elective PCI, there were only a limited number of these patients (17 subjects in the prasugrel group, 11 subjects in the clopidogrel group). Therefore, currently there is no enough information on the efficacy and safety of prasugrel 20 + 3.75 mg in Japanese patients with coronary artery disease who are to be managed with PCI and with a history of cerebral infarction or TIA. The applicant presented the data on the effect of prasugrel in patients with asymptomatic cerebral infarction detectable only by diagnostic imaging in the Japanese phase III study in patients with ACS-PCI. However, these data should be handled as a reference only in the discussion of the efficacy and safety of prasugrel in patients who can be clinically assessed as having a history of cerebral infarction or TIA and, even if the data had been gathered from a large number of

patients, they should not be used as the basis for evaluating the usefulness in patients with a history of cerebral infarction or TIA.

In the foreign ACS phase III study, not only the incidence of haemorrhagic adverse events but also the incidence of cardiovascular events were higher in patients with a history of cerebral infarction or TIA in the prasugrel 60 + 10 mg group compared with those in the clopidogrel group, but the cause for this observation is unclear. In the development in Japan, a dosage regimen different from that used in foreign studies was selected by taking account of the rate of inhibition of platelet aggregation in Japanese subjects. Therefore, in patients with a history of cerebral infarction or TIA, prasugrel may provide a benefit-risk balance different from that observed in foreign clinical studies. Given this possibility, it cannot be said currently that, in Japan as in foreign countries, prasugrel should be contraindicated in patients with a history of cerebral infarction or TIA for which clopidogrel is indicated. The appropriateness of administering prasugrel to these patients, a caution statement in the package insert, and details of post-marketing information collection will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).7) Measures to be taken for patients scheduled to undergo CABG

PMDA asked the applicant to explain what cautions are required in performing CABG in patients on prasugrel, by taking account of the number of subjects who underwent CABG during the period of each Japanese phase III study, the withdrawal period for prasugrel or clopidogrel before CABG, occurrences of haemorrhagic adverse events and of efficacy events, as well as the results of the foreign ACS phase III study and the rules stipulated in the US labeling.

The applicant responded as follows:

In the Japanese phase III study in patients with ACS-PCI, CABG was performed in 15 subjects in the prasugrel group and in 14 subjects in the clopidogrel group. CABG was performed as the initial revascularization procedure in 9 subjects in the prasugrel group and in 6 subjects in the clopidogrel group; as a procedure within the pre-scheduled stepwise revascularization procedures in 1 subject and in 3 subjects, respectively; and as an unscheduled, non-emergency revascularization procedure in 5 subjects and in 5 subjects, respectively. In the Japanese phase III study in patients with elective PCI, CABG was performed in 3 subjects in the prasugrel group and in 1 subject in the clopidogrel group: as the initial revascularization procedure in 1 subject and in 1 subject, respectively; and as an unscheduled, non-emergency revascularization procedure in 2 subjects and 0 subjects, respectively. No subjects underwent an unscheduled emergency revascularization procedure in either of the studies. In the prasugrel group, CABG was performed within 14 days after the last dose of study drug treatment in 13 subjects (10 subjects in the Japanese phase III study in patients with ACS-PCI, 3 subjects in the Japanese phase III study in patients with elective PCI), and the incidence of CABG-related “major or minor bleeding” in subjects who underwent CABG was 92.3% (12 of 13 subjects). Of 13 subjects, except for subjects who underwent CABG on the day or the next day of the last dose of study drug treatment, the number of subjects who underwent CABG was 4 in the Japanese phase III study in patients with ACS-PCI and 2 in the Japanese phase III study in patients with elective PCI. The withdrawal period in these subjects was 6 days in 1 subject, 8 days in 2 subjects, 12 days in 2 subjects, and 14 days in 1 subject, and CABG-related bleeding events were major bleeding in 4 subjects and minor bleeding in 1 subject. In the clopidogrel group, CABG was performed within 14 days after the last dose of study drug treatment in 10 subjects (9 subjects in the Japanese phase III study in patients with ACS-PCI, 1 subject in the Japanese phase III study in patients with elective PCI), and the incidence of CABG-related “major or minor bleeding” in subjects who underwent CABG was 80.0% (8 of 10 subjects), according to the available data. Of the 10 subjects, except for subjects who underwent CABG on the day or the next day of the last dose of study drug treatment, the number of subjects who underwent CABG was 6 in the Japanese phase III study in patients with ACS-PCI and 1 in the Japanese phase III study in patients with elective PCI. The withdrawal period in these subjects was 4 days in 1 subject, 6 days in 2 subjects, and 7, 8, 9, and 10 days in 1 subject each, and CABG-related bleeding events were major bleeding in 5 subjects and other bleeding in 1 subject. In both studies, no efficacy events occurred in either of the treatment groups during the period from the completion, discontinuation, or suspension of the study drug treatment to CABG.

In the foreign ACS phase III study, the percentage of subjects who underwent CABG as the initial revascularization procedure was 0.54% (72 of 13,457 subjects). Of the 213 subjects who underwent CABG in the prasugrel group, 33 subjects received the surgery at the first hospitalization, and of the 224 subjects who underwent CABG in the clopidogrel group, 39 subjects received the surgery at the first hospitalization. Most of them received emergency CABG. Among these subjects, the incidence of "major or minor bleeding" was higher in the prasugrel group than in the clopidogrel group (18.18% [6 of 33 subjects] in the prasugrel group, 2.56% [1 of 39 subjects] in the clopidogrel group). In response to this result, the US labeling stipulated that administration of prasugrel should not be started in patients likely to undergo urgent CABG. As regards the relationship between the withdrawal period before CABG and CABG-related bleeding event in the foreign ACS phase III study, the incidence of CABG-related "major or minor bleeding" in 437 patients who underwent CABG (213 patients in the prasugrel group, 224 patients in the clopidogrel group) was 17.24% (10 of 58 patients) in the prasugrel group and 6.15% (4 of 65 patients) in the clopidogrel group when the withdrawal period was ≤2 days before CABG; 15.79% (12 of 76 patients) and 4.40% (4 of 91 patients), respectively, when the withdrawal period was 3 to 7 days before CABG; and 10.13% (8 of 79 patients) and 2.90% (2 of 69 patients), respectively, when the withdrawal period was >7 days before CABG. In response to this result, the US labeling stipulated that if possible, prasugrel should be discontinued at least 7 days prior to CABG.

In Japanese clinical studies, CABG was performed in a limited number of subjects, reflecting the clinical situation in Japan. Thus, it was difficult to evaluate the safety of prasugrel solely based on the results of Japanese clinical studies. Nevertheless, the incidence of CABG-related bleeding events was comparable between the prasugrel group and the clopidogrel group, at least during the period where data were available for aggregation. It is reported that hemoglobin decrease corresponding to major bleeding may occur only in subjects who have undergone CABG, which suggests that prasugrel administration may further enhance bleeding by its antiplatelet effect. Therefore, the applicant considers that it is desirable to include a sufficiently long withdrawal period of at least 7 days in reference to the rules stipulated in the US labeling. The applicant also considers that caution should be provided about the possible occurrence of serious bleeding unless a sufficient length of the withdrawal period is allowed.

PMDA considers as follows:
Because of the small number of patients who underwent CABG in the Japanese phase III study in patients with ACS-PCI, it is difficult to accurately determine the increase in CABG-related bleeding risk caused by prasugrel and the appropriate withdrawal period before CABG. However, in light of the high incidence (12 of 13 subjects) of "major or minor bleeding" in subjects who underwent CABG within 14 days after the last dose of prasugrel, it is necessary to provide a due caution on the bleeding risk when prasugrel is administered to patients who are scheduled to undergo CABG and to set a rule for the withdrawal period. A specific caution statement for patients scheduled to undergo CABG and the setting of the rules for the withdrawal period will be discussed in the next section.

4.(iii).B.(4).8) Withdrawal period before invasive procedure (e.g., surgery)
PMDA asked the applicant to provide the number of subjects who had to undergo invasive procedures (e.g. surgery) during the study period in the Japanese phase III studies, the details of specific procedures given, the withdrawal period for prasugrel or clopidogrel before the surgery, occurrences of haemorrhagic adverse events, and occurrences of efficacy events. PMDA further asked the applicant to justify the description "it is recommended to discontinue the treatment at least 7 days before surgery if the antiplatelet effect of Efient (prasugrel) is likely to pose problems in the surgery" in the "Important Precautions" section of the package insert, taking account of the Warning statement stipulated by the labeling of the US (i.e., "When possible, discontinue Effient at least 7 days prior to any surgery." ["Effient" is the brand name of prasugrel approved in US]).

The applicant responded as follows:
In the Japanese phase III study in patients with ACS-PCI, withdrawal of the study drug before the procedure was deemed necessary by the investigator during the study period in 1.3% (10 of 762 procedures) in the prasugrel group and in 2.0% (14 of 696 procedures) in the clopidogrel group. The incidence of bleeding events up to 14 days after study drug discontinuation was 6.6% (50 of 752 procedures) in the prasugrel group and 3.5% (24 of 682 procedures) in the clopidogrel group without the withdrawal period and 30.0% (3 in 10 procedures; 1 event each of "other bleeding" associated with

open surgery of fracture, minor bleeding associated with CABG, and minor bleeding associated with pacemaker implantation) in the prasugrel group and 14.3% (2 of 14 procedures; 1 event each of "other bleeding" associated with CABG and major bleeding) in the clopidogrel group with the withdrawal period. In subjects who had bleeding events, the withdrawal period was 4, 6, and 6 days in the prasugrel group and 6 and 7 days in the clopidogrel group. No MACE1 occurred after withdrawal of the study drug in either group. In the Japanese phase III study in patients with elective PCI, withdrawal of the study drug before the procedure was deemed necessary by the investigator during the study period in 3.9% (13 of 337 procedures) in the prasugrel group and in 1.2% (5 of 406 procedures) in the clopidogrel group. The incidence of bleeding events up to 14 days after study drug discontinuation was 5.6% (18 of 324 procedures) in the prasugrel group and 4.7% (19 of 401 procedures) in the clopidogrel group without the withdrawal period and 23.1% (3 of 13 procedures; 1 event of major bleeding associated with CABG, 2 events of "other bleeding" associated with tooth extraction) in the prasugrel group and 20.0% (1 of 5 procedures; "other bleeding" associated with polypectomy) in the clopidogrel group with the withdrawal period. In subjects who had bleeding events, the withdrawal period was 8 days (CABG) and 6 and 8 days (tooth extraction) in the prasugrel group and 6 days in the clopidogrel group. No MACE occurred after withdrawal of the study drug in either group.

In the Japanese phase III study in patients with ACS-PCI, the invasive procedure performed most frequently after the initial revascularization procedure was CAG[9] (402 procedures in 333 subjects in the prasugrel group, 370 procedures in 309 subjects in the clopidogrel group), followed by PCI (307 procedures in 239 subjects, 284 procedures in 226 subjects). The incidence of bleeding events associated with CAG tended to be higher in the prasugrel group (4.2% [17 of 402 procedures]) than in the clopidogrel group (1.4% [5 of 370 procedures]), whereas bleeding events associated with PCI was comparable between the prasugrel group (7.8% [24 of 307 procedures]) and the clopidogrel group (5.3% [15 of 284 procedures]). Other procedures such as CABG, tooth extraction, and skin incision were performed in only a limited number of subjects, precluding the evaluation, but the incidence of bleeding events associated with these procedures was not markedly higher in the prasugrel group compared with the clopidogrel group.

In the Japanese phase III study in patients with elective PCI, the invasive procedure performed most frequently after the initial revascularization procedure was CAG (217 procedures in 207 subjects, 203 procedures in 191 subjects), followed by PCI (90 procedures in 76 subjects, 91 procedures in 82 subjects). The incidence of bleeding events associated with CAG was 4.1% (9 of 217 procedures) and 3.4% (7 of 203 procedures), and the incidence of bleeding events associated with PCI was 4.4% (4 of 90 procedures) and 7.7% (7 of 91 procedures); neither of the incidences was higher in the prasugrel group compared with the clopidogrel group. Other procedures such as CABG, tooth extraction, and skin incision were performed in only a limited number of subjects, precluding the evaluation, but the incidence of bleeding events associated with these procedures was not markedly higher in the prasugrel group compared with the clopidogrel group.

The US labeling stipulates, regarding the withdrawal period before invasive procedures other than CABG, that prasugrel should be withdrawn for at least 7 days before the procedure if possible as is the case with CABG, based on the data on CABG.

Based on the above, the applicant considers that, among bleeding risks associated with procedures, the incidence of bleeding events associated with CAG is higher in the prasugrel group compared with the clopidogrel but, for other procedures, the incidence is similar between the two groups. Among all invasive procedures, there were few that required withdrawal of the study drug and, as a consequence, it was difficult to accurately evaluate the safety and efficacy of the study drug. Still, withdrawal was required only before procedures that were expected to be possibly accompanied by severe bleeding, such as CABG and pacemaker implantation, and the incidence of bleeding events during these procedures was comparable between the prasugrel group and the clopidogrel group. Therefore, the applicant considers that it is necessary to set the withdrawal period in relation to CABG and other invasive procedures in the Japanese package insert as is the case with the US labeling and to raise caution about the possible serious bleeding if a sufficient withdrawal period is not allowed. Based on the above, the

[9] Only cases of CAG alone were counted. Cases of CAG performed simultaneously with PCI were counted as cases of PCI.

"Important Precautions" section of the proposed package insert included, regarding the invasive procedures (e.g., surgery) during prasugrel administration, the following description: "It is recommended to discontinue the treatment for at least 7 days before surgery if the antiplatelet effect of prasugrel is likely to pose problems in the surgery. In addition, it is reported that there is an increased risk of serious bleeding if a sufficient withdrawal period is not allowed. Patients should be carefully monitored."

PMDA considers as follows:
Prasugrel is to be indicated for patients with ischemic heart disease scheduled to undergo PCI, and it is expected that repeated CAG or PCI is required in many of them during the treatment with prasugrel. Under such situations, it should be considered seriously that, in the Japanese phase III study in patients with ACS-PCI, bleeding events associated with invasive procedures (e.g., CAG, PCI) occurred in the prasugrel group more frequently than in the clopidogrel group. Thus, adequate caution is required. In the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, there are only limited data on withdrawal of prasugrel associated with surgical procedures etc. The rules for withdrawal in surgery etc., and a caution statement are at least necessary for prasugrel as stipulated in the Japanese package insert of clopidogrel, for the following reasons: (i) the mechanism of the antiplatelet effect of prasugrel is the same as that of clopidogrel, i.e., blockade of platelet $P2Y_{12}$ receptor; (ii) in the Japanese phase III studies, prasugrel showed the efficacy and bleeding risk at least comparable to those of clopidogrel; and (iii) the possibility cannot be excluded that there is a higher bleeding risk associated with an invasive procedure in the presence of prasugrel than in the presence of clopidogrel. Therefore, in surgical operations in which the antiplatelet effect of prasugrel poses a safety problem, there is no justification for considering it sufficient only to recommend withdrawal of prasugrel for $\geq$7 days before the procedure, as proposed by the applicant. Instead, PMDA considers that the administration should be discontinued for at least 14 days before the procedure, as is the case with clopidogrel. Setting of the withdrawal period before invasive procedures (e.g., surgery) and the details of description in the package insert on the bleeding risk associated with invasive procedures and on the risk of events such as thrombosis during the withdrawal period will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).9) Concomitant use of prasugrel with anticoagulants
The applicant explained the concomitant use of prasugrel with anticoagulant as follows:
In the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, concomitant use with anticoagulants (including drugs that have an anticoagulant effect and at the same time may possibly enhance bleeding) was prohibited. In the foreign ACS phase III study, concomitant use with oral anticoagulants was prohibited but, in the foreign labeling, dose adjustment is not required although there is a description in "Warnings and Precautions" on the possible increase in bleeding risk by concomitant use with oral anticoagulants.

PMDA considers as follows:
In patients who are already being treated with an anticoagulant because of concurrent atrial fibrillation, etc., and in patients for whom a long-term treatment with an anticoagulant is indicated, it is assumed that 3-drug combination therapy with aspirin, prasugrel, and warfarin or other oral anticoagulants is performed in clinical settings in Japan. On the other hand, since the 3-drug combination therapy is supposed to increase the bleeding risk, concomitant use with an anticoagulant becomes a critical issue. However, during the development stage of prasugrel, long-term concomitant use with oral anticoagulants was prohibited in all Japanese and foreign clinical studies and, as a result, there are no clinical data on the 3-drug combination therapy. Although it is necessary currently to supply prasugrel under conditions allowing concomitant use, particular caution should be exercised against bleeding risk in concomitant use with an anticoagulant. Therefore, it is essential to include concomitant use with anticoagulants in the "Important Precautions" and "Precautions for coadministration" sections of the package insert to raise caution, and to collect information on the safety (bleeding risk in particular) in patients receiving the 3-drug combination therapy after the market launch. A caution statement in the package insert and the details of post-marketing information collection will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).10) Concomitant use of prasugrel with drugs that have antiplatelet activity or possibly enhance bleeding tendency in some other way

The applicant explained as follows regarding the concomitant use of prasugrel with drugs that have antiplatelet activity or possibly enhance bleeding tendency in some other way:
In the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, concomitant use with a drug having antiplatelet activity or thrombolytic activity was considered likely to increase bleeding risk. Therefore, such concomitant use was prohibited except when it was deemed necessary by the investigator for the benefit of the subject.

In the Japanese phase III study in patients with ACS-PCI, the incidence of non-CABG-related bleeding events by use experience of acidic non-steroidal anti-inflammatory drugs (NSAIDs), in the prasugrel group was as follows: major bleeding 3.5% (8 of 231 subjects) with NSAIDs and 1.1% (5 of 454 subjects) without NSAIDs; "major or minor bleeding," 8.7% (20 of 231 subjects) and 4.2% (19 of 454 subjects); "major, minor, or clinically significant bleeding," 13.0% (30 of 231 subjects) and 7.9% (36 of 454 subjects); minor bleeding, 5.6% (13 of 231 subjects) and 3.1% (14 of 454 subjects); and "clinically significant bleeding," 5.2% (12 of 231 subjects) and 3.7% (17 of 454 subjects); showing a tendency of higher incidence of bleeding events in subjects with concomitant use of NSAIDs than in subjects without NSAIDs. In the clopidogrel group, the incidence of non-CABG-related bleeding events by use experience of NSAIDs was as follows: major bleeding, 3.3% (7 of 210 subjects) and 1.7% (8 of 468 subjects); "major or minor bleeding," 4.8% (10 of 210 subjects) and 4.1% (19 of 468 subjects); "major, minor, or clinically significant bleeding," 11.4% (24 of 210 subjects) and 8.8% (41 of 468 subjects); minor bleeding, 1.4% (3 of 210 subjects) and 2.6% (12 of 468 subjects); and "clinically significant bleeding," 7.1% (15 of 210 subjects) and 5.1% (24 of 468 subjects). Thus, the incidence of major bleeding in subjects with concomitant use of NSAID was similar between the prasugrel group and the clopidogrel group, whereas the incidence of minor bleeding tended to be higher in the prasugrel group than in the clopidogrel group.

In the Japanese phase III study in patients with elective PCI, the incidence of non-CABG-related bleeding events by use experience of NSAIDs, in the prasugrel group was as follows: major bleeding not observed; minor bleeding 2.2% (2 of 93 subjects) with NSAIDs and 1.4% (4 of 277 subjects) without NSAID; "major, minor, or clinically significant bleeding," 4.3% (4 of 93 subjects) and 5.8% (16 of 277 subjects); and "clinically significant bleeding," 2.2% (2 of 93 subjects) and 4.3% (12 of 277 subjects). In the clopidogrel group, the incidence of non-CABG-related bleeding events by use experience of NSAIDs was as follows: major bleeding, 3.0% (3 of 99 subjects) and 1.8% (5 of 273 subjects); "major or minor bleeding," 4.0% (4 of 99 subjects) and 2.6% (7 of 273 subjects); "major, minor, or clinically significant bleeding," 7.1% (7 of 99 subjects) and 5.9% (16 of 273 subjects); minor bleeding 1.0% (1 of 99 subjects) and 0.7% (2 of 273 subjects); and "clinically significant bleeding," 3.0% (3 of 99 subjects) and 3.3% (9 of 273 subjects). Thus, the incidence of bleeding events in subjects with concomitant use of NSAIDs in the prasugrel group was lower than, or comparable to, that in the clopidogrel group. As described above, there were only limited safety data in concomitant use with a drug having antiplatelet activity or thrombolytic activity, but the frequency of serious bleeding events in subjects with concomitant use of NSAIDs was not high and not significantly different between the prasugrel group and the clopidogrel group.

In the foreign ACS phase III study, the incidence of "major or minor bleeding" within 3 days after the start of study drug treatment by use or non-use of NSAIDs, was investigated. The results showed that the incidence of bleeding tended to increase in concomitant use of prasugrel with NSAIDs than in concomitant use of clopidogrel with NSAID (6.06% [18 of 297 subjects] with NSAID and 4.42% [285 of 6444 subjects] without NSAIDs in the prasugrel group, 4.37% [15 of 343 subjects] with NSAIDs and 3.39% [216 of 6373 subjects] without NSAIDs in the clopidogrel group). The "Warnings and Precautions" section of the US labeling and the "Special warnings and precautions for use" section of the European labeling state that "concomitant use of oral anticoagulants, NSAIDs, or fibrinolytics increases bleeding risk," but do not require dose adjustment.

Based on the above, the applicant considers it appropriate to include these drugs in the "Precautions for coadministration" section of the package insert as are the cases with US and European labeling.

PMDA considers as follows:
Both in the Japanese phase III studies and in the foreign ACS phase III studies, concomitant use of NSAIDs with prasugrel was shown to cause an increase in haemorrhagic adverse events compared with prasugrel alone. Although the results of the Japanese phase III studies did not show a tendency for marked increase in the incidence of haemorrhagic adverse events following the concomitant use of prasugrel with NSAIDs compared with the concomitant use of clopidogrel with NSAIDs, caution should be exercised against bleeding risk in administration of prasugrel in combination with NSAIDs in clinical settings. The package insert should include this caution statement, and relevant information should be collected after the market launch. No sufficient information was available at the development stage of prasugrel regarding the concomitant use of prasugrel with drugs that have antiplatelet activity other than NSAIDs or possibly enhance bleeding tendency in some other way. Therefore, bleeding risk should be included in the "Precautions for coadministration" section to raise caution and the relevant information should be collected after the market launch. A description on the concomitant use of these drugs in the package insert and the details of information collection after the market launch will be finalized, taking account of comments raised in the Expert Discussion.

4.(iii).B.(4).11) Risk of thrombotic thrombocytopenic purpura and of abnormality in blood cell series, and monitoring by blood test during prasugrel administration

PMDA asked the applicant to justify the description in the "Important Precautions" section of the proposed package insert "Serious adverse drug reactions such as thrombotic thrombocytopenic purpura (TTP) may occur. Consideration should be given to performing a blood test etc., approximately once every 2 weeks during the first 2 months of the treatment," by taking account of rules set for the frequency and timing of blood tests in Japanese and foreign clinical studies, as well as of the occurrences of adverse events such as thrombotic thrombocytopenic purpura (TTP), anaemia, platelet count decreased, white blood cell count decreased, and hepatic dysfunction in the prasugrel group as compared with the clopidogrel group.

The applicant explained as follows:
Both in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, hematology and clinical chemistry were to be performed before the start of study drug treatment and at Week 2, 4, 8, 12, 24, 36, and 48 of administration, all at the central laboratory. In the foreign ACS phase III study, on the other hand, the examinations were to be performed before PCI, at 24 ± 4 hours after PCI, and on Day 30, 90, 180, 270, 360, and 450 of administration (or at the last visit), also all at the central laboratory. TTP was observed in only 1 subject in the clopidogrel group in the foreign ACS phase III study, and was not observed either in the prasugrel group or in the clopidogrel group of the Japanese phase III study in patients with ACS-PCI and the Japanese phase III study in patients with elective PCI. The incidence of anaemia in the foreign ACS phase III study was 1.34% (90 of 6741 subjects) in the prasugrel group and 1.16% (78 of 6716 subjects) in the clopidogrel group during the period from the start to Week 8 of study drug treatment, and 0.86% (58 of 6741 subjects) and 0.85% (57 of 6716 subjects) from >Week 8 of study drug treatment to 7 days after the end of study drug treatment. The incidence of anaemia in the Japanese phase III study in patients with ACS-PCI was 2.9% (20 of 685 subjects) and 1.5% (10 of 678 subjects) from the start to Week 8 of study drug treatment, and 0.4% (3 of 685 subjects) and 1.6% (11 of 678 subjects) after Week 8. Among these, 4 events in the clopidogrel group (3 events of them occurring within 8 weeks) were assessed as serious. The incidence of anaemia in the Japanese phase III study in patients with elective PCI was 0.5% (2 of 370 subjects) and 0.3% (1 of 372 subjects) from the start to Week 8 of study drug treatment, and 0.5% (2 of 370 subjects) and 0.8% (3 of 372 subjects) after Week 8. All events were assessed as non-serious. The incidence of platelet count decreased in the foreign ACS phase III study was 0.58% (39 of 6741 subjects) and 0.61% (41 of 6716 subjects) from the start to Week 8 of study drug treatment, and 0.22% (15 of 6741 subjects) and 0.13% (9 of 6716 subjects) from >Week 8 of study drug treatment to 7 days after the end of study drug treatment. The incidence of platelet count decreased in the Japanese phase III study in patients with ACS-PCI was 1.0% (7 of 685 subjects) and 0.7% (5 of 678 subjects) from the start to Week 8 of study drug treatment, and 0.1% (1 of 685 subjects) and 0.1% (1 of 678 subjects) after Week 8. All events were assessed as non-serious. The incidence of platelet count decreased in the Japanese phase III study in patients with elective PCI was 0.3% (1 of 370 subjects) and 0.5% (2 of 372 subjects) from the start to Week 8 of study drug treatment, and 0% (0 of 370 subjects) and 0.8% (3 of 678 subjects) after Week 8. All events were assessed as non-serious. The incidences of white blood cell

count decreased, neutrophil count decreased, and pancytopenia in the foreign ACS phase III study were 0.00% (0 of 6741 subjects), 0.06% (4 of 6741 subjects), and 0.01% (1 of 6741 subjects), respectively, in the prasugrel group, and 0.01% (1 of 6716), 0.06% (4 of 6716 subjects), and 0.00% (0 of 6716 subjects), respectively, in the clopidogrel group from the start to Week 8 of study drug treatment, and 0.06% (4 of 6741 subjects), 0.00% (0 of 6741 subjects), and 0.00% (0 of 6741 subjects) in the prasugrel group, and 0.04% (3 of 6716 subjects), 0.07% (5 of 6716 subjects), and 0.01% (1 of 6716 subjects) in the clopidogrel group from >Week 8 of study drug treatment to 7 days after the end of study drug treatment. The incidences of white blood cell count decreased, neutrophil count decreased, and pancytopenia in the Japanese phase III study in patients with ACS-PCI was 0.1% (1 of 685 subjects), 0.1% (1 of 685 subjects), and 0.0% (0 of 685 subjects), respectively, in the prasugrel group, and 0.6% (4 of 678 subjects), 0.0% (0 of 678 subjects), and 0.1% (1 of 678 subjects), respectively, in the clopidogrel group from the start to Week 8 of study drug treatment. Among these, neutrophil count decreased in 1 subject in the prasugrel group and white blood cell count decreased and pancytopenia in 1 subject each in the clopidogrel group were assessed as serious, but recovered after study drug discontinuation (neutrophil count decreased in the prasugrel group, pancytopenia in the clopidogrel group) or without any intervening treatment (white blood cell count decreased in the clopidogrel group). After Week 8 of study drug treatment, white blood cell count decreased, neutrophil count decreased, and pancytopenia were not observed in either of the treatment groups. In the Japanese phase III study in patients with elective PCI, neither neutrophil count decreased nor pancytopenia was observed. The incidence of white blood cell count decreased was 0.3% (1 of 370 subjects) in the prasugrel group and 0.0% (0 of 372 subjects) in the clopidogrel group from the start to Week 8 of study drug treatment, and 0% in the prasugrel group and 0.5% (2 of 372 subjects) in the clopidogrel group after Week 8. All events were assessed as non-serious.

The incidence of hepatic dysfunction in the foreign ACS phase III study was 0.71% (48 of 6741 subjects) in the prasugrel group and 0.60% (40 of 6716 subjects) in the in the clopidogrel group from the start to Week 8 of study drug treatment, and 0.43% (29 of 6741 subjects) and 0.50% (34 of 6716 subjects), respectively, from >Week 8 of study drug treatment to 7 days after the end of study drug treatment. The incidence of hepatic dysfunction in the Japanese phase III study in patients with ACS-PCI was 9.3% (64 of 685 subjects) and 10.8% (73 of 678 subjects), respectively, from the start to Week 8 of study drug treatment. Among these, events reported by 1 subject in the prasugrel group and by 2 subjects in the clopidogrel group were assessed as serious, but recovered without any intervening treatment. The incidence after Week 8 was 3.1% (21 of 685 subjects) and 1.9% (13 of 678 subjects) and, the event in 1 subject in the prasugrel group was assessed as serious. This event was liver injury caused by a traffic accident and improved after study drug discontinuation. The incidence of hepatic dysfunction in the Japanese phase III study in patients with elective PCI was 3.2% (12 of 370 subjects) and 3.2% (12 of 372 subjects), respectively, from the start to Week 8 of study drug treatment. Among these, events in 1 subject each in the prasugrel group and in the clopidogrel group were assessed as serious but recovered without any intervening treatment. The incidence after Week 8 was 3.8% (14 of 370 subjects) and 2.7% (10 of 372 subjects) and all events were assessed as non-serious.

Thus, in the Japanese phase III study in patients with ACS-PCI and in the Japanese phase III study in patients with elective PCI, no TTP was observed, while anaemia, platelet count decreased, white blood cell count decreased, and hepatic dysfunction occurred mostly within 8 weeks of study drug treatment. In the foreign ACS phase III study also, anaemia and platelet count decreased occurred frequently within 8 weeks of study drug treatment, and TTP also occurred in 1 subject in the clopidogrel group within 8 weeks of study drug treatment. According to the foreign post-marketing information, 22 cases of serious TTP for which a causal relationship to prasugrel could not be ruled out were reported as of February 25, 2013. All events were spontaneously reported cases with most of them lacking detailed information, but there were cases that occurred within 2 months after the start of treatment.

These results indicate the necessity of paying attention to the occurrence of adverse events particularly within 8 weeks after the start of prasugrel. Since the possibility cannot be excluded that serious adverse drug reactions such as TTP may occur within 2 months after the start of treatment, the description “Serious adverse drug reactions such as thrombotic thrombocytopenic purpura (TTP) may occur. Consideration should be given to performing a blood test etc., approximately once every 2 weeks during the first 2 months of the treatment” was entered in the “Important Precautions” section to raise caution.

PMDA considers as follows:
Adverse events such as blood cell disorders (e.g., anaemia, platelet count decreased, and white blood cell count decreased) and hepatic dysfunction, which are commonly observed with other thienopyridine antiplatelet drugs such as clopidogrel, were also observed with prasugrel in Japanese and foreign clinical studies. It should particularly be noted that these events occurred in Japanese clinical studies as well and that treatment discontinuation due to neutrophil count decreased was observed in some subjects. As regards TTP, its frequency of occurrence is unknown and there is no report of TTP in Japanese clinical studies, but attention should be paid to the fact that a case of TTP for which a causal relationship to prasugrel could not be ruled out was reported in a foreign country. In the Japanese clinical studies, the incidences of these blood disorders and hepatic dysfunction were at least similar, albeit not particularly higher, in the prasugrel group compared with the clopidogrel group. In particular, the incidence of these adverse events was high during the first 8 weeks after the start of study drug treatment. Therefore, the package insert should stipulate that, in using prasugrel in clinical settings, consideration should be given to performing a blood test approximately once every 2 weeks during the first 2 months of the treatment, as is the case with clopidogrel. A description of the caution statement in the package insert regarding adverse events such as blood disorders (e.g., anaemia, platelet count decreased, and white blood cell count decreased) and hepatic dysfunction and the details of the rule for monitoring by blood test will be further investigated taking account of comments raised in the Expert Discussion.

4.(iii).B.(5) Post-marketing investigations
The applicant explained the post-marketing investigations as follows:
In order to obtain information on the drug utilization in patients during the early phase after the market launch and to promptly grasp the safety and efficacy in the short-term use of prasugrel in routine clinical practice (incidence of cardiovascular events and bleeding events, in particular), a specified use-results survey (a survey on utilization in ACS patients during the early stage of treatment with prasugrel) will be conducted in ACS patients who use prasugrel for the first time. The results of clinical studies showed that most of the haemorrhagic adverse events associated with prasugrel occurred within 30 days after the start of treatment. Therefore, the applicant considered that, in the specified use-results survey, it was critical for the purpose of risk management to investigate and evaluate the important safety matters centering on bleeding events, which occur early after the start of treatment, in high-risk ACS patients with serious and unstable disease conditions, and to supply the information on proper use to healthcare providers in clinical settings as soon as possible after the market launch. The survey will be conducted for 8 months starting from the market launch, and collect data from 500 patients who start the treatment with prasugrel after the approval of the product, by using the continuous surveillance system. The safety will be evaluated regarding bleeding, anaemia, thrombocytopenia, hepatic dysfunction/jaundice, etc. The rationale for setting the number of patients to be surveyed is as follows. In order to supply information on proper use of prasugrel to healthcare providers in clinical settings as promptly as possible after the market launch, the duration of the survey and the time required for preparing the report were evaluated. As a result, it was considered possible to draw up the report at approximately one and a half year after the market launch if the survey duration is set at 8 months after the market launch (observation period in each patient, ≥1 month after the start of treatment), Therefore, based on the predicted number of subjects who use prasugrel after the market launch, the applicant determined that it would be possible to enroll 500 patients to be treated with prasugrel in the surveyed institutions (those with experiences of PCI on ≥5 ACS patients per month).

Also, in order to confirm the short- and long-term safety and efficacy (cardiovascular events, incidence of bleeding-related events, incidence of these events by patient characteristics, and identification of risk factors in particular), another specified use-results survey (survey on long-term use) will be conducted in patients who are to use prasugre for the first time and are scheduled to do so for a long-term period (ACS patients, non-ACS patients). The survey will be conducted for 3 years (observation period, 2 years) from 1 year after the market launch and collect data from 4000 patients, by using the continuous surveillance system. The safety will be investigated in bleeding, anaemia, thrombocytopenia, hepatic dysfunction/jaundice, in patients with severe cardiac disorder, in patients with severe hepatic impairment, in patients with history of intracranial haemorrhage, cerebral infarction, or TIA, in patients with severe renal impairment, in patients with poorly controlled hypertension, and in long-term treatment. The rationale for setting the number of patients is as follows. The percentage of the population with high

potential bleeding risk (severe cardiac disorder, severe hepatic impairment, severe renal impairment, cerebrovascular disorder, poorly controlled blood pressure), whose safety has not been evaluated because of exclusion from clinical studies, is estimated to be 25% of the total population to be treated. Assuming that the incidence of "major or minor bleeding" in the population without the above risks is approximately 2% and approximately 4% (risk ratio of 2) in the high risk population based on the past Japanese and foreign clinical data, it is necessary to ensure a total of 3200 patients in order to detect the difference with a statistical power of 80% at a two-sided significance level of 5%. Therefore, the planned number of patients was set at 4000 with an estimated drop-out rate of 20% at the end of the 2-year observation period.

PMDA considers as follows:
The loading dose and the maintenance dose proposed in Japan are different from those used in foreign countries. Therefore, it is necessary to collect information in routine clinical use on bleeding risks associated with the loading dose and the maintenance dose of prasugrel, and thereby to investigate the risk factors for bleeding. It is also important to collect information on haemorrhagic adverse events in patients with high risk factors for bleeding, such as elderly patients and low body weight patients. Furthermore, it is necessary to collect information on the following: safety in concomitant use with anticoagulants, drugs with antiplatelet activity, and other drugs that may enhance bleeding tendency; safety in patients with a history of cerebral infarction or TIA in whom prasugrel is contraindicated in foreign countries and its careful administration is considered appropriate in Japan; and pre-operative withdrawal period in patients who undergo CABG or other invasive procedures (e.g., surgery) and the occurrences of haemorrhagic adverse events. It is also necessary to investigate the occurrences of haemorrhagic adverse events in patients with renal or hepatic impairment by severity of the impairment.

In addition, it is necessary to collect information not only on haemorrhagic adverse events but also on the risks of abnormalities in all blood cell series such as TTP, thrombocytopenia, white blood cell count decreased, and pancytopenia, as well as hepatic dysfunction.

It is unclear from the view point of safety in patients scheduled to undergo PCI which is the best timing for the initial dosing of prasugrel, before, during, or after PCI. Therefore, it is essential to investigate the occurrences of haemorrhagic adverse events each time to start the treatment.

Prasugrel was not used for >48 weeks in any subject in the Japanese clinical studies, whereas in routine clinical use, ≥1 year long-term treatment is expected in many patients. Therefore, it is necessary to collect information on the efficacy and safety of long-term treatment with prasugrel.

As proposed by the applicant, it is appropriate to conduct use results surveys with emphasis both on events during the early period after the market launch and on events during long-term treatment. Although it is not recommended to administer prasugrel to hypertensive patients with poorly controlled blood pressure, information should be collected from all such patients if prasugrel is administered. The details of post-marketing information collection including specified use-results surveys will be further investigated taking account of comments raised in the Expert Discussion.

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

The assessment is currently ongoing. The results and PMDA's conclusion will be reported in Review Report (2).

IV. Overall Evaluation

As a result of the review described above, PMDA concluded that the efficacy of prasugrel (Efient) in patients with ischemic heart disease (UA, NSTEMI, STEMI, SA, OMI) who are to be managed with PCI has been demonstrated and its safety is not significantly different from that of the approved similar drug, and therefore that Efient may be made available in clinical settings. However, there are several points to consider regarding safety, including bleeding risk. Thus, it is necessary to collect information, after the market launch, on the safety in patients with risk factors for bleeding such as elderly patients

and low body weight patients and on the safety in patients with cerebral infarction or TIA, and to take appropriate measures.

PMDA considers that Efient may be approved if it can be concluded based on comments from the Expert Discussion that there are no particular problems.

Review Report (2)

January 30, 2014

I. Product Submitted for Registration

[Brand name]	Efient 3.75 mg/5 mg Tablets
[Non-proprietary name]	Prasugrel Hydrochloride
[Applicant]	Daiichi Sankyo Company, Limited
[Date of application]	June 18, 2013

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. Clinical positioning of prasugrel in ischemic heart disease to be managed with PCI

The sample size in the Japanese phase III studies was not sufficiently large to allow verification of the efficacy, and the dosage regimen investigated was different from that employed in the foreign ACS phase III study which demonstrated the superiority of prasugrel in efficacy to clopidogrel. Therefore, it cannot be concluded that prasugrel is more effective than clopidogrel in preventing cardiovascular events in Japanese patients. However, taking account of the submitted data on the prasugrel group and on the clopidogrel group in the Japanese and foreign clinical studies, the results of Japanese and foreign clinical studies of clopidogrel, and data on utilization of clopidogrel gathered so far, prasugrel is expected to be at least as effective as clopidogrel and is also presumed to have a similar level of safety to clopidogrel. Therefore, PMDA concluded that prasugrel may be positioned as an option for antiplatelet therapy with aspirin in patients with ischemic heart disease who are to be managed with PCI. This conclusion was supported by the expert advisors.

2. Indication

From the results of the foreign ACS phase III study, the Japanese phase III study in patients with ACS-PCI, and the Japanese phase III study in patients with elective PCI, the efficacy of prasugrel in Japanese patients is suggested, and it is considered that patients with ACS (UA, NSTEMI, STEMI), SA, or OMI who are to be managed with PCI are the patient population eligible for treatment with prasugrel. Therefore, PMDA concluded that prasugrel should be indicated for the disease conditions described below. This conclusion was supported by the expert advisors.

[Indication]
The following ischemic heart diseases in patients who are to be managed with percutaneous coronary intervention (PCI):

- Acute coronary syndrome (unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction)
- Stable angina pectoris and or old myocardial infarction

3. Dosage and administration

(1) Dosage and administration

Although the efficacy in Japanese patients has not been clearly verified, PMDA concluded that the dosage regimen of prasugrel should be set as shown below, as proposed by the applicant, taking account of the results of the efficacy and safety in the Japanese phase III studies. The following comments were raised from the expert advisors: (i) The conclusion of PMDA is appropriate; and (ii) the proposed doses in Japan are lower than those approved in foreign countries but the results of the Japanese phase III study suggest efficacy, and there was a higher incidence of haemorrhagic adverse events compared with clopidogrel, from which the proposed dosage regimen is considered to be the only viable option. Thus, the PMDA's conclusion was supported by the expert advisors.

[Dosage and administration]
The usual adult dosage of prasugrel is 20 mg administered orally as a single loading dose on Day 1, and then 3.75 mg once daily orally as the maintenance dose from Day 2 onward.

(2) Timing of the loading dose

PMDA concluded the timing of the loading dose as follows:
In the Foreign Study ACCOAST, the incidence of haemorrhagic adverse events including non-CABG-related major bleeding at 7 and 30 days after the start of prasugrel treatment was higher in the pre-administration group than in the non-pre-administration group, whereas there was no difference in the efficacy between the two groups. These results are important in evaluating the timing of the loading dose of prasugrel. In Japan, however, both the loading dose and the maintenance dose are lower than those used in foreign countries, precluding the conclusion that similar efficacy and safety as observed in the Foreign Study ACCOAST would be achieved in Japanese patients as well. In the Japanese phase III study in patients with ACS-PCI, similar efficacy was suggested regardless of the timing of the loading dose. Therefore, currently the timing of the initial load of prasugrel may be determined according to the clinical conditions etc., of patients. However, the results of this study showed that "major, minor or clinically significant bleeding" tended to occur more frequently when the loading dose was administered before PCI compared with the administration during or after PCI. Therefore, the Important Precautions section of the package insert should include the description "When the loading dose is administered before coronary angiography, due caution should be paid to bleeding," and information on the occurrences of haemorrhagic adverse events by timing of loading dose administration should be collected via post-marketing surveillance. To the above conclusion of PMDA, the following comments of the expert advisors were raised: (i) the conclusion of PMDA is appropriate; and (ii) although it is necessary to provide caution regarding the relationship between the timing of the loading dose and bleeding risk, the caution statement should not overemphasize the risk of administering prasugrel before coronary angiography, taking account of the types of events observed in clinical studies. Thus, the conclusion of PMDA was supported by the expert advisors.

Based on the above discussion, PMDA instructed the applicant to include the caution statement "When the loading dose is administered before coronary angiography, due caution should be paid to bleeding from the puncture site because of the increased bleeding risk due to the antiplatelet effect of Efient" in the "Important Precautions" section of the package insert, and the applicant followed the instructions appropriately.

(3) Cases where the loading dose is unnecessary

PMDA concluded that, in patients with SA or OMI who are scheduled to undergo PCI, it is unnecessary to administer the 20-mg loading dose provided that the antiplatelet effect of prasugrel has reached a steady state by the administration of the maintenance dose before PCI, and that the maintenance dose should be administered for 5 days, the period sufficient for the antiplatelet effect to reach a steady state, as expected from the results of the phase I repeated administration study etc. To the above conclusion of PMDA, the following comments were raised from the expert advisors: (i) the conclusion of PMDA is appropriate; and (ii) since 3-day administration of the 3.75-mg maintenance dose is unlikely to fully ensure the efficacy, it is appropriate to set the duration of the maintenance dose at 5 days; on the other hand (iii) if the duration of the administration is set at 5 days and an emergency operation becomes necessary after 3 to 4 days of the maintenance dose administration, it becomes necessary to administer the 20-mg loading dose and consequently safety concerns may arise. To this comment, PMDA explained that it is appropriate to specify the recommended duration of administration as 5 days in the package inert since time course changes in PK and PD after administration of prasugrel at the maintenance dose for 3 to 4 days followed by the 20-mg loading dose are expected to be within the range so far observed, and since in most of the patients who undergo PCI on a scheduled basis, and therefore it is possible to work out the schedule in a flexible manner. The conclusion of PMDA was supported by the expert advisors.

Based on the above discussion, PMDA instructed the applicant to include the following description in the "Precautions for Dosage and Administration" section of the package insert: "When Efient 3.75 mg has been administered for approximately 5 days before PCI, it is not mandatory to administer the loading

dose, i.e., 20 mg on the Day 1 of administration, (because the antiplatelet effect of Efient is considered to reach a steady state after 5-day administration).” The applicant responded to the instructions appropriately.

4. Safety

(1) Bleeding risk

The occurrences of bleeding events in the prasugrel group of the Japanese phase III studies were within the clinically acceptable range. However, in the Japanese phase III study in patients with ACS-PCI, the incidence of bleeding events associated with PCI was higher in the prasugrel group compared with the clopidogrel group. Thus, PMDA concluded that a caution statement should be provided in the package insert, taking account of these observations. This conclusion was supported by the expert advisors.

Based on the above, PMDA instructed the applicant to provide the information on the incidence of bleeding events in the prasugrel group and in the clopidogrel group of the Japanese phase III study in patients with ACS-PCI via package insert. The applicant responded to the instructions appropriately.

(2) Administration in patients with body weight of ≤50 kg

Taking account of the facts that, in foreign countries, a half-dose administration is considered for patients with low body weight (<60 kg), that, in the Japanese phase III studies, bleeding risk after prasugrel administration tended to be higher in patients weighing ≤50 kg than in those weighing >50 kg, and that, in the Japanese phase II dose-finding study, there was no tendency of inferior efficacy in prasugrel 20 + 2.5 mg compared with 20 + 3.75 mg in elderly or low body weight patients, PMDA concluded that, in patients weighing ≤50 kg, it is important first to carefully evaluate the appropriateness of treatment with prasugrel as the antiplatelet drug, and then to allow consideration of administering 20 + 2.5 mg depending on patients, based on the comprehensive evaluation of bleeding risk factors such as age and renal function and the severity of the risk of vascular events. To the conclusion of PMDA, the expert advisors commented that the conclusion of PMDA is appropriate, and that since there are many patients weighing ≤50 kg in Japan, consideration should be given to other options including use of clopidogrel in such patients. Finally, the conclusion of PMDA was supported by the expert advisors.

Based on the above discussion, PMDA instructed the applicant to provide, in the package insert, a caution statement including consideration of administering 20 + 2.5 mg to patients weighing ≤50 kg. The applicant responded appropriately.

(3) Administration in patients aged ≥75 years

The results of the Japanese phase III studies suggested that prasugrel is effective in patients aged ≥75 years to the same extent expected with clopidogrel, as is the case with patients aged <75 years. However, the results of the Japanese phase III study in patients with ACS-PCI suggested a higher bleeding risk in patients aged ≥75 years in the prasugrel group than in those in the clopidogrel group. Therefore, PMDA concluded that it is necessary to carefully evaluate the appropriateness of treatment with prasugrel to patients aged ≥75 years and to pay close attention to PCI-related bleeding after the procedure. This conclusion of PMDA was supported by the expert advisors.

(4) Administration in patients with renal impairment

Given the results of the Japanese phase III study in patients with ACS-PCI, prasugrel may be administered to patients with mild to moderate renal impairment. However, it should be determined in a comprehensive manner whether to use prasugrel, also taking account of the benefit-risk balance of other antiplatelet drugs depending on patients. Even if it is concluded that prasugrel can be indicated, due caution should be exercised to the possible increase in bleeding risk depending on the severity of renal impairment. Although the safety of prasugrel in patients with severe renal impairment is unknown, there is no clear tendency of an increase in the bleeding risk in patients with renal impairment when treated with prasugrel as compared with the risk following clopidogrel administration, albeit based on limited information. Therefore, it is appropriate currently to require careful administration in these patients as is the case for clopidogrel. The above conclusions of PMDA were supported by the expert advisors.

(5) Administration in patients with hepatic impairment

The Japanese phase III studies did not show any possibility of a significant decrease in the efficacy or safety of prasugrel in patients with mild to moderate hepatic impairment compared with patients with normal hepatic function. Similarly, the foreign clinical studies did not show any possibility of increased bleeding risk in patients with mild to moderate hepatic impairment compared with patients with normal hepatic function. Therefore, it is appropriate to administer prasugrel to these patients without modification of the dosage regimen. This conclusion of PMDA was supported by the expert advisors. Prasugrel has never been administered to patients with severe hepatic impairment in either Japanese or foreign clinical studies, and these patients generally have an increased bleeding risk compared with patients with mild to moderate hepatic impairment. Therefore, whether or not to administer prasugrel to these patients should be carefully determined by also taking account of other factors for bleeding risk and, even if it is deemed appropriate to administer prasugrel, careful administration is warranted to guard against haemorrhagic adverse events. This conclusion of PMDA was supported by the expert advisors.

(6) Administration in patients with a history of cerebral infarction or TIA

In foreign countries, prasugrel is contraindicated in patients with a history of cerebral infarction or TIA, based on the results of the foreign ACS phase III study. In the development in Japan, different doses were used from those used in foreign countries, by referring to the rate of inhibition of platelet aggregation, etc., in Japanese subjects. Therefore, it is possible that, in Japanese patients with a history of cerebral infarction or TIA, prasugrel may show a benefit-risk balance different from that observed in the foreign ACS phase III study and, currently it cannot be asserted that prasugrel should be contraindicated in patients with a history of cerebral infarction or TIA. Instead, prasugrel should be administered carefully while collecting information via post-marketing surveillance. This conclusion of PMDA was supported by the expert advisors. Also, the expert advisors commented that the data of the foreign ACS phase III study and the information that, in foreign countries, prasugrel is contraindicated in patients with a history of cerebral infarction or TIA should be provided to healthcare providers in clinical settings.

Based on the above, PMDA instructed the applicant to provide healthcare providers in clinical settings with the data of the foreign ACS phase III study and the information that, in foreign countries, prasugrel is contraindicated in patients with a history of cerebral infarction or TIA, and the applicant agreed to take appropriate measures.

(7) Withdrawal period before surgery

In the Japanese phase III study in patients with ACS-PCI, "major or minor bleeding" occurred in 12 of 13 subjects who underwent CABG within 14 days after the last dose in prasugrel group, and bleeding events associated with invasive procedures (e.g., CAG, PCI) were observed more frequently in the prasugrel group than in the clopidogrel group. Taking account of these observations, PMDA concluded that prasugrel should be discontinued ≥14 days before the surgery, as is required for clopidogrel. Some expert advisors agreed with the PMDA's conclusion, whereas other advisors commented that the withdrawal period for prasugrel before surgery should be determined not uniformly but based on the risk of bleeding and thrombosis, and that the justification for setting the withdrawal period at 14 days should be clarified. Based on the above discussion, PMDA explained that the description that the recommended withdrawal period is at least 14 days based on the results of the Japanese phase III studies would be included in the package insert together with the justification for the duration of the withdrawal period. This conclusion of PMDA was supported by the expert advisors.

Based on the above discussion, PMDA instructed the applicant to describe, in the "Important Precautions" section of the package insert, to the effect that it is desirable to discontinue the treatment ≥14 days before the surgery if the patient undergoes a surgery for which the antiplatelet effect of Efient is likely to pose a problem. PMDA also instructed the applicant to provide via package insert the information on the incidence of major and minor bleeding in subjects who underwent CABG within 14 days after the last dose of prasugrel in the Japanese phase III studies. The applicant took appropriate measures in response to these instructions.

(8) Concomitant use of prasugrel with anticoagulants

In patients who are already being treated with an anticoagulant because of atrial fibrillation etc., and in patients for whom a long-term treatment with an anticoagulant is indicated, it is assumed that they receive 3-drug combination therapy with aspirin, prasugrel, and warfarin or other oral anticoagulant. However, no data were available on 3-drug combination therapy in either Japanese or foreign clinical studies. Therefore, PMDA concluded that it is necessary not only to include anticoagulants in the "Precautions for coadministration" section of the package insert but also to provide a specific caution statement on concomitant use with anticoagulants in the "Important Precautions" section as well. This conclusion of PMDA was supported by the expert advisors.

Based on the above, PMDA instructed the applicant to provide a caution statement on concomitant use with anticoagulants in the "Important Precautions" section of the package insert, and the applicant responded appropriately.

(9) Concomitant use of prasugrel with drugs that have antiplatelet activity or possibly enhance bleeding tendency in some other way

NSAIDs were shown to increase the incidence of haemorrhagic adverse events when concomitantly administered with prasugrel in the Japanese phase III studies and in the foreign ACS phase III study. In addition to NSAIDs, there are other drugs that have antiplatelet activity or possibly enhance bleeding tendency in some other ways, but no sufficient information on concomitant use of such drugs with prasugrel was available during the development stage. Since caution should be exercised against bleeding risk in concomitant use of these drugs with prasugrel, PMDA concluded that they should be included in the "Precautions for coadministration" section of the package insert as the first step, as proposed by the applicant. This conclusion of PMDA was supported by the expert advisors.

(10) Risk of thrombotic thrombocytopenic purpura and of abnormality in blood cell series, and monitoring by blood test during prasugrel administration

Taking account of the occurrences of adverse events related to blood disorder and hepatic dysfunction in Japanese and foreign clinical studies, and of the post-marketing information in foreign countries, PMDA concluded that consideration should be given to performing a blood test approximately once every 2 weeks during the first 2 months after the start of prasugrel treatment, as is the case with clopidogrel. To this conclusion of PMDA, the expert advisors commented that since the safety profile of prasugrel in Japanese patients is largely unknown, it is necessary to take similar measures to those for clopidogrel, and the conclusion of PMDA is therefore acceptable. On the other hand, some expert advisors commented that, instead of simply applying the rule for blood testing during the initial stage of administration, which was set for the safety of ticlopidine, a rule for a blood test etc., should be determined as necessary based on the results of the post-marketing surveillance. PMDA responded to this comment that in the Japanese and foreign clinical studies, the incidence of adverse events related to blood disorders and hepatic dysfunction was higher within 8 weeks after the start of prasugrel treatment compared with the incidence after >8 weeks, and this situation was similar to that observed with clopidogrel. Therefore, currently it is impossible to conclude that a blood test should be exempted only for prasugrel. Instead, PMDA considers it appropriate for safety purpose to require, as the first step, that consideration be given to performing a blood test approximately once every 2 weeks during the first 2 months of treatment and, based on the results of the post-marketing surveillance etc., to evaluate the appropriateness of the rules. The conclusion of PMDA was finally supported by the expert advisors.

5. Post-marketing surveillance, etc.

Taking account of the results of the review in "4.(iii).B.(5) Post-marketing investigations" in Review Report (1) and of the comments raised from the expert advisors in the Expert Discussion, PMDA considers that the following points should be added to the post-marketing surveillance.

- Safety in concomitant use with anticoagulants, drugs that have antiplatelet activity, or other drugs that possibly enhance bleeding tendency in some other way
- Safety in patients who have undergone CABG or other invasive procedures (e.g., surgery)
- Occurrences of haemorrhagic adverse events by timing of the loading dose
- Efficacy of prasugrel at a 2.5-mg maintenance dose in patients weighing ≤50 kg

PMDA instructed the applicant to investigate the above points in the post-marketing surveillance, and in response to this, the applicant submitted an appropriate proposal for the post-marketing surveillance plan (Tables 34 and 35).

Based on the above discussion, PMDA concluded, regarding the risk management plan for prasugrel currently, that it is appropriate to perform the safety and efficacy evaluations as listed in Table 32 and to perform additional pharmacovigilance activities and risk minimization activities as shown in Table 33. In response, the applicant submitted a proposal for the risk management plan based on Tables 32 and 33.

Table 32. Safety and efficacy specifications in risk management plan

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Bleeding • Anaemia • Thrombotic thrombocytopenic purpura (TTP) • Thrombocytopenia • Hypersensitivity (including angioedema)	• Hepatic dysfunction, jaundice • Agranulocytosis, pancytopenia including aplastic anaemia • Colorectal cancer	• Safety in patients with severe cardiac disorder • Safety in patients with hepatic impairment • Safety in patients with a history of intracranial haemorrhage, cerebral infarction, or transient ischemic attack (TIA) • Safety in patients with renal impairment • Safety in long-term treatment • Safety in concomitant use with anticoagulants, drugs that have antiplatelet activity, or other drugs that possibly enhance bleeding tendency in some other way • Safety in patients who have undergone CABG or other invasive procedure (e.g., surgery) • Safety by the timing of the loading dose
Efficacy specifications		
• Efficacy in long-term treatment • Efficacy of a 2.5-mg maintenance dose		

Table 33. Outline of additional pharmacovigilance activities and risk minimization activities in the risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results surveys (survey on usage conditions in patients with acute coronary syndrome during the initial phase of administration) • Specified use-results surveys (survey on long-term use in patients with ischemic heart disease)	• Information provision based on the early post-marketing phase vigilance • Preparation and supply of materials for healthcare professionals and for patients

Table 34. Outline of the proposed specified use-results survey plan draft (survey on usage conditions in patients with acute coronary syndrome during the initial phase of administration)

Objective	Evaluation of safety and efficacy of prasugrel in routine clinical practice
Survey method	Continuous surveillance system
Patients surveyed	ACS patients before or after PCI
Observation period	≥1 month from the start of prasugrel treatment (the last day of the survey is handled as the last day of the all-case observation period)
Planned sample size	500 patients
Priority item	• Bleeding-related events
Main survey items	• Patient characteristics (e.g., height, body weight, haemorrhagic diathesis, past illness, concurrent illness) • Prasugrel administration conditions (e.g., the loading dose and the daily maintenance dose, day of starting treatment, treatment duration, day of treatment completion) • Administration conditions of antiplatelet drugs, anticoagulants, and other concomitant drugs • PCI implementation (e.g., whether or not PCI was used, whether or not the initial CAG was performed) • Implementation condition of CABG and other invasive procedures • Cardiovascular events and adverse events

Table 35. Outline of the specified use-results survey plan draft (survey on long-term use in patients with ischemic heart disease)

Objective	Evaluation of safety and efficacy of long-term use of prasugrel in routine clinical practice
Survey method	Continuous surveillance system
Patients surveyed	Patients with the following ischemic heart disease before or after PCI ACS (unstable angina, non ST segment elevation myocardial infarction, ST segment elevation myocardial infarction) Stable angina pectoris, and old myocardial infarction
Observation period	2 years
Planned sample size	4000 patients
Priority items	• Bleeding-related events • Cardiovascular events
Main survey items	• Patient characteristics (e.g., height, body weight, haemorrhagic diathesis, past illness, concurrent illness) • Prasugrel administration conditions (e.g., the loading dose and the daily maintenance dose, day of starting treatment, treatment duration, day of treatment completion) • Administration conditions of antiplatelet drugs, anticoagulants, and other concomitant drugs • PCI implementation (e.g., whether or not PCI was used, whether or not the initial CAG was performed) • Implementation conditions of CABG and other invasive procedures • Cardiovascular events and adverse events

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

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

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

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.5.1-1, 5.3.5.1-2, 5.3.5.1-3). As a result, the following findings were noted at some trial sites: protocol deviations (non-compliance with rules related to study drug administration), and lack of records on the information provision to a subject before repeated tests not specified in the written information for subjects and on the confirmation of subjects' willingness to continue the study. Thus, there were cases requiring improvements. However, since they were handled appropriately, PMDA concluded that the clinical studies as a whole were conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

Based on the above review, PMDA concludes that the product may be approved after modifying the indication and the dosage and administration as shown below. The re-examination period is 8 years. Neither the drug substance nor the drug product is classified as a poisonous drug or a powerful drug. The product is not classified as a biological product or a specified biological product.

[Indication]
The following ischemic heart diseases in patients who are to be managed with percutaneous coronary intervention (PCI):

- Acute coronary syndrome (unstable angina, non-ST segment elevation myocardial infarction, or ST segment elevation myocardial infarction)
- Stable angina pectoris or old myocardial infarction

[Dosage and administration]
The usual adult dosage of prasugrel is 20 mg administered orally as a single loading dose on Day 1, and then 3.75 mg once daily orally as the maintenance dose from Day 2 onward.