**Report on the Deliberation Results**

November 30, 2018
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| **Brand Name** | Vizimpro Tablets 15 mg |
| | Vizimpro Tablets 45 mg |
| **Non-proprietary Name** | Dacomitinib Hydrate (JAN*) |
| **Applicant** | Pfizer Japan Inc. |
| **Date of Application** | May 28, 2018 |

**Results of Deliberation**

In its meeting held on November 29, 2018, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

**Approval Conditions**

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

** Japanese Accepted Name (modified INN)*

**Review Report**

November 9, 2018
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

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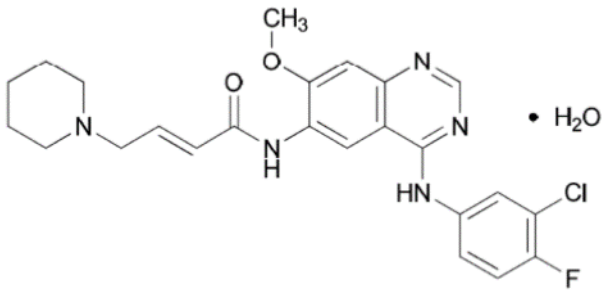
|---|---|
| **Brand Name** | Vizimpro Tablets 15 mg<br>Vizimpro Tablets 45 mg |
| **Non-proprietary Name** | Dacomitinib Hydrate |
| **Applicant** | Pfizer Japan Inc. |
| **Date of Application** | May 28, 2018 |
| **Dosage Form/Strength** | Tablets, each contains 15.576 or 46.729 mg of Dacomitinib Hydrate (equivalent to 15 or 45 mg of Dacomitinib, respectively) |
| **Application Classification** | Prescription drug, (1) Drugs with a new active ingredient |
| **Chemical Structure** |  |
| Molecular formula: | $C_{24}H_{25}ClFN_5O_2 \cdot H_2O$ |
| Molecular weight: | 487.95 |
| Chemical name: | (2*E*)-*N*-{4-[(3-Chloro-4-fluorophenyl)amino]-7-methoxyquinazolin-6-yl}-4-(piperidin-1-yl)but-2-enamide monohydrate |
| **Items Warranting Special Mention** | Priority review (PSEHB/PED Notification No. 0706-2 dated July 6, 2018 by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) |
| **Reviewing Office** | Office of New Drug V |

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of epidermal growth factor receptor (EGFR) mutation-positive, unresectable or recurrent non-small cell lung cancer, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Interstitial lung disease (ILD) needs to be further investigated through post-marketing surveillance.

**Indication**

EGFR mutation-positive, unresectable or recurrent non-small cell lung cancer

**Dosage and Administration**

The usual adult dosage is 45 mg of dacomitinib administered orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition.

**Approval Conditions**

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

**Attachment**

# Review Report (1)

October 2, 2018

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Vizimpro Tablets 15 mg<br>Vizimpro Tablets 45 mg |
| **Non-proprietary Name** | Dacomitinib Hydrate |
| **Applicant** | Pfizer Japan Inc. |
| **Date of Application** | May 28, 2018 |
| **Dosage Form/Strength** | Tablets, each contains 15.576 or 46.729 mg of Dacomitinib Hydrate (equivalent to 15 or 45 mg of Dacomitinib, respectively) |
| **Proposed Indication(s)** | EGFR mutation-positive, unresectable or recurrent non-small cell lung cancer |
| **Proposed Dosage and Administration** | The usual adult dosage is 45 mg of dacomitinib administered orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition. |

**Table of Contents**



**List of Abbreviations**

See Appendix.

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

### 1.1 Outline of the proposed product

The epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that is activated by binding of its ligands including epidermal growth factor (EGF) and forming a dimer and is thought to be involved in cell growth and survival, etc. (*Nat Rev Cancer*. 2005;5:341-54). In non-small cell lung cancer (NSCLC) with EGFR mutations, phosphorylation of tyrosine residues in the EGFR kinase domain is considered to activate downstream signaling pathways (e.g., mitogen-activated protein kinase [MAPK] pathway), thereby inducing the growth of tumor cells (*Nat Rev Cancer*. 2005;5:341-54).

Dacomitinib hydrate (hereinafter, dacomitinib), an EGFR tyrosine kinase inhibitor (EGFR-TKI) discovered by Pfizer Inc. (the US), is thought to inhibit the growth of EGFR mutation-positive NSCLC cells by suppressing EGFR tyrosine kinase phosphorylation.

Gefitinib, erlotinib, afatinib, and osimertinib, which inhibit the phosphorylation of EGFR tyrosine kinases similarly to dacomitinib, have been approved for the indication of EGFR mutation-positive, unresectable or recurrent NSCLC.

### 1.2 Development history etc.

Outside Japan, a phase I study in patients with advanced solid tumors (Study 1001) was initiated by Pfizer Inc. (the US) in October 2005. Later, the following 2 global phase III studies, (a) and (b), were initiated by companies including Pfizer Inc. (the US) in June 2011 and May 2013, respectively.

(a) Study 1009 in patients with unresectable advanced or recurrent NSCLC who were previously treated with 1 or 2 chemotherapy regimens
(b) Study 1050 in chemotherapy-naïve patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC

In Study 1009 conducted in patients with unresectable advanced or recurrent NSCLC with or without EGFR mutation, prolongation of progression free survival (PFS), the primary endpoint, was not demonstrated [see Section 7.1.3.2]. Taking account of the above, applications for approval of dacomitinib were submitted in the US and EU in January 2018 and February 2018, respectively, using the results from Study 1050 in patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC as the pivotal data. These applications are currently under review.

As of August 2018, dacomitinib has not been approved in any countries or regions.

In Japan, a phase I study in patients with advanced solid tumors (Study 1005) was initiated by the applicant in November 2008. In addition, enrollment of patients in the above-mentioned Study 1009 and Study 1050 was initiated in July 2011 and May 2013, respectively.

With the results of Study 1050 as the pivotal data, the application for approval of dacomitinib has now been submitted.

## 2. Data Relating to Quality and Outline of the Review Conducted by PMDA

### 2.1 Drug substance

#### 2.1.1 Characterization

The drug substance is a white to pale yellow powder. Its description, solubility, dissociation constant, partition coefficient, hygroscopicity, and thermal analysis have been determined. Although the drug substance exists in 3 crystalline forms including anhydride and hydrate ([redacted], [redacted] and [redacted]), it is manufactured commercially only in its [redacted] (monohydrate) form, and stability testing has confirmed that this [redacted] (monohydrate) form remains unchanged.

The chemical structure of the drug substance has been elucidated by ultraviolet-visible spectrophotometry (UV/VIS), infrared absorption spectrophotometry (IR), nuclear magnetic resonance spectrometry ($^{1}$H-, $^{13}$C-, $^{19}$F-, and $^{15}$N-NMR), mass spectrometry, X-ray crystallography, and elemental analysis.

#### 2.1.2 Manufacturing process

The drug substance is synthesized using [redacted],[1)] [redacted],[2)] and [redacted][3)] as starting materials.

Quality control strategies have been established based mainly on the following investigations, using a quality-by-design (QbD) approach (Table 1).

- Identification of critical quality attributes (CQAs)
- Based on the quality risk assessment and on the design of experiments, (a) identification of critical process parameters (CPPs) and critical material attributes and (b) investigation of acceptable ranges of manufacturing process parameters

**Table 1. Summary of control strategies for drug substance**

| CQA | Control methods |
|---|---|
| [redacted] | Manufacturing process, [redacted] |
| [redacted] | Manufacturing process, [redacted] |
| [redacted] | [redacted], [redacted] |
| [redacted] | [redacted] |
| [redacted] | Manufacturing process, [redacted] |
| [redacted] | [redacted] |
| [redacted] | Manufacturing process, [redacted] |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| [redacted] | Manufacturing process, [redacted] |

1) [redacted]
2) [redacted]
3) [redacted]

The purification step for [redacted] is defined as a critical step, and process control parameters and control values have been established for each step of [redacted] and [redacted]. [redacted][4)] is controlled as a critical intermediate.

### 2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of strength, description, identification (IR), purity (related substances [liquid chromatography (LC)] and residual solvents [gas chromatography (GC)]), water content, residue on ignition, [redacted], and assay (LC).

### 2.1.4 Stability of drug substance

The main stability studies of the drug substance are shown in Table 2. Photostability testing demonstrated that the drug substance is photostable.

**Table 2. Stability studies of the drug substance**

| Study | Primary batch | Temperature | Humidity | Storage container | Storage period |
|---|---|---|---|---|---|
| Long-term testing | 3 production batches | 25ºC | 60% RH | Double LDPE bag + HDPE drum | 60 months |
| Accelerated testing | 3 production batches | 40ºC | 75% RH | | 6 months |

LDPE, low density polyethylene; HDPE, high density polyethylene

Based on the above, a retest period of [redacted] months has been proposed for the drug substance when placed in a double layer low density polyethylene (LDPE) bag and stored in a high density polyethylene (HDPE) drum at room temperature.

## 2.2 Drug product

### 2.2.1 Description and composition of drug product and formulation development

The drug product is a film-coated, immediate-release tablet, each containing 15.576 or 46.729 mg of the drug substance (15 or 45 mg as dacomitinib). The drug product contains microcrystalline cellulose, lactose hydrate, sodium starch glycolate, magnesium stearate, and Opadry II Blue (85F30716) as excipients.

### 2.2.2 Manufacturing process

The drug product is manufactured through a process comprising the [redacted], [redacted] and [redacted], tableting, film coating, and packaging and labeling steps.

Quality control strategies have been established based mainly on the following investigations, using a QbD approach (Table 3).

- Identification of CQAs
- Based on the quality risk assessment and on the design of experiments, (a) identification of CPPs and (b) investigation of acceptable ranges of manufacturing process parameters

4) [redacted]

**Table 3. Summary of control strategies for drug product**

| CQA | Control methods |
|---|---|
| [redacted] | Manufacturing process, [redacted] |
| [redacted] | Manufacturing process, [redacted] |
| [redacted] | Manufacturing process, [redacted] |
| [redacted] | Manufacturing process, [redacted] |
| [redacted] | Manufacturing process, [redacted] |
| [redacted] | Manufacturing process, [redacted] |
| [redacted] | Manufacturing process, [redacted] |
| [redacted] | Manufacturing process, [redacted] |

The [redacted] and [redacted] steps are defined as critical steps, and process control parameters and control values have been established for the [redacted] step.

### 2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description, identification (LC and UV/VIS), purity (degradation products [LC]), [redacted], uniformity of dosage units (content uniformity [LC]), dissolution ([redacted]), and assay (LC).

### 2.2.4 Stability of drug product

The main stability studies of the drug product are shown in Table 4. [redacted] method ([redacted]) was used. Photostability testing demonstrated that the drug product is photostable.

**Table 4. Stability studies of drug product**

| Study | Primary batch | Temperature | Humidity | Storage container | Storage period |
|---|---|---|---|---|---|
| Long-term testing | 3 pilot-scale batches | 30ºC | 75% RH | PTP pack ([redacted]/ aluminum foil/[redacted] and aluminum foil) | 60 months |
| Accelerated testing | 3 pilot-scale batches | 40ºC | 75% RH | | 6 months |

Based on the above, a shelf life of 60 months has been proposed for the drug product when packaged in a press through pack (PTP) ([redacted]/aluminum foil/[redacted] and aluminum foil) and stored at room temperature in accordance with ICH Q1D Guidelines.

### 2.R Outline of the review conducted by PMDA

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

## 3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

### 3.1 Primary pharmacodynamics

#### 3.1.1 Inhibitory effects on phosphorylation of kinases including EGFR

##### 3.1.1.1 *In vitro* (CTD 4.2.1.1.1)

The inhibitory effect of dacomitinib on phosphorylation of human epidermal growth factor receptor (HER)1 (EGFR), HER2, and HER4, recombinant proteins, was investigated by enzyme-linked immunosorbent assay

(ELISA). The 50% inhibitory concentration ($IC_{50}$) value (mean ± standard error; n = 4) of dacomitinib was 6.0 ± 2.8 nmol/L against EGFR, 45.8 ± 2.4 nmol/L against HER2, and 69.6 ± 8.5 nmol/L against HER4.

The inhibitory effects of dacomitinib and its metabolite, PF-05199265, on phosphorylation of wild-type and mutant human EGFR (recombinant protein) were investigated by ELISA. The inhibition constant (Ki) values[5)] of dacomitinib and its metabolite, PF-05199265, were as shown in Table 5.

**Table 5. Inhibitory effects of dacomitinib and PF-05199265 on phosphorylation of EGFR**

| EGFR | Ki (nmol/L) | | | |
|---|---|---|---|---|
| | n | Dacomitinib | n | PF-05199265 |
| Wild-type | 4 | 0.4 ± 0 | 1 | 4.4 |
| L858R | 4 | 1.0 ± 0.1 | 1 | 1.4 |
| Ex19del | 4 | 3.8 ± 0.5 | 1 | 0.14 |
| Ex19del/T790M | 4 | 17 ± 1.0 | 1 | 21 |
| L858R/T790M | 44 | 2.2 ± 0 | — | |

Mean ± standard error (individual data if n = 1); —, not evaluated

The inhibitory effect of dacomitinib on 130 different kinases (recombinant proteins) was investigated by the fluorescence resonance energy transfer (FRET) approach. The inhibition rate of 1 μmol/L dacomitinib on phosphorylation of the kinases shown in Table 6 was ≥50%.

**Table 6. Inhibitory effect of dacomitinib on phosphorylation of kinases**

| Kinase | Inhibition rate (%)[*1] | Kinase | Inhibition rate (%)[*1] | Kinase | Inhibition rate (%)[*1] |
|---|---|---|---|---|---|
| EGFR | >100 | ABL2 | 67 | LYN A | 85 |
| $EGFR^{L858R}$ | 93 | BLK | 95 | PTK6 | 55 |
| $EGFR^{L861Q}$ [*2] | >100 | BTK | 73 | RET | 66 |
| HER2 | 99 | EPHB4 | 59 | VEGFR2 | 51 |
| HER4 | 100 | FGR | 90 | YES1 | 54 |
| ABL1 | 77 | $FLT3^{D835Y}$ [*4] | 71 | | |
| $ABL1^{T351I}$ [*3] | 57 | LCK | 87 | | |

n = 1 (individual data); [*1], {1 – (phosphorylation rate in the dacomitinib group/phosphorylation rate in the control [untreated] group)} × 100; [*2], Replacement of leucine at position 861 in EGFR with glutamine; [*3], Replacement of threonine at position 351 in ABL1 with isoleucine; [*4], Replacement of aspartic acid at position 835 in FLT3 with tyrosine

The inhibitory effect of dacomitinib on phosphorylation of EGFR was investigated in human squamous cell carcinoma-derived cell line, A431, by Western blotting. Dacomitinib inhibited the phosphorylation of EGFR with $IC_{50}$ (n = 1, individual data) of 21 nmol/L.

### 3.1.1.2 *In vivo* (CTD 4.2.1.1.1)

The inhibitory effect of dacomitinib on phosphorylation of (a) EGFR and (b) HER2 was investigated by Western blotting, using severe combined immunodeficient (SCID) mice implanted subcutaneously with (a) human NSCLC-derived NCI-H1975 cell line and (b) human ovarian cancer-derived SKOV3 cell line, respectively. The results are shown below.

5) Ki values were calculated based on the inhibition rates of dacomitinib and PF-05199265 against wild-type and mutant EGFR.

(a) Dacomitinib was orally administered at 7.5 or 15 mg/kg once daily (*quaque die* [QD]) for 14 days. The inhibition rate of dacomitinib against phosphorylation of EGFR 2 hours after completion of administration was 69% and 91%, respectively.

(b) Dacomitinib was orally administered at 30 mg/kg QD for 2 days. The inhibition rate of dacomitinib against phosphorylation of HER2 at the completion of administration was >85%.

### 3.1.2 Anti-tumor activity against malignant tumor-derived cell lines

#### 3.1.2.1 *In vitro* (CTD 4.2.1.1.1, 4.2.1.1.3)

The anti-tumor effects of dacomitinib and gefitinib, which has an inhibitory effect on EGFR, on 10 different human malignant tumor-derived cell lines were investigated using reductase activity as a measure of cell viability. The $IC_{50}$ values of dacomitinib and gefitinib were as shown in Table 7.

**Table 7. Anti-tumor effects of dacomitinib and gefitinib on human malignant tumor-derived cell lines**

| Cell source | Cell line | Genetic mutation or amplification | | | $IC_{50}$ (nmol/L) | |
|---|---|---|---|---|---|---|
| | | EGFR | HER2 | KRAS or BRAF | Dacomitinib | Gefitinib |
| NSCLC | HCC827 | Ex19del | None | None | 2.2 | 5.4 |
| | HCC4006 | Ex19del | None | None | 1.4 | 27.0 |
| | NCI-H125 | None | None | None | 27 | 202 |
| | HCC70 | None | None | None | 1600 | 5900 |
| | A549 | None | None | $KRAS^{G12V}$ *1 | >10,000 | — |
| | NCI-H1666 | None | None | $BRAF^{G465V}$ *2 | 8000 | 1900 |
| Colorectal cancer | HT-29 | None | None | $BRAF^{V600E}$ *3 | >10,000 | — |
| Breast cancer | MDA-MB-231 | None | None | $BRAF^{G464V}$ *4 | 5500 | >10,000 |
| | BT-474 | None | Amplified | None | 37 | 466 |
| Ovarian cancer | SKOV3 | None | Amplified | None | 392 | 1100 |

n = 1 (individual data); —, Not evaluated; *1, Replacement of glycine at position 12 in KRAS with valine; *2, Replacement of glycine at position 465 in BRAF with valine; *3, Replacement of valine at position 600 in BRAF with glutamic acid; *4, Replacement of glycine at position 464 in BRAF with valine

The anti-tumor effect of dacomitinib on NCI-H1975 cell line expressing mutant EGFR (L858R/T790M) was investigated using reductase activity as a measure of cell viability. The $IC_{50}$ value of dacomitinib (n = 1, individual data) was 342 nmol/L.

#### 3.1.2.2 *In vivo* (CTD 4.2.1.1.1)

##### 3.1.2.2.1 NSCLC cell lines

The anti-tumor activity of dacomitinib was investigated in SCID mice (n = 8/group) bearing subcutaneously implanted human NSCLC-derived NCI-H125 cells. Starting at the time point where tumor volume reached 200 to 250 $mm^3$, dacomitinib was administered orally at 15 or 30 mg/kg QD for 14 days. After administration, tumor volume was determined. Compared with the control (50 mmol/L sodium lactate buffer), dacomitinib showed statistically significant inhibition of tumor growth at a dose of 30 mg/kg ($P < 0.05$, one-way analysis of variance).

The anti-tumor activity of dacomitinib and erlotinib was investigated in SCID mice (n = 8/group) bearing subcutaneously implanted NCI-H1975 cells expressing mutant EGFR (L858R/T790M). Starting at the time

point where tumor volume reached 150 $mm^3$, dacomitinib at 7.5 or 15 mg/kg QD or erlotinib at 10 or 20 mg/kg QD was administered orally for 14 days. After administration, tumor volume was determined. Compared with the control (50 mmol/L sodium lactate buffer), both doses of dacomitinib showed statistically significant inhibition of tumor growth (Figure 1).

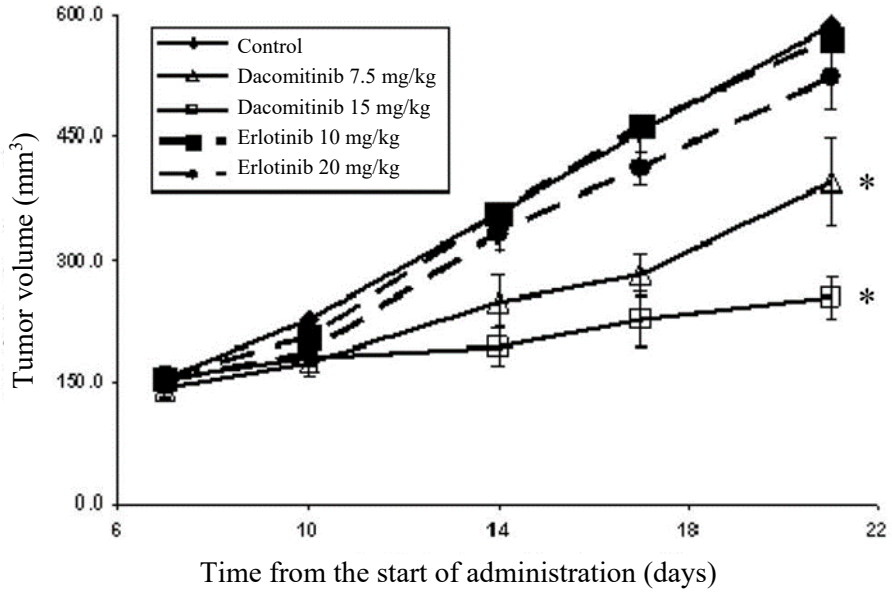



**Figure 1. Anti-tumor effect of dacomitinib in SCID mice bearing subcutaneously implanted NCI-H1975 cells**
n = 8; Mean ± standard error; *, $P < 0.05$ against the control group (one-way analysis of variance)

#### 3.1.2.2.2 Cell lines derived from non-NSCLC malignant tumors

The anti-tumor activity of dacomitinib was investigated in SCID mice bearing subcutaneously implanted (a) SKOV3 cell line (n = 6/group), (b) A431 cell line (n = 8/group), and (c) human breast cancer-derived BT-474 cell line (n = 10/group). The results were as shown below.

(a) Starting at the time point where tumor volume reached 200 to 250 $mm^3$, dacomitinib was administered orally at 15 or 30 mg/kg QD for 14 days. Compared with the control group (50 mmol/L sodium lactate buffer), both dacomitinib groups showed a statistically significant delay in tumor growth ($P < 0.001$, one-way analysis of variance).

(b) Starting at the time point where tumor volume reached 200 to 250 $mm^3$, dacomitinib was administered orally at 11 or 33 mg/kg QD for 14 days. Compared with the control group (50 mmol/L sodium lactate buffer), both dacomitinib groups showed a statistically significant delay in tumor growth ($P < 0.001$, one-way analysis of variance).

(c) Starting at the time point where tumor volume reached 200 to 250 $mm^3$, dacomitinib was administered orally at 15 or 30 mg/kg QD for 7 days. Compared with the control group (50 mmol/L sodium lactate buffer), both dacomitinib groups showed a statistically significant delay in tumor growth ($P < 0.05$, log-rank test).

## 3.2 Secondary pharmacodynamics

### 3.2.1 Effects on receptors, enzymes, transporters, and ion channels (CTD 4.2.1.2.1)

The effects of dacomitinib on 62 different receptors, enzymes, transporters, and ion channels were investigated. The $IC_{50}$ values against receptors, etc., on which 10 μmol/L of dacomitinib showed ≥50% inhibitory effect, are shown in Table 8.

**Table 8. Inhibitory effects of dacomitinib on receptors, enzymes, transporters, and ion channels**

| Receptors, etc. | $IC_{50}$ (μmol/L) | Receptors, etc. | $IC_{50}$ (μmol/L) |
|---|---|---|---|
| Nicotinic acetylcholine receptor | 18 | Muscarinic M1 receptor | 4.1 |
| L-type calcium ion channel (Dihydropyridine binding site) | 5.0 | ABL | 0.51 |
| L-type calcium ion channel (Verapamil binding site) | 4.3 | VEGFR2 | 0.55 |
| Sodium ion channel | 5.1 | LCK | 1.7 |
| Norepinephrine transporter | 5.9 | MAPK14 | 6.4 |
| Dopamine transporter | 5.6 | SRC | 0.56 |
| Choline transporter | 2.6 | | |

n = 1 (individual data)

Considering that the $C_{max}$ of unbound dacomitinib in plasma after administration at the recommended clinical dose, 45 mg QD, was $3.25 \times 10^{-3}$ μmol/L,[6)] the applicant interpreted the above results as showing that dacomitinib is unlikely to cause safety issues attributed to its inhibition of these receptors, etc., when used in clinical practice.

## 3.3 Safety pharmacology

### 3.3.1 Effects on the central nervous system (CTD 4.2.1.3.5, 4.2.1.3.6)

A single dose of dacomitinib was orally administered at 5, 50, or 500 mg/kg to rats (n = 6/group) to investigate the effects of the drug on nervous function using a functional observational battery and quantitative measurement of locomotor activity. No effects of dacomitinib were observed.

A single dose of dacomitinib was orally administered at 10 or 30 mg/kg to dogs (n = 3 or 4/group) to investigate the effects of the drug on clinical signs. Vomiting and soft faeces were observed in the dacomitinib 10 mg/kg group, and vomiting, soft faeces, conjunctival redness, half closed eyes, and corneal abnormalities (e.g., corneal oedema, conjunctival hyperaemia) were observed in the 30 mg/kg group.

Taking account of gastrointestinal and eye disorders observed in clinical studies [see Sections 7.R.3.3, 7.R.3.4, and 7.3] in addition to the above results, the applicant explained that information regarding these findings will be provided appropriately to healthcare professionals through the package insert.

6) The value was calculated based on the $C_{max}$ (79.5 ng/mL) on Day 14 of Cycle 1 in Japanese patients with advanced solid tumors in Study 1005 of multiple doses of dacomitinib administered at 45 mg QD [see Section 6.2.1.1].

### 3.3.2 Effects on the cardiovascular system

#### 3.3.2.1 Effects on human *ether-a-go-go* related gene potassium current (CTD 4.2.1.3.1)

The effects of 0.2, 0.7, 2.3, and 9.3 μmol/L dacomitinib on human *ether-a-go-go* related gene (hERG) potassium current were investigated in human embryonic kidney-derived HEK293 cells transfected with hERG. The inhibition rate (mean ± standard deviation [SD], n = 3-5) of dacomitinib against hERG potassium current was 4.5% ± 2.1% at 0.2 μmol/L, 26.5% ± 12.5% at 0.7 μmol/L, 63.1% ± 19.7% at 2.3 μmol/L, and 92.0% ± 3.6% at 9.3 μmol/L. Compared with the control (0.1% DMSO-containing Tyrode's solution[7)]), dacomitinib at any concentration showed statistically significant inhibition of hERG potassium current ($P < 0.05$, Student's t-test) with $IC_{50}$ of 1.58 μmol/L.

#### 3.3.2.2 Effects on action potential (CTD 4.2.1.3.3)

The effects of 0.3, 1, 3, and 10 μmol/L dacomitinib on cardiac action potential (resting membrane potential, action potential amplitude [APA], maximum rate of depolarization [$V_{max}$], action potential duration at 50% repolarization [$APD_{50}$], and action potential duration at 90% repolarization [$APD_{90}$]) were investigated in cardiac Purkinje fibers obtained from dogs. No effects of dacomitinib were observed.

#### 3.3.2.3 Effects on blood pressure, heart rate, and electrocardiogram (CTD 4.2.1.3.6)

A single dose of dacomitinib was orally administered at 10 or 30 mg/kg to dogs (n = 3 or 4/group) to investigate the effects of the drug on blood pressure (systolic, diastolic, and mean), heart rate, and electrocardiogram (PR, QRS, RR, QT, and QTc intervals). Compared with the control (0.5% methylcellulose), dacomitinib statistically significantly increased systolic blood pressure when administered at 30 mg/kg ($P < 0.05$[8)]).

Considering that the $C_{max}$ of unbound dacomitinib in plasma (45.1 ng/mL) in dogs after administration of the drug at 30 mg/kg was 30-fold that (1.53 ng/mL[6)]) after administration of the drug to humans at the recommended clinical dose (45 mg QD), the applicant interpreted the above results as showing that dacomitinib is unlikely to cause safety issues when used in clinical settings.

### 3.3.3 Effects on the respiratory system (CTD 4.2.1.3.4)

A single dose of dacomitinib was orally administered at 5, 50, or 500 mg/kg to rats (n = 6/group) to investigate the effects of the drug on the respiratory function (respiratory rate and tidal volume). Compared with the control (0.5% methylcellulose), dacomitinib statistically significantly increased tidal volume when administered at 5 mg/kg ($P < 0.05$[9)]).

Considering that no increase in tidal volume was observed in the 50 or 500 mg/kg group, the applicant explained that the above increase in tidal volume was unlikely to be associated with dacomitinib.

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7) 137 mmol/L sodium chloride, 4 mmol/L potassium chloride, 1.8 mmol/L calcium chloride, 1 mmol/L magnesium chloride, 10 mmol/L glucose, and 10 mmol/L HEPES

8) A statistically significant difference ($P < 0.05$) was considered to be observed when 95% confidence interval (CI) calculated using the mean and standard error of each dose group did not contain 0.

9) The *P* value determined based on comparison using a mixed effect model with dose group, time point, and interaction between dose group and time point as fixed effects and individual animals as random effect

### 3.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation of the nonclinical pharmacology of dacomitinib, excluding the following issues discussed in the sections below, is acceptable.

#### 3.R.1 Mechanism of action and efficacy of dacomitinib

The applicant explained the mechanism of action and efficacy of dacomitinib as follows.

The applicant's explanation:

Dacomitinib, an EGFR-TKI, is considered to inhibit the growth of EGFR mutation-positive tumors by suppressing the tyrosine kinase activity of EGFR with activating mutations (Ex19del and L858R) [see Sections 3.1.1 and 3.1.2].

Ex19del and L858R activating mutations account for approximately 90% of EGFR mutations observed in NSCLC (*Clin Cancer Res.* 2015;21:5305-13). In patients with NSCLC with the remaining 10% of EGFR mutations, activating mutations other than Ex19del and L858R have been reported (*Nat Rev Cancer.* 2007;7:169-81, etc.). In addition to the mechanism of action of dacomitinib, the inhibitory effect of dacomitinib on the phosphorylation of EGFR with activating mutations other than Ex19del and L858R was observed (*Clin Cancer Res.* 2015;21:5305-13). Therefore, dacomitinib is expected to be effective for treating patients with NSCLC with activating mutations including Ex19del and L858R.

T790M mutation was reported as the primary mechanism of acquiring resistance to existing EGFR-TKIs (gefitinib and erlotinib) (*Proc Natl Acad Sci USA.* 2005;102:7665-70). Considering that the anti-tumor activity of dacomitinib was observed in SCID mice bearing subcutaneously implanted cells derived from human T790M mutation-positive NSCLC [see Section 3.1.2], dacomitinib may also be effective in treating patients with T790M mutation-positive NSCLC.

Furthermore, the applicant explained how the pharmacological properties of dacomitinib are different from those of other EGFR-TKIs approved in Japan (i.e., gefitinib, erlotinib, afatinib, and osimertinib) as follows.

The applicant's explanation:

The following differences between dacomitinib and gefitinib, erlotinib, and osimertinib have been reported. While both dacomitinib and afatinib have an inhibitory effect on phosphorylation of EGFR, no differences in the pharmacological properties of these drugs have been reported at present.

- Dacomitinib inhibited phosphorylation of not only EGFR but also HER2 and HER4 [see Section 3.1.1]. Meanwhile, gefitinib and erlotinib inhibited phosphorylation of EGFR but not of HER2 or HER4 (*Nat Rev Cancer.* 2005;5:341-54).
- Both dacomitinib and osimertinib inhibited phosphorylation of EGFR with T790M mutation (mutation that is resistant to gefitinib and erlotinib) (*Cancer Discov.* 2014;4:1046-61).

PMDA's view:

The applicant's explanation is generally accepted. However, given the limited information available about the extent to which activating mutations other than Ex19del and L858R are involved in cancer progression, the efficacy of dacomitinib remains unknown in patients with NSCLC with such mutations. Information on relationships between the types of EGFR activating mutations and the efficacy of dacomitinib would be beneficial from the viewpoint of selecting appropriate patients in clinical settings. Therefore, collection of the relevant information should continue. New findings should be provided to healthcare professionals appropriately.

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

In this section, doses and concentrations of dacomitinib are expressed as anhydride. The pharmacokinetics (PK) of dacomitinib in animals such as rats and dogs was investigated. Investigation of plasma protein binding, drug-metabolizing enzymes, and transporters of dacomitinib was performed using human- or animal-derived biological samples.

### 4.1 Absorption

#### 4.1.1 Single-dose studies

Following a single intravenous dose of dacomitinib 5 or 25 mg/kg or a single oral dose of dacomitinib 50 or 750 mg/kg to male rats, plasma concentrations of dacomitinib were determined (Table 9). The bioavailability (BA) of dacomitinib orally administered at 50 mg/kg was 79.5%.[10)]

**Table 9. PK parameters of dacomitinib (male rats, single intravenous or oral administration)**

| Administration route | Dose (mg/kg) | n | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $AUC_{inf}$ (ng·h/mL) | $t_{1/2}$ (h) | $CL_{tot}$ (mL/min/kg) | $V_{ss}$ (L/kg) |
|---|---|---|---|---|---|---|---|---|
| Intravenous | 5 | 3 | 1540 ± 581 | — | 2060 ± 90.7 | 9.8 ± 0.7 | 49.1 ± 2.2 | 34.2 ± 2.8 |
| | 25 | 3 | 10,100 ± 10,700 | — | 12,900 ± 1420 | 16.7 ± 1.5 | 32.6 ± 3.4 | 39.8 ± 5.1 |
| Oral | 50 | 2 | 636, 623 | 6.0, 4.0 | 21,900, 19,100 | 24.5, 14.3 | — | — |
| | 750 | 2 | 1090, 1240 | 8.0, 72.0 | — | — | — | — |

Mean ± SD (individual data if n = 2); —, Not calculated

#### 4.1.2 Repeated-dose studies

Dacomitinib was orally administered at 0.03, 0.1, or 1 mg/kg QD for 39 weeks to male and female dogs to determine plasma concentrations of dacomitinib (Table 10). No clear sex differences were observed in the PK parameters of dacomitinib. Within the dose range studied, the $C_{max}$ and $AUC_{24h}$ of dacomitinib increased nearly dose-proportionally. Repeated administration of dacomitinib had no clear effects on the $C_{max}$ or $AUC_{24h}$.

10) The BA was determined using $AUC_{inf}$ data following an intravenous administration at 25 mg/kg.

**Table 10. PK parameters of dacomitinib (male and female dogs, 39-week repeated oral administration)**

| Measurement day (Day) | Dose (mg/kg) | Sex | n | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $AUC_{24h}$ (ng·h/mL) |
|---|---|---|---|---|---|---|
| 1 | 0.03 | Male | 5 | 0.723 ± 0.112 | 3.6 ± 0.89 | 6.32 ± 3.37 |
| | | Female | 6 | 0.769 ± 0.0930 | 4.0 ± 0 | 9.12 ± 1.11 |
| | 0.1 | Male | 6 | 2.38 ± 0.349 | 3.7 ± 0.82 | 30.3 ± 5.84 |
| | | Female | 6 | 1.73 ± 0.427 | 5.0 ± 1.5 | 21.8 ± 4.90 |
| | 1 | Male | 6 | 17.8 ± 6.01 | 4.2 ± 1.6 | 221 ± 72.7 |
| | | Female | 6 | 18.3 ± 7.99 | 4.2 ± 1.6 | 233 ± 97.7 |
| 90 | 0.03 | Male | 5 | 0.642 ± 0.0310 | 4.6 ± 1.3 | 8.30 ± 0.931 |
| | | Female | 6 | 0.647 ± 0.109 | 4.3 ± 2.3 | 8.76 ± 0.528[*1] |
| | 0.1 | Male | 6 | 2.52 ± 1.09 | 4.8 ± 2.5 | 35.8 ± 13.8 |
| | | Female | 6 | 2.16 ± 0.444 | 4.7 ± 2.0 | 30.5 ± 7.82 |
| | 1 | Male | 6 | 22.8 ± 3.71 | 3.0 ± 1.1 | 302 ± 51.0 |
| | | Female | 6 | 22.7 ± 3.49 | 3.8 ± 1.8 | 337 ± 71.3 |
| 272 | 0.03 | Male | 1 | 0.518 | 4.0 | — |
| | | Female | 4 | 0.591 ± 0.0699 | 2.0 ± 0 | 2.33, 2.36[*2] |
| | 0.1 | Male | 6 | 1.64 ± 0.693 | 4.2 ± 1.6 | 26.3 ± 12.7 |
| | | Female | 6 | 1.59 ± 0.364 | 5.5 ± 1.6 | 22.6 ± 9.29 |
| | 1 | Male | 6 | 20.3 ± 6.11 | 3.7 ± 0.82 | 294 ± 83.0 |
| | | Female | 6 | 20.4 ± 3.57 | 5.0 ± 1.5 | 322 ± 67.8 |

Mean ± SD (individual data if n = 1 or 2); —, Not calculated; [*1], n = 4; [*2], n = 2

### 4.1.3 *In vitro* membrane permeability

A human colon carcinoma-derived cell line (Caco-2) was used to investigate the membrane permeability of dacomitinib. The apparent permeability in the apical-to-basolateral direction ($P_{app\ A\rightarrow B}$) of $^{14}$C-dacomitinib at 2 to 100 μmol/L was 2.66 to 8.00 × $10^{-6}$ cm/sec. Taking into account the above results and that the $P_{app\ A\rightarrow B}$ of 1 to 10 × $10^{-6}$ cm/sec is categorized as moderate permeability (*Drug Metab Dispos.* 2008;36:268-75), the applicant considers that dacomitinib has moderate membrane permeability.

## 4.2 Distribution

### 4.2.1 Tissue distribution

A single dose of $^{14}$C-dacomitinib was orally administered at 4.98 mg/kg to pigmented male rats to investigate tissue distribution of radioactivity using quantitative whole-body autoradiography.

Radioactivity was broadly distributed in various tissues, and its levels peaked by 24 hours post-dose in any tissue. Radioactivity was markedly higher in the uvea, meninges, Harderian gland, and lacrimal gland than in the blood at any measurement time point. Radioactivity was detected in cerebrospinal fluid and most of the central nervous system tissues. This finding, according to the applicant, suggests that dacomitinib or its metabolites cross the blood brain barrier.

Radioactivity was the highest in the uvea at 18 hours post-dose (44.0 μg Eq./g), and was still detected in the uvea at 504 hours post-dose at the highest level of 36%. The applicant interpreted these findings as suggesting that dacomitinib or its metabolites bind to melanin.

### 4.2.2 Plasma protein binding

Plasma samples from mice, rats, dogs, and humans were incubated with $^{14}$C-dacomitinib (250 or 1000 ng/mL) at 37ºC for 6 hours, and the plasma protein binding of dacomitinib was evaluated by the equilibrium dialysis method. The plasma protein binding rate of dacomitinib in these samples was 97.8% and 97.5% for mice, 97.4% and 96.8% for rats, 96.9% and 97.2% for dogs, and 98.0% and 98.2% for humans.

Human serum albumin and human α1-acidic glycoprotein were incubated with dacomitinib (470 ng/mL) at room temperature for 2 minutes, and the binding of dacomitinib to human serum albumin and human α1-acidic glycoprotein was evaluated by the equilibrium dialysis method. The binding rate of dacomitinib to human serum albumin and human α1-acidic glycoprotein was 92.7% and 87.1%, respectively. The above findings, according to the applicant, suggest that dacomitinib binds to both serum albumin and α1-acidic glycoprotein in human plasma.

### 4.2.3 Distribution in blood cells

Blood samples from mice, rats, dogs, monkeys, and humans were incubated with $^{14}$C-dacomitinib (500 ng/mL) at 37ºC for 30 minutes, and distribution of dacomitinib into blood cells was determined. The blood-to-plasma ratio of radioactivity in these samples was 1.75 for mice, 1.57 for rats, 1.50 for dogs, 1.91 for monkeys, and 1.08 for humans. These findings, according to the applicant, suggest that there is little variation in the distribution of dacomitinib into red blood cells and plasma in humans and that the distribution of dacomitinib into red blood cells is slightly higher than it is in plasma in the other animal species investigated.

### 4.2.4 Placental permeability and placental transfer to the fetus

Placental permeability and placental transfer of dacomitinib to the fetus have not been investigated. In an embryo-fetal development study in rats, decreased body weight of the fetus was observed [see Section 5.5]. The above finding, according to the applicant, suggests that dacomitinib or its metabolites cross the placenta into the fetus.

## 4.3 Metabolism

### 4.3.1 *In vitro*

According to the applicant, the results of the following investigations suggest that the major metabolic pathways of dacomitinib are oxidation and glutathione conjugation.

- Rat, dog, monkey, and human liver microsomes were incubated with $^{14}$C-dacomitinib (20 μmol/L) at 37ºC for 30 minutes in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) to investigate metabolites of dacomitinib. In any of rat, dog, monkey, and human samples, M6 (hydroxy pyrrolidine metabolite) and M8 (*N*-oxidized piperidine ring metabolite) were detected. In dog and monkey samples, M3 (defluorinated and hydroxylated metabolite) was also detected.
- Rat and human hepatocytes were incubated with $^{14}$C-dacomitinib (10 μmol/L) at 37ºC for 4 hours to investigate metabolites of dacomitinib. In both rat and human hepatocytes, M6, M8, and M9

(oxopiperidine metabolite) were detected. In human hepatocytes, M2 (cysteine conjugate metabolite) and M3 were also detected.

The results of the following investigations, according to the applicant, suggest that cytochrome P450 (CYP) 2D6 is mainly involved in the metabolism of dacomitinib into PF-05199265 (*O*-desmethyl metabolite) and that CYP3A4 is mainly involved in the metabolism of dacomitinib into other oxidized metabolites.

- Recombinant human CYP isozymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, and CYP3A5) were incubated with dacomitinib (1 μmol/L) at 37ºC for 45 minutes in the presence of NADPH to investigate CYP isozymes involved in the metabolism of dacomitinib and formation of PF-05199265. The results showed that CYP2J2 and CYP3A4 decreased the amount of dacomitinib. The intrinsic clearance ($CL_{int}$) of CYP2J2 and CYP3A4 calculated based on the elimination rate of dacomitinib was 0.119 and 0.487 μL/min/pmol, respectively. PF-05199265 was formed by CYP2C9 and CYP2D6.
- Recombinant human CYP3A4 was incubated with dacomitinib (10 μmol/L) at 37ºC for 30 minutes in the presence of NADPH to investigate metabolites of dacomitinib. M9 (oxopiperidine metabolite), M10 (carboxylic acid metabolite), and M20 (di-oxygenated metabolite) were detected.
- Microsomes prepared from insect cells in which human CYP2C9 and CYP2D6 were expressed were incubated with dacomitinib (0.005-10 μmol/L) at 37ºC for 30 minutes in the presence of NADPH to investigate $CL_{int}$. The $CL_{int}$ of CYP2C9 and CYP2D6 calculated based on the formation rate of PF-05199265 was 0.0106 and 0.392 μL/min/pmol, respectively.

#### 4.3.2 *In vivo*

A single dose of $^{14}$C-dacomitinib was administered at 1 mg/kg orally to intact or bile duct-cannulated male and female dogs to investigate metabolites of dacomitinib in plasma, urine, feces, and bile. The results are shown below.

- In plasma collected from intact male and female dogs by 12 hours post-dose, unchanged dacomitinib (29.6% and 54.8% of the total radioactivity in plasma in male and female dogs, respectively) was mainly detected. In urine collected by 48 hours post-dose, unchanged dacomitinib (1.4% and 3.6% of the administered radioactivity in male and female dogs, respectively) was mainly detected. Any metabolite detected was <1% of the administered radioactivity. In feces collected by 120 hours post-dose, the following was mainly detected: a mixture of PF-05199265 and M10 (23.5% and 19.2%), M12 (hydroxy-piperidine ring metabolite) (16.3% and 18.1%), unchanged dacomitinib (12.9% and 13.1%), a mixture of M3 and M11 (de-piperidine ring metabolite) (10.4% and 7.77%), M13 (dihydroxylated metabolite) (5.37% and 5.29%), M14 (mercaptoacetic acid conjugate metabolite) (5.02% and 5.44%), and M2 (4.84% and 5.15%).
- In bile collected from bile duct-cannulated male and female dogs by 48 hours post-dose, unchanged dacomitinib (5.33% and 0.63%) was mainly detected.

### 4.4 Excretion

#### 4.4.1 Urinary, fecal, and biliary excretion

A single dose of $^{14}$C-dacomitinib was administered at 1 mg/kg orally to intact or bile duct-cannulated male and female dogs to investigate excretion (expressed as a percentage of the administered radioactivity) in urine, feces, and bile. In intact dogs, excretion in urine and feces up to 168 hours post-dose was 2.73% and 88.9%, respectively, in males and 5.90% and 82.3%, respectively, in females. In bile duct-cannulated dogs, the radioactivity recovered in bile up to 48 hours post-dose was 9.08% in males and 2.64% in females. The above results, according to the applicant, suggest that dacomitinib and its metabolites are mainly excreted in feces.

#### 4.4.2 Excretion in milk

Excretion of dacomitinib in milk has not been investigated. Taking into account the physicochemical properties (e.g., at pH of 7.4, the logD value, 4.2; pKa value, 5.03 and 8.46; molecular weight, 469.94) and that dacomitinib has been confirmed to be a substrate of breast cancer resistance protein (BCRP) [see Section 4.5.3], the applicant explained that dacomitinib may be excreted in milk.

### 4.5 Pharmacokinetic interactions

#### 4.5.1 Enzyme inhibition

Based on the results of the following investigations and the steady-state $C_{max}$ of dacomitinib (0.169 μmol/L[11)]) after administration at the proposed dosage regimen, the applicant explained that pharmacokinetic interaction may be mediated by dacomitinib-induced inhibition of CYP2D6 and UGT1A1 in clinical settings.

- Human liver microsomes were incubated with substrates[12)] of CYP isozymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) in the presence of dacomitinib (0.095-30 μmol/L) and NADPH to investigate inhibitory effects of dacomitinib on CYP isozymes. Dacomitinib inhibited metabolism of substrates of CYP2D6 and CYP3A with $IC_{50}$ values of 0.063 and 16 μmol/L, respectively. Dacomitinib showed no clear inhibitory effect on the metabolism of other CYP isozyme substrates tested.
- Human liver microsomes were incubated in the presence of dacomitinib (300 μmol/L[13)]) and NADPH, and then incubated with substrates[12)] of CYP isozymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) to investigate time-dependent inhibitory effects of dacomitinib on CYP isozymes. Dacomitinib showed no clear time-dependent inhibitory effect on the metabolism of any CYP isozyme substrates tested.
- Human liver microsomes were incubated with substrates[14)] of uridine diphosphate glucuronosyl transferase (UGT) isozymes (UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15) in the presence or absence of bovine serum albumin (BSA), and then with dacomitinib (1-100 μmol/L[15)]) and

11) The $C_{max}$ on Day 14 of Cycle 1 in Japanese patients with advanced solid tumors receiving multiple doses of dacomitinib at 45 mg QD in Study 1005
12) As substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, phenacetin, bupropion, amodiaquine, diclofenac, *S*-mephenytoin, and dextromethorphan, respectively, were used. As substrates of CYP3A, midazolam, testosterone, and felodipine were used. For investigation of time-dependent inhibitory effects, midazolam and testosterone were used.
13) For investigation for CYP2D6, dacomitinib was used at a concentration of 0.217 μmol/L.
14) As substrates of UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15, β-estradiol, trifluoperazine, 5-hydroxytryptophol, propofol, zidovudine, and oxazepam, respectively, were used.
15) Inhibitory effect on UGT2B15 in the presence of BSA was examined using 6 to 300 μmol/L dacomitinib.

uridine diphosphate glucuronic acid (UDPGA) to investigate inhibitory effects of dacomitinib on UGT isozymes. In the absence of BSA, dacomitinib inhibited metabolism of substrates of UGT1A1, UGT1A4, UGT2B7, and UGT2B15 with $IC_{50}$ values of 2.1, 24, 38, and 38 μmol/L, respectively. Meanwhile, dacomitinib showed no clear inhibitory effect on the metabolism of other UGT isozyme substrates tested. In the presence of BSA, dacomitinib inhibited metabolism of substrates of UGT1A1, UGT2B7, and UGT2B15 with $IC_{50}$ values of 3.2, 99, and 204 μmol/L, respectively. Dacomitinib showed no clear inhibitory effect on the metabolism of other UGT isozyme substrates tested.

#### 4.5.2 Enzyme induction

Human hepatocytes were treated with dacomitinib (at 0.03-10 μmol/L) for 2 days to investigate mRNA expression and enzyme activities of CYP isozymes (CYP1A2, CYP2B6, and CYP3A) induced by dacomitinib. Dacomitinib did not clearly induce mRNA expression and enzyme activities of any CYP isozymes. Based on the above results and the steady-state $C_{max}$ of dacomitinib (0.169 μmol/L[11)]) after administration at the proposed dosage regimen, the applicant explained that pharmacokinetic interaction is unlikely to be mediated by CYP isozymes induced by dacomitinib in clinical settings.

#### 4.5.3 Transporters

The results of the following investigations demonstrated that dacomitinib is a substrate of P-glycoprotein (P-gp) and BCRP. However, given that the absolute BA of dacomitinib in humans is 80.0% [see Section 6.1.3.2], P-gp and BCRP is unlikely to be involved in the gastrointestinal absorption of dacomitinib. Based on the above, the applicant considers that the use of dacomitinib in combination with a P-gp- or BCRP-inhibitor is unlikely to cause pharmacokinetic interactions.

- Transport of dacomitinib (0.29-10.4 μmol/L) via P-gp or BCRP was investigated in Madin-Darby canine kidney (MDCK) cells expressing human P-pg or BCRP. The ratio of the efflux ratio of dacomitinib in cells expressing P-gp or BCRP to that in cells expressing no P-gp or BCRP was 1.0 to 2.3 and 0.8 to 3.6, respectively.
- Transport of dacomitinib (0.1-100 μmol/L) via organic anion transporting polypeptide (OATP)1B1 or OATP1B3 was investigated in HEK293 cells expressing human OATP1B1 or OATP1B3. The ratio of the uptake of dacomitinib in cells expressing OATP1B1 or OATP1B3 to that in cells expressing no OATP1B1 or OATP1B3 was <2 for both transporters.

Based on the results of the following investigations, the steady-state $C_{max}$ of dacomitinib (0.169 μmol/L[11)]) after administration at the proposed dosage regimen, and the estimated concentration of dacomitinib (383 μmol/L) in the gastrointestinal tract after administration at the proposed dosage regimen, the applicant considers that pharmacokinetic interaction may be mediated by dacomitinib-induced inhibition of BCRP, OCT1, or P-gp in the gastrointestinal tract.

- The inhibitory effect of dacomitinib (0.2-30 μmol/L) on the transport of digoxin (12 μmol/L) via P-gp was investigated in Caco-2 cells. Dacomitinib inhibited the transport of the substrate of P-gp with $IC_{50}$ of 7.74 μmol/L.

- The inhibitory effect of dacomitinib (0.1-100 μmol/L) on the transport of $^{3}$H-prazosin (1 μmol/L) via BCRP was investigated in MDCK II cells expressing human BCRP. Dacomitinib inhibited the transport of the substrate of BCRP with $IC_{50}$ of 0.5 μmol/L.
- The inhibitory effect of dacomitinib (0.1-100 μmol/L) on the transport of $^{3}$H- taurocholic acid (2 μmol/L) via bile salt export pump (BSEP) was investigated in membrane vesicles prepared from insect cell-derived Sf9 cells expressing human BSEP. Dacomitinib inhibited the transport of the substrate of BSEP with $IC_{50}$ of 5.3 μmol/L.
- The inhibitory effect of dacomitinib (0.041-30 μmol/L) on the transport of a substrate[16)] of each transporter via OATP1B1, OATP1B3, or OCT1 was investigated in HEK293 cells expressing human OATP1B1, OATP1B3, or OCT1. Dacomitinib at the highest concentration tested inhibited the transport of the substrate of OATP1B1 and OATP1B3 by 17% and 14%, respectively. Dacomitinib inhibited the substrate of OCT1 with $IC_{50}$ of 0.25 μmol/L.
- The inhibitory effect of dacomitinib (0.03-30 μmol/L) on the transport of substrates[17)] of each transporter via OAT1, OAT3, or OCT2 was investigated in Chinese hamster ovary (CHO) cells expressing human OAT1 or OCT2 or HEK293 cells expressing OAT3. Dacomitinib showed no clear inhibitory effect on the transport of substrates of OAT1 or OAT3. Meanwhile, dacomitinib inhibited the transport of the substrate of OCT2 with $IC_{50}$ of 4.0 μmol/L.

### 4.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA concluded that the applicant's explanation of the nonclinical pharmacokinetics of dacomitinib is acceptable.

#### 4.R.1 Tissue distribution

In consideration of the findings suggestive of melanin binding of dacomitinib or its metabolites [see Section 4.2.1], PMDA asked the applicant to explain the safety of dacomitinib in melanin-containing tissues.

The applicant's response:

Distribution of dacomitinib or its metabolites in melanin-containing tissues is unlikely to cause safety issues in clinical settings, in light of the following points:

- In a 9-month repeated oral dose toxicity study in dogs and a 6-month repeated oral dose toxicity study in rats, toxicity findings were observed in skin regardless of the presence of melanin [see Section 5.2]. Therefore, these toxicity findings were unlikely to be attributable to the distribution of dacomitinib in melanin-containing tissues.
- In a global phase III study (Study 1050), the incidence of skin and subcutaneous tissue disorders and eye disorders was 83.7% (190 of 227 patients) and 7.5% (17 of 227 patients), respectively; however, most of these adverse events were assessed as Grade ≤2.

16) As substrates of (a) OATP1B1 and OATPIB3 and (b) OCT1, (a) rosuvastatin (5 μmol/L) and (b) $^{14}$C-metformin (10 μmol/L) were used.
17) As substrates of (a) OAT1 and OAT3 and (b) OCT2, (a) *P*-aminohippuric acid (1.6 μmol/L) and estrone-3-sulfate (1 μmol/L) and (b) metformin (2 μmol/L) were used.

PMDA's view:
PMDA accepted the applicant's explanation. PMDA's conclusion about dacomitinib-induced skin disorders based on the incidence of skin disorders in clinical studies is presented in Section 7.R.3.

### 4.R.2 Pharmacokinetic interactions

The applicant's explanation:
While *in vitro* studies have suggested that dacomitinib inhibits UGT1A1, P-gp, BCRP, and OCT1 [see Sections 4.5.1 and 4.5.3], no particular safety concerns attributable to the use of dacomitinib in combination with substrates of UGT1A1, P-gp, BCRP, or OCT1 were identified in the global phase III study (Study 1050). Therefore, the concomitant use of dacomitinib with these substrates is unlikely to raise safety concerns in clinical settings.

Studies have suggested that dacomitinib serves as a substrate of CYP2D6 and inhibits CYP2D6 [see Sections 4.3.1 and 4.5.1]. The details of this issue are presented in Section "6.2.3 Drug interaction studies."

PMDA's view:
The applicant's explanation is generally accepted. However, information on the pharmacokinetic interaction of dacomitinib mediated by its inhibition of UGT1A1, P-gp, BCRP, and OCT1 is considered significant for the proper use of dacomitinib. Relevant information, therefore, should continue to be collected, and useful information should be provided to healthcare professionals appropriately when it becomes available.

## 5. Toxicity and Outline of the Review Conducted by PMDA

In this section, doses and concentrations of dacomitinib are expressed as anhydride.

In *in vivo* studies, 0.5% methylcellulose solution was used as vehicle unless otherwise specified.

### 5.1 Single-dose toxicity

Single oral dose toxicity studies were conducted in rats and dogs (Table 11).

**Table 11. Single-dose toxicity studies**

| Test system | Route of administration | Dose[a] (mg/kg) | Major findings | Approximate lethal dose (mg/kg) | Attached document CTD |
|---|---|---|---|---|---|
| Male and female rats (Sprague Dawley) | Oral | 50, 2000 | Death<br>2000 mg/kg (male, 3 of 6; female, 2 of 6)[b]<br>2000 mg/kg<br>Soft stools, loose stools, decreased weight, decreased food consumption, dehydration, increased neutrophil count, monocyte count, and platelet count, decreased lymphocyte count, increased red blood cell count, hemoglobin, and hematocrit, decreased reticulocyte count, and increased BUN, AST, and ALT (female)<br>50 mg/kg<br>No toxicological abnormalities | 2000 | Reference 4.2.3.2.1 |
| Male and female dogs (Beagle) | Oral | 30, 100, 200[c] | 200 mg/kg<br>Oral mucosal redness<br>≥100 mg/kg<br>Skin lesion, skin redness, corneal injury, lacrimation, half closed eyes, and decreased weight<br>100 mg/kg<br>Alopecia and thinning of fur<br>≥30 mg/kg<br>Soft stools, loose stools, vomiting, and decreased food consumption | >200 | Reference 4.2.3.1.1 |

BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase
a) A solution containing 0.5% methylcellulose and 0.1% polysorbate 80 was used as a vehicle.
b) Surviving animals were sacrificed moribund on Day 7 because of the worsening of clinical signs.
c) Dacomitinib was administered at 30 mg/kg on Day 1, and at 200 mg/kg after 6-day observation.

## 5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies were conducted in rats (1 and 6 months) and dogs (1 and 9 months) (Table 12). The primary target organs and tissues for toxicity were kidney, liver, skin, gastrointestinal tract, epithelial tissues including eyes, and blood cells. At the no-observed-adverse-effect level (NOAEL) in (a) a 6-month repeated oral dose toxicity study in rats and (b) a 9-month repeated oral dose toxicity study in dogs, that is, 0.5 mg/kg/day for (a) and 0.1 mg/kg/day for (b), the exposure of unbound dacomitinib in plasma ($C_{max}$ and $AUC_{24h}$) was 0.52 ng/mL and 9.33 ng·h/mL, respectively, for (a) and 0.05 ng/mL and 0.79 ng·h/mL, respectively, for (b), which was 0.34- and 0.27-fold, respectively, for (a) and 0.03- and 0.02-fold, respectively, for (b) higher than the clinical exposure.[18]

[18] Following repeated administration of dacomitinib at 45 mg QD to Japanese patients with advanced solid tumors in Study 1005, the $C_{max}$ and $AUC_{24h}$ of unbound dacomitinib on Day 14 of Cycle 1 were 1.53 ng/mL and 33.95 ng·h/mL, respectively.

**Table 12. Repeated dose toxicity studies**

| Test system | Route of admin. | Duration | Dose (mg/kg /day) | Major findings | NOAEL (mg/kg/ day) | Attached documents CTD |
|---|---|---|---|---|---|---|
| Male and female rats (SD) | Oral | 1 month (QD) + Recovery 1 month | 0[a], 0.5, 5, 20/10[b] | Death or moribund sacrifice: 5 mg/kg/day (1 of 15 males in the main study group, and 1 of 6 males and 1 of 6 females in the TK group); 20/10 mg/kg/day (10 of 15 males and 14 of 15 females in the main study group, and 6 of 6 males and 6 of 6 females in the TK group)<br><br>20/10 mg/kg/day<br>Decreased weight, decreased food consumption, increased GGT<br>≥5 mg/kg/day<br>Alopecia, skin redness, edema, soft stools, loose stools, increased neutrophil count, monocyte count, eosinophil count, basophil count, and platelet count, decreased red blood cell count, hemoglobin, and hematocrit, increased reticulocyte count and mean red cell distribution width, increased ALT and AST, increased GGT (male), decreased albumin, decreased calcium (male), increased globulin, decreased A/G ratio, increased BUN and creatinine, decreased sodium, decreased chloride (female), increased inorganic phosphorus (female), increased urinary NAG-creatinine ratio, GGT-creatinine ratio (female), total protein-creatine ratio, glucose-creatinine ratio, and μ-GST-creatinine ratio (female), presence of white blood cells, red blood cells, and epithelial cells in urine, increased urine specific gravity (male), crust formation, epithelial atrophy of the esophagus, forestomach, cornea, mammary gland (male), vagina, and uterine cervix, renal papillary necrosis, skin inflammation, erosion, and ulcer, bone marrow hyperplasia, and decreased lymphocytes in the spleen, thymus, and lymph node<br>5 mg/kg/day<br>Pyelectasis (male), increased renal weight (female), and decreased thymus gland weight (female)<br><br>Reversibility<br>Reversible[c] | 0.5 | 4.2.3.2.3 |
| Male and female rats (SD) | Oral | 6 months (QD) + Recovery 1 month | 0[a], 0.2, 0.5, 2[d] | Death or moribund sacrifice: 0 mg/kg/day (2 of 20 females in the main study group); 2 mg/kg/day (15 of 20 males and 15 of 20 females in the main study group, and 6 of 6 males and 6 of 6 females in the TK group)<br><br>2 mg/kg/day<br>Decreased weight, suppressed weight gain (male), loose stools, decreased red blood cell count, hemoglobin, and hematocrit, increased red cell distribution width, reticulocyte count, platelet count, neutrophil count, white blood cell count, monocyte count, large unstained cell count, fibrinogen, and eosinophil count (female), basophil count (male), increased BUN, decreased total protein and albumin, decreased A/G ratio, increased globulin, decreased glucose, cholesterol, ALP, calcium, and sodium (all in males), increased creatinine and inorganic phosphorus (both in females), increased incidence of urinary occult blood, red blood cells in urinary sediment, and urinary protein (female), increased urinary total protein-creatinine ratio (female), decreased incidence of urine ketone (male), crusted skin and subcutaneous tissue, scaly skin and subcutaneous tissue, enlarged mandibular lymph nodes, enlarged renal pelvis, hyperkeratosis and imperfect keratinization, chronic active inflammation, acanthosis, epidermal necrosis, ulcer, renal tubule atrophy, renal papillary necrosis, renal tubular degeneration and enlargement, pyelitis, pyelonephritis, hepatic cell atrophy, epithelial atrophy of the forestomach, decreased prostate secretion, and ill-defined villi borders or fused villi in the duodenum and ileum<br>≥0.5 mg/kg/day<br>Increased AST and ALT, skin pustule, hair follicle atrophy and dysplasia, epithelial atrophy, sebaceous gland atrophy, epithelial atrophy of the tongue, esophagus, eye, uterine cervix, and vagina, increased plasma cells in lymph nodes and lymphoid hyperplasia, and increased granulocyte formation in the bone marrow<br>0.5 mg/kg/day<br>Decreased renal weight (male)<br>≥0.2 mg/kg/day<br>Coarse hair, skin sore and crust, and increased AST and ALT (female)<br><br>Reversibility<br>Reversible[e] | 0.5 | 4.2.3.2.4 |

| Test system | Route of admin. | Duration | Dose (mg/kg /day) | Major findings | NOAEL (mg/kg/ day) | Attached documents CTD |
|---|---|---|---|---|---|---|
| Male and female dogs (Beagle) | Oral | 1 month (QD) + Recovery 1 month | 0[a], 0.3, 1, 3 | 3 mg/kg/day<br>Skin redness (male), alopecia (male), thinned fur (male), halitosis, increased neutrophil count, monocyte count, and fibrinogen, decreased albumin, increased globulin, reddish contents of the cecum and colon (female), colon mucosal redness (female), dermatitis (female), hair shaft degeneration (male), and plasma cell infiltration in the liver<br>≥1 mg/kg/day<br>Loose stools, fluorescein-stained cornea, corneal edema, and corneal epithelial atrophy<br>≥0.3 mg/kg/day<br>Redness of oral mucosa and conjunctiva, soft stools<br><br>Reversibility<br>Reversible[f] | 0.3 | 4.2.3.2.5 |
| Male and female dogs (Beagle) | Oral | 9 months (QD) + Recovery 3 months | 0[a], 0.03, 0.1, 1 | 1 mg/kg/day<br>Conjunctival redness and swelling, conjunctivitis, exposed third eyelid, half-closed eye, gingival erythema (female), edema of the muzzle (female), corneal deposit (female), cornea dystrophy (female), decreased albumin, decreased A/G ratio, increased fibrinogen (female), increased adrenal gland weight (female), thinned corneal epithelium, corneal ulcer (female), submandibular gland atrophy, and erosion and ulcer of lingual mucosa (male)<br>≥0.1 mg/kg/day<br>Alopecia, skin redness, and skin erythema (female)<br>≥0.03 mg/kg/day<br>Ocular discharge, soft stools, loose stools, excessive hair loss, skin erythema (male), and vacuolation of zona reticularis of the adrenal cortex (female)<br><br>Reversibility<br>Reversible[g] | 0.1 | 4.2.3.2.6 |

SD, Sprague Dawley; TK, toxicokinetics; GGT, gamma-glutamyl transferase; BUN, blood urea nitrogen; A/G, albumin/globulin; NAG, N-acetyl-β-D-glucosaminidase; μ-GST, μ-glutathione-S-transferase; ALP, alkaline phosphatase; admin., administration

a) Only vehicle was administered.
b) Due to worsening of clinical signs, the following actions were taken: (a) Administration was discontinued on Day 7 in males in the 20 mg/kg/day group. Ten animals in the main study group were sacrificed moribund on Day 16, and reversibility was evaluated in 5 animals in the recovery group after a 53-day recovery period. (b) In females in the 20 mg/kg/day group, administration was discontinued on Day 6 and resumed on Day 15 at a dose reduced from 20 mg/kg/day to 10 mg/kg/day. Ten animals in the main study group were sacrificed moribund on Day 25, and reversibility was evaluated in 5 animals in the recovery group after a 34-day recovery period.
c) The following abnormalities persisted: increased neutrophil count, increased globulin, decreased A/G ratio, increased urine NAG-creatinine ratio and total protein-creatinine ratio, presence of white blood cells, red blood cells, and epithelial cells in urine, increased urine specific gravity, renal papillary necrosis, and skin inflammation.
d) Due to worsening of clinical signs, the following actions were taken: (a) In males, administration was discontinued on Day 89, and 13 animals in the main study group and 5 animals in the recovery group were sacrificed moribund on Day 90 and after completion of a 98-day recovery period, respectively. (b) In females, administration was discontinued on Day 130, and 12 animals in the main study group and 5 animals in the recovery group were sacrificed moribund on Day 131 and after completion of an 85-day recovery period, respectively.
e) The following abnormalities persisted: coarse hair, abnormal urinalysis findings, hair follicle atrophy and hyperplasia, and renal papillary necrosis.
f) The following abnormalities persisted: skin redness, mucosal redness, conjunctival redness, alopecia, thinned fur, increased globulin, and hair shaft degeneration.
g) Skin redness and erythema and vacuolation of zona reticularis of the adrenal cortex persisted.

## 5.3 Genotoxicity

Genotoxicity studies consisted of a bacterial reverse mutation assay and a chromosomal aberration assay in human peripheral blood lymphocytes as *in vitro* studies and a rodent micronucleus assay as an *in vivo* study (Table 13). While structural chromosomal aberration was induced in human peripheral lymphocytes treated with dacomitinib for 3 hours with or without a metabolic activation system in the chromosomal aberration assay, a negative result was obtained in the rodent micronucleus assay. Based on these results, the applicant explained that dacomitinib is unlikely to induce chromosomal damage in the body.

**Table 13. Genotoxicity studies**

| Study type | | Test system | Metabolic activation (Treatment) | Concentration (μg/plate or μg/mL) or dose (mg/kg/day) | Result | Attached document CTD |
|---|---|---|---|---|---|---|
| *in vitro* | Bacterial reverse mutation assay (Ames test) | *Salmonella typhimurium* TA98, TA100, TA1535, TA1537<br>*Escherichia coli* WP2 *uvrA* pKM101 | S9− | 0[a], 0.005, 0.015, 0.05, 0.15, 0.5, 1.5 | Negative | 4.2.3.3.1.1 |
| | | | S9+ | 0[a], 0.015, 0.05, 0.15, 0.5, 1.5, 5 | | |
| | Chromosomal aberration assay in human peripheral blood lymphocytes | Human peripheral blood lymphocytes | S9− (3 hours) | 0[a], 0.64, 0.8, 1, 2, 4 | Positive[c] (0.8) | 4.2.3.3.1.2 |
| | | | S9+ (3 hours) | 0[a], 0.8, 1, 2, 4 | Positive[c] (≥1) | |
| | | | S9− (24 hours) | 0[a] ,0.512, 0.64, 0.8, 1, 2 | Positive[d] (0.8) | |
| *in vivo* | Rodent micronucleus assay | Male and female rats (Sprague Dawley) Bone marrow | | 0[b], 5, 250, 2000 (QD, 2 days, oral) | Negative | 4.2.3.3.2.1 |

a) Only vehicle (DMSO) was added; b) Only vehicle was added; c) Structural aberration; d) Polyploidy

## 5.4 Carcinogenicity

No carcinogenicity studies have been conducted with dacomitinib because dacomitinib is an antineoplastic agent intended to treat patients with advanced cancer.

## 5.5 Reproductive and developmental toxicity

No studies of effects on fertility and early embryonic development to implantation or effects on pre- and postnatal development, including maternal function have been conducted with dacomitinib because dacomitinib is an antineoplastic agent intended to treat patients with advanced cancer.

Based on the effects of dacomitinib on male and female reproductive organs observed in repeated dose toxicity studies [see Section 5.2], the applicant explained the possibility that dacomitinib could affect fertility as follows.

The applicant's explanation:

In repeated dose toxicity studies in rats, epithelial atrophy of the mammary gland and decreased prostate secretion in males and epithelial atrophy of the uterine cervix and vagina in females were observed. Given that EGFR activation is involved in the maintenance and proliferation of epithelial cells (*Int J Radiat Oncol Biol Phys.* 2004;58:903-13, etc.), epithelial atrophy was considered to be attributable to the pharmacological action of dacomitinib. Dacomitinib is unlikely to affect fertility because the above findings (a) were not severe or not observed frequently; (b) were reversible; and (c) were not accompanied by any relevant abnormalities of other reproductive organs.

Studies to evaluate effects on embryo-fetal development were conducted in rats and rabbits (Table 14). Although low fetal weights were observed in rats in the 5 mg/kg/day group, no effects were observed on embryo-fetal development in rabbits even in the maximum dose group. In rats, the exposure ($C_{max}$ and $AUC_{24h}$ at gestation day 17) of unbound dacomitinib in plasma after administration at the NOAEL for maternal animals and for embryo-fetal development (1 mg/kg/day) was 0.66 ng/mL and 9.55 ng·h/mL, respectively, which was

0.4- and 0.3-fold, respectively, the clinical exposure.[18)] In rabbits, the exposure ($C_{max}$ and $AUC_{24h}$ at gestation day 19) of unbound dacomitinib in plasma after administration at the NOAEL for (a) maternal animals (1.5 mg/kg/day) and for (b) embryo-fetal development (4 mg/kg/day) was (a) 0.39 ng/mL and 4.64 ng·h/mL, respectively, and (b) 0.89 ng/mL and 11.8 ng·h/mL, respectively, which was (a) 0.3- and 0.1-fold, respectively, and (b) 0.6- and 0.3-fold, respectively, the clinical exposure.[18)]

**Table 14. Reproductive and developmental toxicity studies**

| Study type | Test system | Route of admin. | Duration of dosing | Dose (mg/kg/day) | Major findings | NOAEL (mg/kg/day) | Attached document CTD |
|---|---|---|---|---|---|---|---|
| Embryo-fetal develop-ment | Female rats (SD) | Oral (QD) | Gestation days 6-17 | 0[a)], 0.2, 1, 5 | Maternal animals<br>5 mg/kg/day<br>Colored nasal discharge, reddish tears, alopecia, thinned fur, skin lesion, reduced skin elasticity, decreased food consumption, suppressed weight gain<br><br>Embryo-fetus<br>5 mg/kg/day<br>Low fetal weight, incomplete ossification of fetal metatarsal | Maternal, 1<br>Embryo-fetal, 1 | 4.2.3.5.2.3 |
| | Female rabbits (NZW) | Oral (QD) | Gestation days 7-19 | 0[a)], 0.5, 1.5, 4 | Death: 0 mg/kg/day (1 of 20 rabbits)<br><br>4 mg/kg/day<br>Suppressed weight gain<br>≥1.5 mg/kg/day<br>Decreased food consumption | Maternal, 1.5<br>Embryo-fetal, 4 | 4.2.3.5.2.4 |

SD, Sprague Dawley; NZW, New Zealand White; admin., administration
a) Only vehicle was administered.

## 5.6 Local tolerance

A local tolerance study was conducted (Table 15). There were no findings indicating that dacomitinib has the potential to cause irritation. The results suggest that dacomitinib is unlikely to have any irritant effect on intravascular or perivascular tissues.

**Table 15. Local tolerance study**

| Test system | Application site | Study method | Major findings | Attached document CTD |
|---|---|---|---|---|
| Female rabbits (NZW) | Marginal ear vein | Administration of a single dose of 0.2 mg/mL dacomitinib at 1 mL | None | Reference 4.2.3.6.1 |
| | Perivascular area | Administration of a single dose of 1 mg/mL dacomitinib at 0.1 mL | None | |

NZW, New Zealand White

## 5.7 Other toxicity studies

### 5.7.1 Photo-safety testing

A phototoxicity study was conducted in rats (Table 16). There were no findings indicative of phototoxicity. The results suggested that dacomitinib is unlikely to be phototoxic.

**Table 16. Phototoxicity study**

| Study type | Test system | Study method | Major findings | Attached document CTD |
|---|---|---|---|---|
| Photo-toxicity | Female rats (Long-Evans) | A single dose of dacomitinib was administered orally at 0, 10, 30, or 100 mg/kg/day. At 4 hours post-dose, ultraviolet irradiation was performed at a dose equivalent to the minimal erythema dose. After irradiation, examination of clinical signs, body weight measurement, ophthalmologic examination, and histopathological examination of eyes were performed. | None | 4.2.3.7.7.4 |

### 5.7.2 Evaluation of impurities

Although no impurities exceeding the safety threshold defined in ICH Q3A and ICH Q3B Guidelines were detected, the following bacterial reverse mutation assays were conducted with respect to impurities contained in the drug substance (Table 17). While some impurities induced reverse mutations, these impurities are controlled during the manufacturing process [see Section 2.1.2] and are confirmed to be reduced to a sufficiently low level. Therefore, the mutagenic character of these impurities is unlikely to cause safety concerns.

**Table 17. Genotoxicity studies of impurities**

| Study type | | Test system | Metabolic activation (Treatment) | Concentration (μg/plate) | Study results | Attached document CTD |
|---|---|---|---|---|---|---|
| *in vitro* | Bacterial reverse mutation assay of Related Substance A | *Salmonella typhimurium* TA98, TA100, TA1535, TA1537<br>*Escherichia coli* WP2 *uvrA* | S9−/+ | 0[a)]-5000 | Negative | 4.2.3.7.6.2 |
| | Bacterial reverse mutation assay of Related Substance B | *Salmonella typhimurium* TA98, TA100, TA1535, TA1537<br>*Escherichia coli* WP2 *uvrA* | S9−/+ | 0[b)]-5000 | Negative | 4.2.3.7.6.6 |
| | Bacterial reverse mutation assay of Related Substance C | *Salmonella typhimurium* TA98, TA100, TA1535, TA1537<br>*Escherichia coli* WP2 *uvrA* pKM101 | S9−/+ | 0[b)]-1000 | Positive | 4.2.3.7.6.7 |
| | Bacterial reverse mutation assay of Related Substance D | *Salmonella typhimurium* TA98, TA100, TA1535, TA1537<br>*Escherichia coli* WP2 *uvrA* | S9−/+ | 0[b)]-5000 | Positive | 4.2.3.7.6.12 |
| | Bacterial reverse mutation assay of Related Substance E | *Salmonella typhimurium* TA98, TA100, TA1535, TA1537<br>*Escherichia coli* WP2 *uvrA* | S9−/+ | 0[b)]-5000 | Negative | 4.2.3.7.6.14 |
| | Bacterial reverse mutation assay of Related Substance F | *Salmonella typhimurium* TA98, TA100, TA1535, TA1537<br>*Escherichia coli* WP2 *uvrA* pKM101 | S9−/+ | 0[b)]-5000 | Negative | 4.2.3.7.6.15 |

a) Only vehicle (ultrapure water) was added.
b) Only vehicle (DMSO) was added.

## 5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the applicant's explanation of the toxicity of dacomitinib is acceptable.

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

As oral formulations of dacomitinib, uncoated tablets, white film-coated (FC) tablets, and blue FC tablets are available. These formulations were used to examine the PK, etc. of dacomitinib (Table 18). The proposed commercial formulation is blue FC tablets (15 and 45 mg tablets). The bioequivalence between the 15 and 45 mg tablets of the proposed commercial formulation has been confirmed by a dissolution study performed in accordance with the "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012).

**Table 18. Formulations used in clinical studies**

| Formulation | Study |
|---|---|
| Uncoated tablets (0.5, 5, 15, and 20 mg) | Japanese phase I study (Study 1005[*1]), global phase II study (Study 1017[*1]), foreign phase I studies (Studies 1001,[*2] 1004,[*1] 1006,[*3] 1014,[*1] 1021,[*3] 1022,[*3] and 1039[*3]), foreign phase Ib study (Study 1031[*3]), foreign phase I/II study (Study 1003[*1]), foreign phase II studies (Studies 1002,[*1] 1027,[*1] and 1028[*1]), and foreign phase III study (Study 1011[*3]) |
| White FC tablets (15, 30, and 45 mg) | Global phase III study (Study 1009), foreign phase I studies (Studies 1018[*4] and 1022[*5]), foreign phase II studies (Studies 1042[*3] and 1047) |
| Blue FC tablets (15, 30, and 45 mg) | Global phase II study (Study 1017[*3]), global phase III study (Study 1050[*6]), foreign phase I studies (Studies 1014,[*3] 1015,[*5] 1046,[*5] and 1051[*5]), foreign phase I/II study (Study 1003[*3]), and foreign phase II studies (Studies 1028[*3] and 1047[*5]) |

[*1], 5 and 20 mg tablets were used; [*2], 0.5, 5, and 20 mg tablets were used; [*3], 15 mg tablets were used;
[*4], 30 mg tablets were used; [*5], 45 mg tablets were used; [*6], 15 and 30 mg tablets were used for dose reduction.

#### 6.1.1 Analytical methods

In Study 1050, EGFR mutation testing methods including a real-time PCR kit by QIAGEN K.K., "therascreen EGFR mutation detection kit RGQ 'Qiagen,'" were used. For this real-time PCR kit by QIAGEN K.K., "therascreen EGFR mutation detection kit RGQ 'Qiagen,'" an application for approval of a partial change was filed on June 13, 2018 as a companion diagnostic to be used with dacomitinib for selecting patients eligible for treatment with the drug.

#### 6.1.2 Assay

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to determine the quantities of dacomitinib and PF-05199265 (*O*-desmethyl metabolite) in human plasma. The lower limit of quantification was 1.00 and 0.100 ng/mL, respectively.

#### 6.1.3 Foreign clinical studies

##### 6.1.3.1 Foreign phase I study (CTD 5.3.1.2.1, Study 1015 [October 2012 - January 2013])

A crossover study was conducted in 24 healthy adult subjects (24 subjects evaluable for PK analysis) to investigate the effect of food and rabeprazole on the PK of dacomitinib. Multiple doses of rabeprazole were orally administered at 40 mg QD from 6 days prior to the start of treatment with dacomitinib to the start day of the treatment. Then, a single dose of dacomitinib was orally administered at 45 mg (a) in the fasted state[19)]

19) Fasting for ≥10 hours (overnight) pre-dose and for ≥4 hours post-dose

or (b) in the fasted state[19] or 5 minutes after a high-fat meal (approximately 800-1000 kcal in total, with approximately 50% of the calories from fat). A washout period was ≥16 days between the 2 treatment periods.

The ratios [90% confidence interval (CI)] of geometric mean $C_{max}$ and $AUC_{inf}$ of dacomitinib administered after a high-fat meal to those in the fasted state were 1.237 [1.053, 1.452] and 1.142 [1.047, 1.245], respectively, and the median $t_{max}$ of dacomitinib administered in the fasted state or after a high-fat meal was 8.0 hours in both cases. The ratios [90% CI] of geometric mean $C_{max}$ and $AUC_{96h}$[20] of dacomitinib administered in combination with rabeprazole to those of dacomitinib alone were 0.495 [0.408, 0.600] and 0.608 [0.526, 0.702], respectively.

Based on the above results, the applicant explained the effect of food on the PK of dacomitinib and coadministration with a proton pump inhibitor as follows.

The applicant's explanation:
High-fat food consumption may have stimulated the secretion of bile acid, resulting in increased solubility of dacomitinib, thereby enhancing the $C_{max}$ after administration following a high-fat meal compared to that after administration in the fasted state. However, considering the geometric coefficient of variation of $C_{max}$ (50% after administration in the fasted state and 30% after a high-fat meal), the effect of food on the $C_{max}$ of dacomitinib is unlikely to cause safety concerns. In light of the above, dacomitinib can be administered regardless of food consumption. The results showed that coadministration with rabeprazole decreased dacomitinib exposure. The applicant thus considers that precautions should be taken for coadministration of dacomitinib with proton pump inhibitors.

#### 6.1.3.2 Foreign phase I study (CTD 5.3.1.1.1, Study 1046 [April - June 2013])

An open-label, uncontrolled study was conducted in 14 healthy adult subjects (14 subjects evaluable for PK analysis) to investigate the absolute BA of dacomitinib. A single dose of dacomitinib was administered orally at 45 mg and, after an interval of ≥16 days, intravenously at 20 mg over 1 hour.

The absolute BA [90% CI] calculated from the $AUC_{inf}$ of dacomitinib was 80.0% [74.9, 85.5].

### 6.2 Clinical pharmacology

The PK of dacomitinib was evaluated in healthy adult subjects and patients with cancer following administration of dacomitinib alone and in combination with paroxetine. In addition, the effect of dacomitinib on the PK of dextromethorphan hydrobromide hydrate (DXM) was evaluated.

[20] $AUC_{inf}$ after administration of dacomitinib in combination with rabeprazole was calculated for only 14 subjects. Therefore, the ratio [90% CI] of geometric mean AUC after administration in combination with rabeprazole to administration of dacomitinib alone was determined based on $AUC_{96h}$.

### 6.2.1 Japanese studies

#### 6.2.1.1 Japanese phase I study (CTD 5.3.3.2.2, Study 1005 [November 2008 - March 2011])

An open-label, uncontrolled study was conducted in 13 patients with advanced solid tumors (13 patients evaluable for PK analysis) to investigate the PK, etc. of dacomitinib. Each cycle in the study consisted of 21 days. Dacomitinib was administered orally at 15 to 45 mg as a single dose 9 days before the start of treatment in Cycle 1 and as multiple doses QD from Day 1 of Cycle 1 onward to evaluate plasma concentrations of dacomitinib.

The PK parameters of dacomitinib are shown in Table 19. The $C_{max}$ and AUC of dacomitinib during a single administration and repeated administration increased nearly dose-proportionally within the dose range tested. The accumulation ratio[21)] after administration of dacomitinib at 45 mg was 1.208. Taking into account that plasma trough concentrations of dacomitinib remained nearly constant from Day 14 onward, the applicant considers that plasma concentration of the drug reaches a steady-state 14 days after the start of treatment.

**Table 19. PK parameters of dacomitinib**

| Dose (mg) | Day of administration | n | $C_{max}$ (ng/mL) | $t_{max}$*1 (h) | $AUC_{24h}$ (ng·h/mL) | $AUC_{inf}$ (ng·h/mL) | $t_{1/2}$*2 (h) | CL/F (L/h) |
|---|---|---|---|---|---|---|---|---|
| 15 | Cycle 1 Day −9 | 3 | 7.74 (31) | 24.0 (6.00, 24.0) | 135.8 (37) | 646.9 (24) | 61.1 ± 15.4 | 23.2 (26) |
| | Cycle 1 Day 14 | 2 | 29.5, 34.4 | 6.00, 24.0 | 627, 799 | — | — | 18.8, 23.9 |
| 30 | Cycle 1 Day −9 | 3 | 11.1 (55) | 8.00 (8.00, 24.0) | 180.4 (51) | 765, 1210*3 | 66.9, 129*3 | 24.7, 39.2*3 |
| | Cycle 1 Day 14 | 3 | 63.5 (19) | 4.00 (0, 8.00) | 1333 (21) | — | — | 22.6 (21) |
| 45 | Cycle 1 Day −9 | 7 | 17.6 (71) | 6.00 (4.00, 24.0) | 316.3 (56) | 1543 (29) | 80.0 ± 12.3 | 29.2 (33) |
| | Cycle 1 Day 14 | 6 | 79.5 (21) | 8.00 (4.00, 8.00) | 1768 (20) | — | — | 25.5 (25) |

Geometric mean (coefficient of variation, %) (individual data if n = 1 or 2); *1, Median (range); *2, Arithmetic mean ± SD; *3, n = 2; —, Not calculated

### 6.2.2 Foreign clinical studies

#### 6.2.2.1 Foreign phase I study (CTD 5.3.3.2.1, Study 1001 [October 2005 - September 2010])

An open-label, uncontrolled study was conducted in 121 patients with advanced solid tumors (120 patients evaluable for PK analysis) to investigate the PK, etc. of dacomitinib. Each cycle in the study consisted of 21 days. In the dose escalation cohort, dacomitinib was administered orally (a) at 1 to 60 mg as a single dose either 3 or 10 days before the start of treatment in Cycle 1 and as multiple doses QD from Day 1 of Cycle 1 onward or (b) at 60 mg as a single dose either 20 or 10 days before the start of treatment in Cycle 1 and as multiple doses QD from Day 1 through Day 14 in Cycle 1 and subsequent cycles to evaluate plasma concentrations of dacomitinib. In the expansion cohort, the effects of an antacid and food on the PK of dacomitinib were investigated in 8 and 11 subjects, respectively. Subjects received a single oral dose of dacomitinib at 45 mg in the fasted state[22)] 20 days before the start of treatment with dacomitinib in Cycle 1,

21) Ratio of $AUC_{24h}$ on Day 14 of Cycle 1 to $AUC_{inf}$ on Day −9 of Cycle 1
22) Fasting for 2 hours each before and after administration

and (i) a single oral dose of an antacid[23] as well as a single oral dose of dacomitinib at 45 mg or (ii) a single oral dose of dacomitinib at 45 mg 5 minutes after taking a meal (approximately 970 kcal in total, with 35% of the calories from fat) 10 days before the start of treatment with dacomitinib in Cycle 1, and then multiple doses of dacomitinib at 45 mg QD from Day 1 of Cycle 1 onward. Plasma concentrations of dacomitinib were evaluated during the treatment. The results of evaluation of the effect of food on the PK of dacomitinib are omitted in this section because the evaluation was performed using a formulation that was different from the proposed commercial formulation [see Section 6.1].

The PK parameters of dacomitinib are shown in Table 20. The accumulation ratio[24] after administration of dacomitinib at 45 mg was 1.201. The ratios [90% CI] of geometric mean $C_{max}$ and $AUC_{inf}$ of dacomitinib administered in combination with the antacid to those of dacomitinib alone were 0.876 [0.618, 1.242] and 1.048 [0.810, 1.357], respectively. Based on the above results, the applicant considers that the use of dacomitinib in combination with an antacid is unlikely to cause pharmacokinetic interaction.

23) An antacid containing aluminum hydroxide and magnesium hydroxide
24) Ratio of $AUC_{24h}$ on Day 14 of Cycle 1 to $AUC_{inf}$ on Day −20, −10, or −3 of Cycle 1

**Table 20. PK parameters of dacomitinib**

| Dose (mg) | Day of administration | n | $C_{max}$ (ng/mL) | $t_{max}$[*1] (h) | $AUC_{24h}$ (ng·h/mL) | $AUC_{inf}$ (ng·h/mL) | $t_{1/2}$[*2] (h) | CL/F (L/h) | $V_z$/F (L) |
|---|---|---|---|---|---|---|---|---|---|
| 1[*3] | Cycle 1 Day 14 | 2 | 1.17, 2.23 | 6.00, 6.00 | 13.9, 41.6 | — | — | 24.0, 71.8 | — |
| 2 | Cycle 1 Day −3 | 1 | 2.07 | 2.00 | 9.49 | — | — | — | — |
| | Cycle 1 Day 14 | 3 | 3.91 (20) | 4.00 (4.00, 6.00) | 71.8 (18) | — | — | 27.8 (18) | — |
| 4 | Cycle 1 Day −3 | 1 | 2.72 | 4.00 | 21.6 | — | — | — | — |
| | Cycle 1 Day 14 | 3 | 5.52 (7) | 4.00 (4.00, 6.00) | 101.6 (11) | — | — | 39.4 (11) | — |
| 8 | Cycle 1 Day −3 | 3 | 2.85 (44) | 4.00 (4.00, 6.00) | 40.0 (38) | — | — | — | — |
| | Cycle 1 Day 14 | 3 | 9.78 (51) | 6.00 (4.00, 8.00) | 186.3 (46) | — | — | 42.9 (38) | — |
| 16 | Cycle 1 Day −3 | 4 | 9.75 (65) | 7.00 (4.00, 8.00) | 147.7 (43) | — | — | — | — |
| | Cycle 1 Day 14 | 3 | 27.4 (26) | 6.00 (4.00, 6.00) | 569.0 (28) | — | — | 28.1 (27) | — |
| 30 | Cycle 1 Day −3[*4] | 13 | 16.3 (37) | 6.00 (4.00, 24.0) | 245.4 (36) | 904.8 (59)[*7] | 59.0 ± 27.9[*7] | 33.2 (47)[*7] | 2641 (12)[*7] |
| | Cycle 1 Day 14 | 9 | 53.9 (38) | 4.00 (4.00, 24.0) | 1061 (37) | — | — | 28.3 (34) | — |
| 45 | Cycle 1 Day −3[*5] | 46 | 23.2 (51) | 6.00 (2.00, 24.0) | 390.6 (41) | 1810 (35)[*8] | 70.3 ± 20.6[*8] | 24.9 (36)[*8] | 2424 (31)[*8] |
| | Cycle 1 Day 14 | 31 | 108.0 (35) | 6.00 (0, 24.0) | 2213 (35) | — | — | 20.4 (33) | — |
| 60[*6] | Cycle 1 Day −10[*6] | 10 | 39.6 (79) | 8.00 (4.00, 8.00) | 704.7 (90) | 3296 (64) | 81.0 ± 28.4 | 18.2 (41) | 2033 (54) |
| | Cycle 1 Day 14 | 4 | 104.6 (57) | 5.00 (4.00, 6.00) | 1720 (70) | — | — | 34.9 (143) | — |

Geometric mean (coefficient of variation, %) (individual data if n = 1 or 2); [*1], Median (range); [*2], Arithmetic mean ± SD;
[*3], Plasma concentrations of dacomitinib on Day −3 of Cycle 1 were below the lower limit of quantitation at any measurement time points; [*4], Including data for Day −10 of Cycle 1; [*5], Including data for Day −20 or −10 of Cycle 1;
[*6], Data from subjects receiving a single oral dose of dacomitinib at 60 mg on Day −20 or −10 of Cycle 1 and multiple oral doses QD from Day 1 to Day 14 of Cycle 1 and subsequent cycles; [*7], n = 3 (calculated based on data for Day −10 of Cycle 1);
[*8], n = 38 (calculated based on data for Day −20 or −10 of Cycle 1); —, Not calculated

### 6.2.2.2 Foreign phase I study (CTD 5.3.3.1.1, Study 1020 [January - February 2010])

An open-label, uncontrolled study was conducted in 6 healthy adult subjects (6 subjects evaluable for PK analysis) to investigate mass balance of dacomitinib. Subjects received a single dose of $^{14}$C-dacomitinib 45 mg orally. Radioactivity levels, etc. were measured in plasma, urine, and feces.

The PK parameters of dacomitinib, PF-05199265, and radioactivity in plasma are shown in Table 21. The ratios of $C_{max}$ and $AUC_{inf}$ of dacomitinib in plasma to total radioactivity in plasma were 0.4703 and 0.1689, respectively. Unchanged dacomitinib and PF-05199265 were mainly detected in plasma by 120 hours post-dose (accounting for 39% and 16%, respectively, of total radioactivity in plasma).

Radioactivity excreted in urine and feces (ratio to the administered radioactivity) by 552 hours post-dose accounted for 3.2% and 78.8%, respectively, of the administered radioactive dose. Any of the unchanged dacomitinib and multiple metabolites detected in urine by 552 hours post-dose accounted for ≤1% of the

administered radioactivity dose. Unchanged dacomitinib, PF-05199265, M2 (cysteine conjugate metabolite), and M7 (mono-oxygenated metabolite) were mainly detected in feces by 552 hours post-dose (accounting for 20%, 20%, 9.5%, and 5.1%, respectively, of the administered radioactive dose).

**Table 21. PK parameters of dacomitinib, PF-05199265, and radioactivity**

| Substance measured | $C_{max}$ (ng/mL[*1]) | $t_{max}$[*2] (h) | $AUC_{inf}$ (ng·h/mL[*3]) | $t_{1/2}$[*4] (h) | CL/F (L/h) | $V_z$/F (L) |
|---|---|---|---|---|---|---|
| Dacomitinib | 17.0 (50) | 12.0 (8.00, 12.0) | 1171 (31) | 54.6 ± 15.0 | 38.4 (31) | 2937 (25) |
| PF-05199265 | 5.75 (58) | 6.00 (4.00, 8.00) | 403.8 (46) | 72.8 ± 13.7 | — | — |
| Total radioactivity | 36.1 (38) | 12.0 (8.00, 12.0) | 6937 (15) | 182.3 ± 34.9 | 6.5 (15) | 1684 (23) |

Geometric mean (coefficient of variation, %), n = 6; [*1], ng Eq./mL for total radioactivity; [*2], Median (range);
[*3], ng Eq.·h/mL for total radioactivity; [*4], Arithmetic mean ± SD; —, Not calculated

### 6.2.3 Drug interaction studies

#### 6.2.3.1 Study on drug interaction of dacomitinib with DXM (CTD 5.3.3.4.3, Study 1039 [October - December 2009])

A crossover study was conducted in 14 healthy adult subjects[25)] (14 subjects evaluable for PK analysis) to investigate the effect of dacomitinib on the PK of DXM (a CYP2D6 substrate). Subjects received a single dose of DXM 30 mg orally, or received a single oral dose of dacomitinib 45 mg and, after 4 hours, a single dose of DXM 30 mg orally. A washout period of ≥14 days was included between 2 treatment periods.

The ratios [90% CI] of geometric mean $C_{max}$ and $AUC_{last}$ of DXM administered in combination with dacomitinib to those of DXM alone were 9.735 [5.900, 16.063] and 9.554 [5.600, 16.301], respectively. The results showed that coadministration of dacomitinib with a CYP2D6 substrate increased exposure to the CYP2D6 substrate. The applicant thus considers that precautions should be taken for coadministration of dacomitinib with substrates of CYP2D6.

#### 6.2.3.2 Study on drug interaction of dacomitinib with paroxetine (CTD 5.3.3.4.2, Study 1021 [March - June 2011])

A 2-period, open-label study was conducted in 14 healthy adult subjects classified as extensive metabolizers (EM) according to CYP2D6 genotype (14 subjects evaluable for PK analysis) to investigate the effect of paroxetine (a CYP2D6 inhibitor) on the PK of dacomitinib. Subjects received a single oral dose of dacomitinib at 45 mg on Day 1 of Period 1; and multiple oral doses of paroxetine at 30 mg QD from Day 1 to Day 10 and a single oral dose of dacomitinib at 45 mg on Day 4 of Period 2. A washout period of ≥21 days was included between Period 1 and Period 2.

The ratios [90% CI] of geometric mean $C_{max}$ and $AUC_{inf}$ of dacomitinib administered in combination with paroxetine to those of dacomitinib alone were 1.097 [0.829, 1.451] and 1.372 [1.091, 1.726], respectively. However, taking into account that the ratios of geometric mean $C_{max}$ and $AUC_{240h}$ of pharmacologically active substances (sum of dacomitinib and PF-05199265) after administration of dacomitinib in combination with

[25)] Although healthy adult subjects classified as extensive metabolizer (EM), ultra-rapid metabolizer (UM), or intermediate metabolizer (IM) according to CYP2D6 genotype were eligible for the study, all the enrolled subjects were classified as EM.

paroxetine to those of dacomitinib alone were 1.057 and 0.876, respectively, the applicant considers that no precautions need to be taken for coadministration of dacomitinib with CYP2D6 inhibitors.

### 6.2.4 Foreign phase I study to evaluate the effect of hepatic impairment on PK of dacomitinib (CTD 5.3.3.3.1, Study 1018 [April - August 2012])

An open-label study was conducted in 8 healthy adult subjects (8 subjects evaluable for PK analysis) and 17 patients with mild (Child-Pugh A) or moderate (Child-Pugh B) hepatic impairment (8 and 9 patients, respectively; 8 and 9 evaluable for PK analysis) to investigate the effect of hepatic impairment on the PK of dacomitinib. A single dose of dacomitinib was administered orally at 30 mg to evaluate plasma concentrations of dacomitinib.

The PK parameters of dacomitinib are shown in Table 22. No clear differences in $C_{max}$ and $AUC_{inf}$ of dacomitinib were observed between healthy adult subjects and patients with mild hepatic impairment. Meanwhile, the $C_{max}$ and $AUC_{inf}$ of dacomitinib in patients with moderate hepatic impairment were lower than those in healthy adult subjects by 20.0% and 15.3%, respectively. However, taking the coefficient of variation of PK parameters into account, the applicant considers that mild or moderate hepatic impairment has no apparent effect on the PK of dacomitinib. The plasma protein unbound fraction was 0.0160 in healthy adult subjects, 0.0197 in patients with mild hepatic impairment, and 0.0187 in patients with moderate hepatic impairment, showing no clear difference associated with the difference in severity of hepatic impairment.

**Table 22. PK parameters of dacomitinib by severity of hepatic impairment**

| Severity of hepatic impairment | n | $C_{max}$ (ng/mL) | $t_{max}$*1 (h) | $AUC_{inf}$ (ng·h/mL) | $t_{1/2}$*2 (h) | CL/F (L/h) | $V_z$/F (L) |
|---|---|---|---|---|---|---|---|
| Normal | 8 | 12.7 (52) | 8.00 (6.00, 24.0) | 805.1 (42) | 59.5 ± 24.8 | 37.3 (42) | 2943 (48) |
| Mild | 8 | 13.1 (58) | 8.00 (6.00, 12.0) | 811.3 (32) | 72.9 ± 42.0 | 37.0 (32) | 3413 (45) |
| Moderate | 9 | 10.2 (35) | 6.00 (1.00, 12.0) | 682.2 (39) | 92.2 ± 42.6 | 44.0 (39) | 5291 (35) |

Geometric mean (coefficient of variation, %); *1, Median (range); *2, Arithmetic mean ± SD

### 6.2.5 Relationship between exposure and changes in QT/QTc interval

Based on the data from the foreign phase II study (Study 1047), an analysis using a linear mixed-effects model was performed for the relationship of plasma dacomitinib concentrations and changes from baseline in QT interval corrected for heart rate using the Fridericia formula (ΔQTcF). The analysis revealed no clear relationship between plasma dacomitinib concentrations and ΔQTcF. The upper bound of the 90% CI for ΔQTcF after administration of 6 doses of dacomitinib at 45 mg BID[26)] and that before the sixth dose of dacomitinib administered at 60 mg BID[27)] were below 10 ms at any measurement time point. On the basis of the above, the applicant considers that prolongation of QT/QTc interval is unlikely to occur during treatment with dacomitinib in clinical settings.

26) The geometric mean plasma dacomitinib concentration after the sixth dose at each measurement time point ranged from 72.8 to 86.6 ng/mL.
27) The geometric mean plasma dacomitinib concentration at this time point was 104.9 ng/mL.

### 6.2.6 Population pharmacokinetic (PPK) analysis

A population pharmacokinetic (PPK) analysis using a non-linear mixed-effects model was performed on the PK data of dacomitinib collected in the Japanese clinical study (Study 1005), global clinical studies (Studies 1009, 1017, and 1050), and foreign clinical studies (Studies 1001, 1002, 1003, 1014, 1015, 1018, 1020, 1021, 1022, 1027, 1028, 1031, 1039, 1042, 1046, 1047, and 1051) (data from 1381 subjects at 10,156 time points) (software used, NONMEM Version 7.3.0). The PK of dacomitinib was described by a two-compartment model with first-order absorption and elimination.

This model included the effect of body weight on clearance (CL). To identify covariates for (a) CL, (b) volume of distribution of the central compartment (V2), and (c) absorption rate constant ($K_a$) and relative bioavailability (F), the following factors were examined in this analysis: (a) creatinine clearance (CrCL),[28] aspartate aminotransferase (AST), albumin, total bilirubin, age, sex, race, smoking history, coadministration of CYP2D6 inhibitors, Eastern Cooperative Oncology Group performance status (ECOG PS), presence or absence of disease, cancer type, EGFR gene status, CYP2D6 genotype, and hepatic impairment;[29] (b) sex, race, cancer type, EGFR gene status, and smoking history; and (c) food consumption conditions. As a result, the factors selected as significant covariates were albumin, AST, EGFR gene status, race, sex, and coadministration of CYP2D6 inhibitors for CL; and food consumption conditions for $K_a$. The applicant explained the above results as follows.

The applicant's explanation:

- The effect of any of albumin, AST, EGFR gene status, race, and sex on the CL of dacomitinib was limited (≤11.5%); therefore, the effect of any of these covariates on the PK of dacomitinib is of no clinical significance.
- A simulation in the above PPK model revealed that the CL after coadministration of a CYP2D6 inhibitor is decreased by 33% and that the $K_a$ after administration in the fed state is higher than that after administration in the fasted state by 23%. However, taking the results of the foreign phase I studies (Study 1015 and Study 1021)[see Sections 6.1.3.1 and 6.2.3.2] into consideration, the effect of coadministration of CYP2D6 inhibitors or food consumption conditions on the PK of dacomitinib is of no clinical significance.

### 6.2.7 Relationship between exposure and efficacy or safety

Based on the data from Cohort A in Study 1017 and the data from Study 1050, the relationship between dacomitinib exposure and efficacy or safety was investigated. The dacomitinib exposure inferred from the PPK analysis [see Section 6.2.6] is used for this investigation.

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[28] Baseline CrCL standardized based on body weight was used.

[29] Severity of hepatic impairment was classified in accordance with the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria.

#### 6.2.7.1 Relationship between exposure and efficacy

A time-to-event model was used to investigate the relationship between the average plasma concentration ($C_{avg}$)[30] of dacomitinib and PFS. The results suggested that PFS decreases with an increase in $C_{avg}$.

#### 6.2.7.2 Relationship between exposure and safety

A logistic regression model was used to investigate the relationship between the $C_{avg}$[30] of dacomitinib, trough concentration ($C_{trough}$)[31] of dacomitinib, $C_{max}$ after the first dose, or $C_{max}$ on the day of onset of an adverse event and Grade ≥3 rash or dermatitis acneiform, other skin toxicity, diarrhoea, or stomatitis. The results suggested that the incidence of the above events increases with an increase in $C_{avg}$. Meanwhile, no clear relationship was observed between the exposure parameters tested other than $C_{avg}$ and the above events.

### 6.2.8 Difference in PK of dacomitinib between Japanese and non-Japanese patients

In studies including the Japanese phase I study (Study 1005) and the foreign phase I study (Study 1001), no apparent differences were observed in the exposure ($C_{max}$ and $AUC_{inf}$) to dacomitinib after administration as a single oral dose at 45 mg or multiple oral doses at 45 mg QD [see Sections 6.2.1.1 and 6.2.2.1]. These results, according to the applicant, suggest that no clear difference exists in the PK of dacomitinib between Japanese and non-Japanese patients.

## 6.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation of the clinical pharmacology, etc. of dacomitinib is acceptable, except for matters outlined in the following sections.

### 6.R.1 Use of dacomitinib in patients with hepatic impairment

The applicant explained the use of dacomitinib in patients with hepatic impairment as follows.

The applicant's explanation:

Based on the data from the foreign phase I study (Study 1018), mild or moderate hepatic impairment is unlikely to have any notable effect, etc. on the PK of dacomitinib [see Section 6.2.4]. Therefore, dose adjustment of dacomitinib is unnecessary for patients with mild or moderate hepatic impairment. Meanwhile, there is no clinical experience with dacomitinib in patients with severe hepatic impairment; therefore, the "Precautions Concerning Dosage and Administration" section of the package insert will include precautionary statements that dose reduction should be considered for patients with severe hepatic impairment and that dacomitinib should be carefully administered when used in this patient population. The results of a clinical study performed to evaluate the effect of severe hepatic impairment on the PK of dacomitinib will become available in [redacted] 20[redacted].

30) $C_{avg}$ was determined as a ratio of cumulative AUC to cumulative exposure time.
31) Plasma dacomitinib concentration at pre-dose on Day 1 of Cycle 2

PMDA's view:
PMDA accepted the applicant's explanation of the use of dacomitinib in patients with mild or moderate hepatic impairment.

Based on the results from the foreign phase I study (Study 1018) [see Section 6.2.4], there is little need to include precautionary statement on dose reduction for patients with severe hepatic impairment in the "Precautions Concerning Dosage and Administration" section of the package insert. However, precautionary statement that dacomitinib should be carefully administered to this patient population should be provided in consideration of the following facts: (a) there are no available data from clinical studies in patients with severe hepatic impairment; and (b) dacomitinib is primarily eliminated by hepatic metabolism. The data from the clinical study performed to evaluate the effect of severe hepatic impairment on the PK of dacomitinib should be provided to healthcare professionals appropriately when they become available.

### 6.R.2 Use of dacomitinib in patients with renal impairment

The applicant explained the use of dacomitinib in patients with renal impairment as follows.

The applicant's explanation:
On the basis of the following points, dose reduction of dacomitinib is considered unnecessary for patients with mild or moderate renal impairment. Because clinical experience with dacomitinib in patients with severe renal impairment is limited, the "Precautions Concerning Dosage and Administration" section of the package insert will include precautionary statements that dose reduction should be considered for patients with severe renal impairment and that dacomitinib should be carefully administered when used in this patient population.

- The results of the foreign phase I study (Study 1020) suggest that renal excretion plays little role in the elimination of dacomitinib [see Section 6.2.2.2].
- In the global phase III study (Study 1050), the incidence of (a) all adverse events, (b) Grade ≥3 adverse events, and (c) serious adverse events in subjects with normal renal function (n = 89), patients with mild renal impairment (n = 99), and patients with moderate renal impairment (n = 38) was (a) 100%, 99.0%, and 100%, respectively, (b) 59.6%, 62.6%, and 71.1%, respectively, and (c) 21.3%, 31.3%, and 31.6%, respectively. These results showed no clear difference in the incidence of adverse events between patients with normal renal function and those with mild or moderate renal impairment.

PMDA's view:
PMDA accepted the applicant's explanation of the use of dacomitinib in patients with mild or moderate renal impairment.

It has been suggested that renal excretion plays little role in the elimination of dacomitinib. In Study 1009, no particular safety issues were detected in 2 patients with severe renal impairment treated with dacomitinib. Based on the above, PMDA concluded that there is little need to include a precautionary statement in the

package insert to the effect that dose reduction should be considered for patients with severe renal impairment or that dacomitinib should be carefully administered when used in this patient population.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from a total of 14 studies including 1 Japanese phase I study, 1 global phase II study, 2 global phase III studies, and 10 foreign phase I studies, as shown in Table 23. The applicant also submitted reference data in the form of results data from a total of 10 studies including 2 foreign phase I studies, 1 foreign phase Ib study, 1 foreign phase I/II study, 5 foreign phase II studies, and 1 foreign phase III study, as shown in Table 23.

**Table 23. List of clinical studies on efficacy and safety**

| Data category | Study site | Study identifier | Phase | Study population | No. of subjects enrolled | Outline of dosage regimen | Main endpoints |
|---|---|---|---|---|---|---|---|
| Evaluation | Japan | 1005 | I | Patients with advanced solid tumors | 13 | Dacomitinib 15, 30, or 45 mg QD oral dose in the fasted state | Safety PK |
| | Global | 1017 | II | (a) Cohort A Chemotherapy-naïve patients with unresectable advanced or recurrent NSCLC[*1] (b) Cohort B Patients with HER2 amplified or HER2 mutant, unresectable advanced or recurrent NSCLC | 119 (a) 89 (b) 30 | Dacomitinib 30 or 45 mg QD oral dose in the fasted state[*2] | Efficacy Safety |
| | | 1009 | III | Patients with unresectable advanced or recurrent NSCLC previously treated with 1 or 2 chemotherapy regimens | 878 (a) 439 (b) 439 | (a) Dacomitinib 45 mg or (b) erlotinib 150 mg QD oral dose | Efficacy Safety |
| | | 1050 | III | Chemotherapy-naïve patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC | 452 (a) 227 (b) 225 | (a) Dacomitinib 45 mg or (b) gefitinib 250 mg QD oral dose | Efficacy Safety |
| | Foreign | 1001 | I | Patients with advanced solid tumors | 121 (a) 111 (b) 10 | (a) Dacomitinib 0.5-60 mg QD oral dose or 45 mg BID oral dose in the fasted state[*3] on Days 1-3 and then 45 mg QD oral dose in the fasted state from Day 4 onward (b) In each cycle consisting of 21 days, dacomitinib 60 mg QD oral dose in the fasted state for 14 days, followed by a 7-day washout period | Safety PK |
| | | 1014 | I | Patients with advanced solid tumors | 16 | Dacomitinib 45 mg QD oral dose in combination with DXM in the fasted state | PK |
| | | 1015 | I | Healthy adults | 24 | (a) In Period 1, a single oral dose of dacomitinib 45 mg in combination with rabeprazole in the fasted state (b) In Periods 2 and 3, crossover administration of a single oral dose of dacomitinib 45 mg in the fasted state or after a high-fat, high-calorie meal with a ≥16-day interval between the 2 doses | PK |
| | | 1018 | I | Healthy adults with normal hepatic function and patients with mild or moderate hepatic impairment | 25 | Single oral dose of dacomitinib 30 mg in the fasted state | PK |
| | | 1020 | I | Healthy adults | 6 | Single oral dose of $^{14}$C-dacomitinib 45 mg in the fasted state | PK |
| | | 1021 | I | Healthy adults | 14 | Single oral dose of dacomitinib 45 mg in the fasted state, followed by a washout period of ≥21 days, and then single oral dose of dacomitinib 45 mg in combination with paroxetine | PK |

| Data category | Study site | Study identifier | Phase | Study population | No. of subjects enrolled | Outline of dosage regimen | Main endpoints |
|---|---|---|---|---|---|---|---|
| | | 1022 | I | Healthy adults | 32 | Crossover administration of a single oral dose of dacomitinib uncoated tablet or white FC tablet 45 mg in the fasted state with a ≥16-day interval between the 2 doses | PK |
| | | 1039 | I | Healthy adults | 14 | Crossover administration of a single oral dose of DXM 30 mg with or without dacomitinib 45 mg in the fasted state with a ≥14-day interval between the 2 doses | PK |
| | | 1046 | I | Healthy adults | 14 | Single oral dose of dacomitinib 45 mg in the fasted state and then, after ≥17 days, a single intravenous dose of dacomitinib 20 mg | PK |
| | | 1051 | I | Healthy adults | 14 | Single oral dose of dacomitinib 45 mg in the fasted state | PK |
| Reference | Foreign | 1004 | I | Patients with advanced solid tumors | 74 | Single oral dose of dacomitinib 10-45 mg QD in combination with figitumumab (FIG) in the fasted state[*4] | Safety |
| | | 1006 | I | Patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy | (a) 33<br>(b) 25<br>(c) 12 | Dose-escalation part<br>(a) Dacomitinib 15, 30, or 45 mg QD oral dose in combination with crizotinib<br>Expansion part<br>(b) Dacomitinib 30 mg QD oral dose in combination with crizotinib<br>(c) Dacomitinib 30 mg QD oral dose, and, in the case of disease progression, dacomitinib 30 mg QD oral dose in combination with crizotinib | Safety<br>PK |
| | | 1031 | Ib | Patients with resectable NSCLC | 22 | Dacomitinib 45 mg BID oral dose on Days 1-3 and QD oral dose on Days 4-8 | PK |
| | | 1003 | I/II | Patients with KRAS wild-type, unresectable advanced or recurrent NSCLC previously treated with chemotherapy[*5] | 55<br>(a) 12<br>(b) 43 | (a) Phase I part<br>Single oral dose of dacomitinib 30 or 45 mg on Day 1, and, after ≥10 days, dacomitinib 30 or 45 mg QD oral dose in the fasted state<br>(b) Phase II part<br>Dacomitinib 45 mg QD oral dose in the fasted state | Efficacy<br>Safety |
| | | 1002 | II | Patients with KRAS wild-type, unresectable advanced or recurrent (a) non-squamous cell NSCLC or (b) squamous cell-NSCLC previously treated with chemotherapy[*6] | 66<br>(a) 50<br>(b) 16 | Dacomitinib 45 mg QD oral dose in the fasted state | Efficacy<br>Safety |
| | | 1027 | II | Patients with recurrent or metastatic head-and-neck squamous cell carcinoma | 69 | Dacomitinib 45 mg QD oral dose in the fasted state | Efficacy<br>Safety |
| | | 1028 | II | Patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy | 188<br>(a) 94<br>(b) 94 | (a) Dacomitinib 45 mg QD oral dose in the fasted state<br>(b) Erlotinib 150 mg QD oral dose in the fasted state | Efficacy<br>Safety |
| | | 1042 | II | (a) Cohort 1 and (b) Cohort 2<br>Patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy<br>(c) Cohort 3<br>Chemotherapy-naïve patients with HER1- or HER2-mutant or HER2-amplified, unresectable advanced or recurrent NSCLC | 236<br>(a) 139<br>(b) 72<br>(c) 25 | (a) Dacomitinib 45 mg QD oral dose in combination with placebo, doxycycline, or alclometasone dipropionate 0.05% cream<br>(b) Dacomitinib 45 mg QD oral dose in combination with probiotics and alclometasone dipropionate 0.05% cream<br>(c) Dacomitinib 45 mg QD oral dose for 10 days, followed by a 4-day washout period, and then dacomitinib 45 mg QD oral dose | Safety<br>PK |

| Data category | Study site | Study identifier | Phase | Study population | No. of subjects enrolled | Outline of dosage regimen | Main endpoints |
|---|---|---|---|---|---|---|---|
| | | 1047 | II | (a) Cohort A<br>Patients with EGFR T790M mutation-positive, unresectable advanced or recurrent NSCLC<br>(b) Cohort B<br>Patients with EGFR T790M mutation-negative or -unknown, unresectable advanced or recurrent NSCLC | 41<br>(a) 16<br>(b) 25 | Dacomitinib 45 or 60 mg QD oral dose on Day 1, BID oral dose on Days 2 and 3, and QD oral dose on Day 4 | Efficacy<br>Safety |
| | | 1011 | III | Patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy | 720<br>(a) 480<br>(b) 240 | (a) Dacomitinib 45 mg QD oral dose<br>(b) Placebo QD oral dose | Efficacy<br>Safety |

[*1], Patients with no or light smoking history or patients with NSCLC with EGFR mutation; [*2], In Cohort B, dacomitinib was administered orally at 45 mg to previously treated patients and at 30 mg to chemotherapy-naïve patients, and the dose for the latter was increased to 45 mg in or after Cycle 2 if tolerability at the previous dose was confirmed; [*3], Dacomitinib was administered within 5 minutes after breakfast to patients who were to be evaluated for food effects; [*4], Dacomitinib was orally administered when FIG treatment was started; [*5], Gefitinib- or erlotinib-containing chemotherapy; [*6], Patients with metastatic NSCLC who were resistant or intolerant to ≥1 chemotherapy regimen or erlotinib, and patients with unresectable, locally advanced NSCLC who were resistant or intolerant to 1 or 2 chemotherapy regimens or erlotinib were enrolled in the study.

The clinical studies are summarized below. Major non-fatal adverse events reported in the clinical studies are shown in Section "7.3 Adverse events reported in clinical studies," and PK data are presented in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

## 7.1 Evaluation data

### 7.1.1 Clinical pharmacology

The applicant submitted the data from the following 10 clinical pharmacology studies in healthy adult subjects, patients with advanced solid tumors, or patients with hepatic impairment [see Sections 6.1 and 6.2]. Death was reported in 11 subjects (8 of 121 in Study 1001, 2 of 11 in Study 1014, and 1 of 25 in Study 1018) during the treatment period or within 28 days after the end of treatment. The causes of these deaths were disease progression in 9 subjects, respiratory failure in 1 subject, and road traffic accident in 1 subject, and a causal relationship to dacomitinib was denied for all these events.

#### 7.1.1.1 Foreign phase I study (CTD 5.3.3.2.1, Study 1001 [October 2005 - September 2010])

#### 7.1.1.2 Foreign phase I study (CTD 5.3.3.4.1, Study 1014 [September 2008 - July 2014])

#### 7.1.1.3 Foreign phase I study (CTD 5.3.1.2.1, Study 1015 [October 2012 - January 2013])

#### 7.1.1.4 Foreign phase I study (CTD 5.3.3.3.1, Study 1018 [April 2012 - August 2012])

#### 7.1.1.5 Foreign phase I study (CTD 5.3.3.1.1, Study 1020 [January 2010 - February 2010])

#### 7.1.1.6 Foreign phase I study (CTD 5.3.3.4.2, Study 1021 [March 2011 - June 2011])

#### 7.1.1.7 Foreign phase I study (CTD 5.3.1.2.2, Study 1022 [April 2011 - May 2011])

#### 7.1.1.8 Foreign phase I study (CTD 5.3.3.4.3, Study 1039 [October 2009 - December 2009])

#### 7.1.1.9 Foreign phase I study (CTD 5.3.1.1.1, Study 1046 [April 2013 - June 2013])

#### 7.1.1.10 Foreign phase I study (CTD 5.3.3.1.2, Study 1051 [July 2014 - September 2014])

### 7.1.2 Japanese clinical study

#### 7.1.2.1 Japanese phase I study (CTD 5.3.3.2.2, Study 1005 [November 2008 - March 2011])

An open-label, uncontrolled study was conducted at 1 study site in Japan to investigate the safety, etc. of dacomitinib in patients with advanced solid tumors (target sample size, 18 subjects).

Dacomitinib was orally administered at 15, 30, or 45 mg as a single dose and then, after a ≥9-day observation period, as QD dose until disease progression or until the discontinuation criteria were met.

All 13 subjects enrolled in the study (3 in the 15 mg group, 3 in the 30 mg group, and 7 in the 45 mg group) received dacomitinib and were included in the safety analysis population.

During the first 21 days of treatment with dacomitinib, subjects were assessed for dose limiting toxicity (DLT). No DLTs occurred in any dose group, demonstrating the tolerability of dacomitinib 45 mg QD oral dose.[32)]

Safety results included death reported in 1 of 13 subjects (7.7%) during the treatment period or within 28 days after the end of treatment. This subject in the 15 mg group died due to disease progression, and a causal relationship to dacomitinib was denied.

### 7.1.3 Global clinical studies

#### 7.1.3.1 Global phase II study (CTD 5.3.5.2.1, Study 1017 [March 2009 - April 2015])

An open-label, uncontrolled study was conducted at 26 study sites in 5 countries and regions including Japan to investigate the efficacy and safety of dacomitinib in patients with unresectable advanced or recurrent NSCLC (target sample size, 80 subjects for Cohort A and 25 subjects for Cohort B).

Chemotherapy-naïve patients with no or light smoking history[33)] or with EGFR activating mutation-positive NSCLC were enrolled in Cohort A, and patients with HER2-amplified[34)] or -mutant[35)] NSCLC were enrolled in Cohort B

Dacomitinib was orally administered at 30 or 45 mg QD.[36)] Treatment was continued until disease progression or until the discontinuation criteria were met.

All 89 subjects (including 6 Japanese subjects) enrolled in Cohort A were included in the Full Analysis Set (FAS) for efficacy analysis. All 119 subjects enrolled in the study (89 in Cohort A and 30 in Cohort B) received

32) The DLT assessment population was defined as patients who received dacomitinib and who experienced DLT during the DLT assessment period or who achieved ≥50% treatment compliance. One subject in the 45 mg group was excluded from DLT assessment because of the treatment compliance of 28.6%.

33) Patients with no smoking history were defined as patients who had smoked <100 cigarettes, etc. in their lives and not smoked in the previous 12 months. Patients with a light smoking history were defined as patients who had smoked no cigarettes for the previous ≥15 years and whose smoking index was <10 pack-years.

34) Defined as a HER2-chromosome 17 centromere ratio of >2 when calculated by using ≥50 nuclei.

35) The number of prior chemotherapy regimens was not specified.

36) Each cycle consisted of 28 days. The dose of patients who started treatment at 30 mg in Cycle 1 was increased to 45 mg in or after Cycle 2 if tolerance to 30 mg was confirmed.

dacomitinib and were included in the safety analysis population (including Japanese subjects, 6 in Cohort A and 2 in Cohort B).

The primary endpoint was the PFS rate at 4 months[37] in Cohort A as assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0.

Efficacy results showed that the PFS rate [95% CI] at 4 months in Cohort A as assessed by the investigator according to RECIST ver. 1.0 was 76.8% [66.4, 84.4] and was statistically significant (*P*-value [one-sided] < 0.0001; binomial test,[38] significance level [one-sided] of 0.05). The PFS rate [95% CI] at 4 months in Japanese subjects was 83.3% [27.3, 97.5].

Safety results included deaths reported in 7 of 119 subjects (5.9%) (3 of 89 in Cohort A and 4 of 30 in Cohort B) during the treatment period or within 28 days after the end of treatment. The causes of these deaths, except for deaths due to disease progression (2 subjects in Cohort A and 3 subjects in Cohort B), were haemorrhagic arteriovenous malformation in 1 subject in Cohort A and hepatic failure in 1 subject in Cohort B. For hepatic failure, a causal relationship to dacomitinib could not be ruled out (no Japanese subjects died due to adverse events in Cohort A or B).

#### 7.1.3.2 Global phase III study (CTD 5.3.5.1.2, Study 1009 [June 2011 - September 2015])

A double-blind, randomized, comparative study was conducted at 134 study sites in 23 countries including Japan to compare the efficacy and safety between dacomitinib and erlotinib in patients with unresectable advanced or recurrent NSCLC who had been treated with 1 or 2 chemotherapy regimens[39] (target sample size, 800 subjects).

Dacomitinib was orally administered at 45 mg QD in the dacomitinib group, and erlotinib was orally administered at 150 mg QD in the erlotinib group. Treatment was continued until disease progression or until the discontinuation criteria were met.

A total of 878 subjects enrolled and randomized in the study (439 in the dacomitinib group and 439 in the erlotinib group) were included in the intention-to-treat (ITT) population for efficacy analysis (including Japanese subjects, 53 in the dacomitinib group and 50 in the erlotinib group). Of the subjects included in the ITT population, 872 subjects (436 each in the dacomitinib group and the erlotinib group), excluding 6 subjects not treated with the study drug (3 each in the dacomitinib group and the erlotinib group), were included in the safety analysis population (including Japanese subjects, 53 in the dacomitinib group and 50 in the erlotinib group).

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37) Four months from the start day of study treatment

38) Considering that the PFS is 4 to 6 months in patients treated with platinum-based chemotherapy (*N Engl J Med.* 2006;355:2542-50), etc., the threshold PFS rate at 4 months was set at 50%.

39) Patients who had been treated with EGFR-TKIs other than dacomitinib or any drug acting on HER family proteins were excluded from the study.

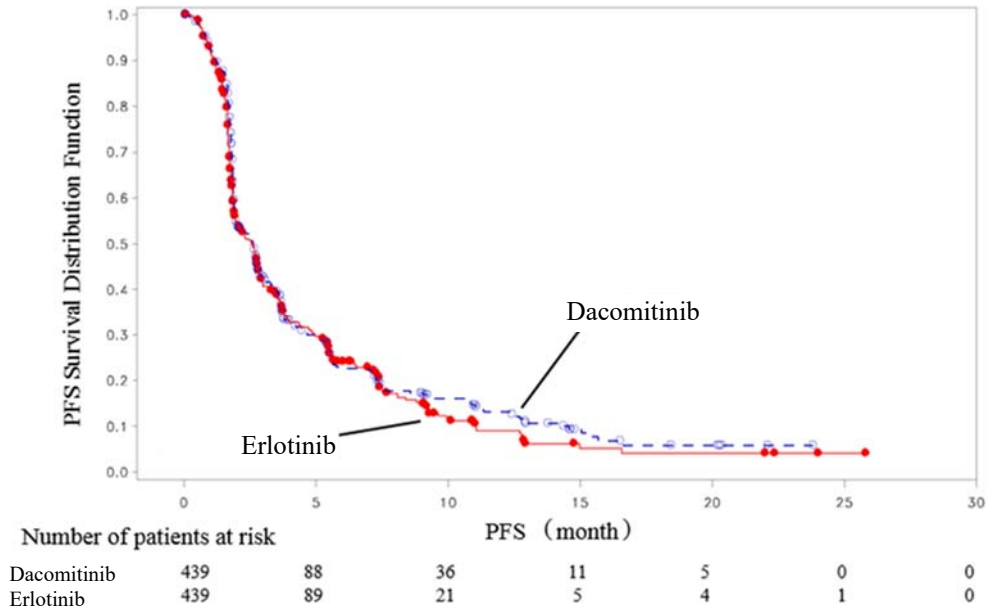
The primary endpoint of the study was PFS in the ITT population and the Kirsten rat sarcoma viral oncogene homolog wild type (KRAS-WT) population as determined by Independent Radiologic Central (IRC) review according to RECIST ver. 1.1. The significance level (one-sided) for PFS analysis in the ITT population and the KRAS-WT population was set at 0.015 and 0.010, respectively, so that the significance level (one-sided) for the entire study was maintained at 0.025.

The results of PFS in the ITT population and the KRAS-WT population as determined by IRC review according to RECIST ver. 1.1 and Kaplan-Meier curves are shown in Table 24 and Figure 2, respectively. Significant prolongation of PFS in the dacomitinib group compared to the erlotinib group was not verified in either population.

**Table 24. Results of final analysis of PFS**
**(IRC review, ITT population and KRAS-WT population, data cut-off on September 30, 2013)**

| | ITT population | | KRAS-WT population | |
|---|---|---|---|---|
| | Dacomitinib | Erlotinib | Dacomitinib | Erlotinib |
| N | 439 | 439 | 256 | 263 |
| Number of events (%) | 313 (71.3) | 308 (70.2) | 189 (73.8) | 190 (72.2) |
| Median [95% CI] (months) | 2.6 [1.9, 2.8] | 2.6 [1.9, 2.8] | 2.6 [1.9, 2.9] | 2.6 [1.9, 3.0] |
| Hazard ratio [95% CI] | 0.941 [0.802, 1.104][*1] | | 1.022 [0.834, 1.253][*2] | |
| *P*-value (one-sided) | 0.229[*3] | | 0.587[*4] | |

[*1], Stratified Cox regression with EGFR genotype (wild-type, mutant), KRAS genotype (wild-type, mutant), and ECOG PS (0-1, 2) as stratification factors; [*2], Stratified Cox regression with EGFR genotype (wild-type, mutant) and ECOG PS (0-1, 2) as stratification factors; [*3], Stratified log-rank test with EGFR genotype (wild-type, mutant), KRAS genotype (wild-type, mutant), and ECOG PS (0-1, 2) as stratification factors, significance level (one-sided) of 0.015; [*4], Stratified log-rank test with EGFR genotype (wild-type, mutant) and ECOG PS (0-1, 2) as stratification factors, significance level (one-sided) of 0.01



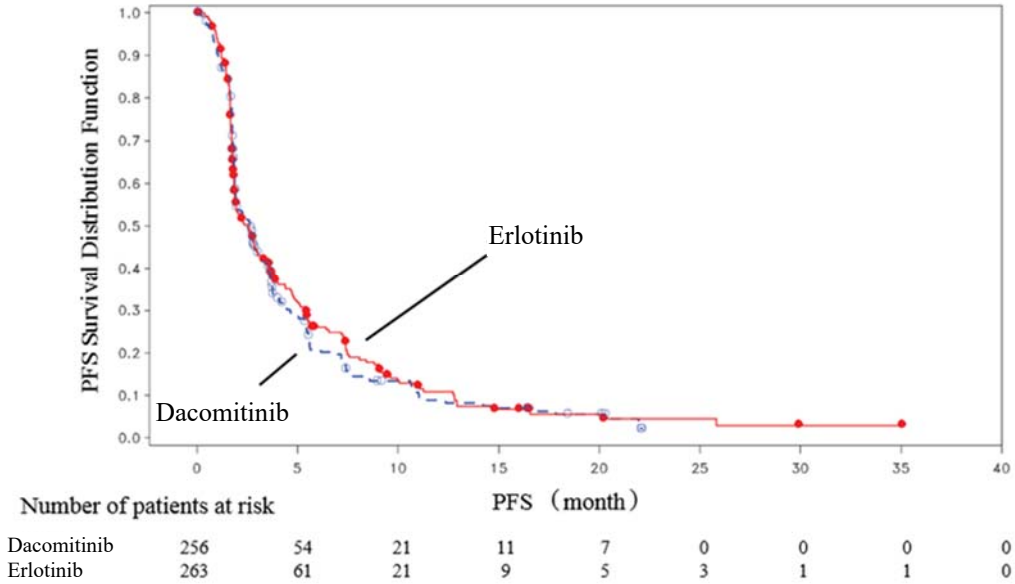




**Figure 2. Kaplan-Meier curves for PFS at the final analysis**
**(IRC review; upper figure, ITT population; lower figure, KRAS-WT population; data cut-off on September 30, 2013)**

Safety results included deaths reported in 85 of 436 subjects (19.5%) in the dacomitinib group and 73 of 436 subjects (16.7%) in the erlotinib group during the treatment period or within 28 days after the end of treatment. The causes of these deaths, except for deaths due to disease progression (53 subjects in the dacomitinib group and 50 subjects in the erlotinib group), were death (5 subjects); pneumonia, NSCLC, and acute respiratory failure (2 subjects each); and febrile neutropenia, acute myocardial infarction, cardiac arrest, myocardial infarction, myocardial ischaemia, pneumoperitoneum, condition aggravated, pneumonia pseudomonal, sepsis, respiratory tract infection, aspiration bronchial, lung cancer metastatic, lung neoplasm malignant, metastatic neoplasm, lung squamous cell carcinoma metastatic, renal failure, dyspnoea, haemoptysis, interstitial lung disease (ILD), internal fixation of fracture, and hypovolaemic shock (1 subject each) in the dacomitinib group; and general physical health deterioration (3 subjects); lung neoplasm malignant, pulmonary embolism, and

respiratory failure (2 subjects each); cardiac arrest, cardiac failure, condition aggravated, death, sepsis, septic shock, lung infection, squamous cell carcinoma of lung, metastases to meninges, neoplasm progression, NSCLC, acute respiratory distress syndrome, pulmonary haemorrhage, and respiratory distress (1 subject each) in the erlotinib group. A causal relationship to the study drug could not be ruled out for cardiac arrest and ILD reported in 1 subject each in the dacomitinib group (The causes of deaths in Japanese subjects who died due to adverse events [4 in the dacomitinib group and 3 in the erlotinib group], excluding death due to disease progression [2 in the dacomitinib group and 2 in the erlotinib group], were condition aggravated and ILD [1 subject each] in the dacomitinib group and cardiac failure [1 subject] in the erlotinib group. A causal relationship to the study drug could not be ruled out for ILD in 1 subject in the dacomitinib group).

#### 7.1.3.3 Global phase III study (CTD 5.3.5.1.1, Study 1050 [May 2013 - February 2017])

An open-label, randomized, comparative study was conducted at 71 study sites in 7 countries and regions including Japan to compare the efficacy and safety between dacomitinib and gefitinib in chemotherapy-naïve patients with EGFR activating mutation-positive,[40)] unresectable advanced or recurrent NSCLC[41)] (target sample size, 440 subjects).

Dacomitinib was orally administered at 45 mg QD in the dacomitinib group, and gefitinib was orally administered at 250 mg QD in the gefitinib group. Treatment was continued until disease progression or until the discontinuation criteria were met.

All 452 subjects enrolled and randomized in the study (227 in the dacomitinib group and 225 in the gefitinib group) were included in the ITT population for efficacy analysis (including Japanese subjects, 40 in the dacomitinib group and 41 in the gefitinib groups). Of the subjects included in the ITT population, 451 subjects (227 in the dacomitinib group and 224 in the gefitinib group), excluding 1 subject not treated with the study drug (1 in the gefitinib group), were included in the safety analysis population (including Japanese subjects, 40 in the dacomitinib group and 41 in the erlotinib group).

The primary endpoint of the study was PFS as determined by IRC review according to RECIST ver. 1.1.

The results of PFS as determined by IRC review according to RECIST ver. 1.1 (primary endpoint) and Kaplan-Meier curves are shown in Table 25 and Figure 3, respectively. Compared to the gefitinib group, it was demonstrated that PFS was significantly prolonged in the dacomitinib group.

40) The study enrolled patients with NSCLC, from whom tumor tissue samples were collected and the presence of Ex19del or L858R, out of EGFR activating mutations, was confirmed in the samples. Patients harboring T790M mutation in their tumor tissue samples were also enrolled in the study.

41) Of patients with NSCLC, those with confirmed adenocarcinoma or tumors categorized in an adenocarcinoma-specific histological type were enrolled in the study.

**Table 25. Results of final analysis of PFS**
**(IRC review, ITT population, data cut-off on July 29, 2016)**

| | Dacomitinib | Gefitinib |
|---|---|---|
| N | 227 | 225 |
| Number of events (%) | 136 (59.9) | 179 (79.6) |
| Median [95%CI] (months) | 14.7 [11.1, 16.6] | 9.2 [9.1, 11.0] |
| Hazard ratio [95%CI][*1] | 0.589 [0.469, 0.739] | |
| *P*-value (one-sided)[*2] | < 0.0001 | |

[*1], Stratified Cox regression with race (Japanese, non-Japanese East Asian, non-Asian) and EGFR genotype (Ex19del, L858R) as stratification factors
[*2], Stratified log-rank regression with race (Japanese, non-Japanese East Asian, non-Asian) and EGFR mutation type (Ex19del, L858R) as stratification factors, significance level (one-sided) of 0.025

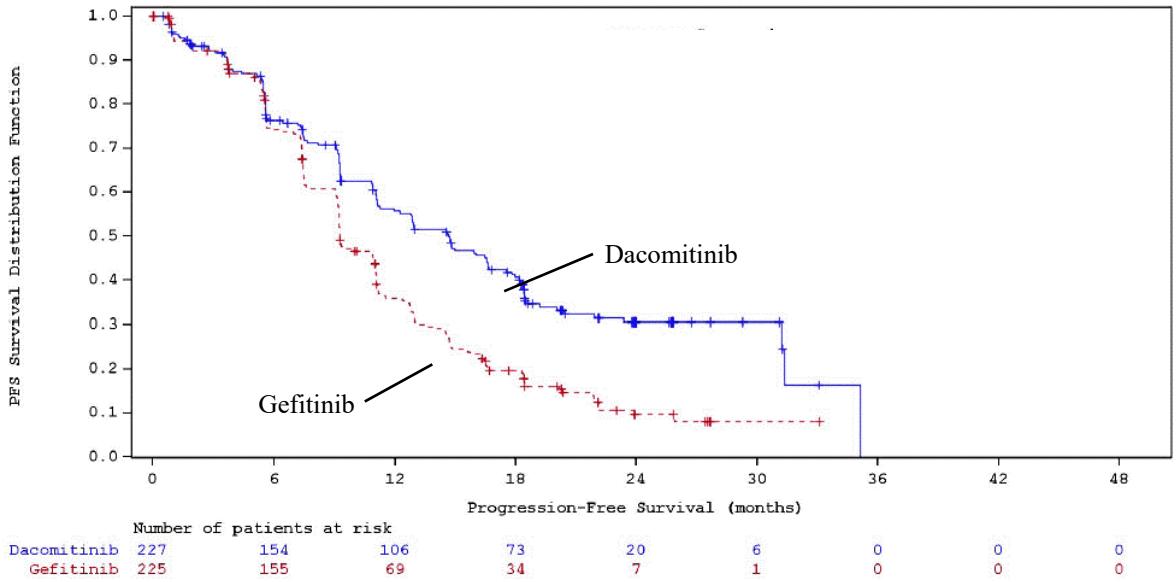



**Figure 3. Kaplan-Meier curves for PFS at the final analysis**
**(IRC review, ITT population, data cut-off on July 29, 2016)**

Safety results included deaths reported in 22 of 227 subjects (9.7%) in the dacomitinib group and 20 of 224 subjects (8.9%) in the gefitinib group during the treatment period or within 28 days after the end of treatment. The causes of these deaths, except for deaths due to disease progression (8 subjects in the dacomitinib group and 11 subjects in the gefitinib group), were pneumonia and respiratory failure (2 subjects each); diarrhoea, death, multiple organ dysfunction syndrome, bronchopulmonary aspergillosis, urinary tract infection, lung infection, overdose, metastases to meninges, cerebral infarction, and pneumonitis (1 subject each) in the dacomitinib group; and dyspnoea (2 subjects); death, general physical health deterioration, pneumonia, malnutrition, malignant neoplasm progression, cerebral infarction, and pleural effusion (1 subject each) in the gefitinib group. A causal relationship to the study drug could not be ruled out for death and diarrhoea in 1 subject each in the dacomitinib group and death and pneumonia in 1 subject each in the gefitinib group (Japanese subject who died due to adverse events was 0 in the dacomitinib group and 1 in the gefitinib group. The cause of the death was disease progression, for which a causal relationship to the study drug was denied).

## 7.2 Reference data

### 7.2.1 Clinical pharmacology

The applicant submitted the data from the following clinical pharmacology study in patients with resectable NSCLC. No deaths were reported during the treatment period or within 28 days after the end of treatment.

#### 7.2.1.1 Foreign phase Ib study (CTD 5.3.3.2.3, Study 1031 [February 2010 - May 2012])

### 7.2.2 Foreign clinical studies

#### 7.2.2.1 Foreign phase I study (CTD 5.3.5.4.3, Study 1004 [August 2008 - January 2013])

An open-label, uncontrolled study was conducted at 4 foreign study sites to investigate the safety etc. of dacomitinib in combination with FIG in patients with advanced solid tumors (target sample size, 71-81 subjects).

A total of 71 subjects enrolled and treated with dacomitinib (24 in the dacomitinib 10 mg + FIG 20 mg group, 25 in the dacomitinib 15 mg + FIG 20 mg group, 7 in the dacomitinib 20 mg + FIG 10 mg group, 10 in the dacomitinib 20 mg + FIG 20 mg group, and 5 in the dacomitinib 30 mg + FIG 20 mg group) were included in the safety analysis population.

Safety results included deaths reported in 8 of 24 subjects (33.3%) in the dacomitinib 10 mg + FIG 20 mg group, 3 of 25 subjects (12.0%) in the dacomitinib 15 mg + FIG 20 mg group, 2 of 7 subjects (28.6%) in the dacomitinib 20 mg + FIG 10 mg group, 4 of 10 subjects (40.0%) in the dacomitinib 20 mg + FIG 20 mg group, and 1 of 5 subjects (20.0%) in the dacomitinib 30 mg + FIG 20 mg group during the treatment period or within 28 days after the end of treatment. All these deaths were caused by disease progression, and a causal relationship to the study drug was denied.

#### 7.2.2.2 Foreign phase I study (CTD 5.3.5.4.4, Study 1006 [August 2010 - February 2014])

An open-label, uncontrolled study was conducted at 4 foreign study sites to investigate the safety etc. of dacomitinib in combination with crizotinib in patients with unresectable advanced or recurrent NSCLC[42)] (target sample size, 70 subjects).

A total of 70 subjects enrolled and treated with the study drug (33 in the dose-escalation part and 37 in the expansion part) were included in the safety analysis population.

Safety results included deaths reported in 4 of 33 subjects (12.1%) in the dose-escalation part and 5 of 37 subjects (13.5%) in the expansion part during the treatment period or within 28 days after the end of treatment. The causes of these deaths, except for deaths due to disease progression (2 subjects in the dose-escalation part

42) Patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy were enrolled in the dose-escalation part, and patients with unresectable advanced or recurrent NSCLC previously treated with erlotinib or gefitinib were enrolled in the expansion part.

and 4 subjects in the expansion part), were lung infection, neoplasm malignant, and hypoxia (1 subject each), and a causal relationship to the study drug was denied for all these events.

#### 7.2.2.3 Foreign phase I/II study (CTD 5.3.5.2.3, Study 1003 [February 2008 - July 2014])

An open-label, uncontrolled study was conducted at 3 foreign study sites to investigate the safety etc. of dacomitinib in patients with KRAS wild-type, unresectable advanced or recurrent NSCLC previously treated with chemotherapy[43] (target sample size, 18 subjects in phase I part and 42 subjects in phase II part).

A total of 55 subjects enrolled and treated with dacomitinib (12 in phase I part and 43 in phase II part) were included in the safety analysis population.

Safety results included deaths reported in 5 of 43 subjects (11.6%) in phase II part during the treatment period or within 28 days after the end of treatment. The causes of all these deaths were disease progression, for which a causal relationship to dacomitinib was denied.

#### 7.2.2.4 Foreign phase II study (CTD 5.3.5.2.2, Study 1002 [April 2008 - June 2012])

An open-label, uncontrolled study was conducted at 6 foreign study sites to investigate the efficacy and safety of dacomitinib in patients with KRAS wild-type, unresectable advanced or recurrent NSCLC[44] previously treated with chemotherapy[45] (target sample size, 49 subjects in Part A and 25 subjects in Part B).

A total of 66 subjects enrolled and treated with dacomitinib (50 in Part A and 16 in Part B) were included in the safety analysis population.

Safety results included deaths reported in 6 of 50 subjects (12.0%) in Part A and 3 of 16 subjects (18.8%) in Part B during the treatment period or within 28 days after the end of treatment. The causes of these deaths, except for deaths due to disease progression (2 subjects in Part A and 1 subject in Part B), were respiratory failure (3 subjects) and disease progression and pneumonia aspiration (1 subject) in Part A; and NSCLC and haemoptysis (1 subject each) in Part B. The causal relationship to dacomitinib was denied for all these events.

#### 7.2.2.5 Foreign phase II study (CTD 5.3.5.4.2, Study 1027 [November 2008 - April 2012])

An open-label, uncontrolled study was conducted at 7 foreign study sites to investigate the efficacy and safety of dacomitinib in patients with recurrent or metastatic head-and-neck squamous cell carcinoma (target sample size, 56 subjects).

A total of 69 subjects enrolled and treated with dacomitinib were included in the safety analysis population.

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43) Patients who were resistant or intolerant to ≥1 platinum-based chemotherapy regimen and gefitinib or erlotinib were enrolled in the study.

44) Patients with adenocarcinoma NSCLC and those with non-adenocarcinoma NSCLC were enrolled in Part A and Part B, respectively.

45) Patients with metastatic NSCLC who were resistant or intolerant to ≥1 chemotherapy regimen or erlotinib and patients with unresectable advanced or recurrent NSCLC who were resistant or intolerant to 1 or 2 chemotherapy regimens or erlotinib were enrolled in the study.

Safety results included deaths reported in 9 of 69 subjects (13.0%) during the treatment period or within 28 days after the end of treatment. The causes of these deaths, except for deaths due to disease progression reported in 4 subjects, were sepsis, brain abscess, septic shock, pulmonary embolism, and haemorrhage (1 subject each). A causal relationship to dacomitinib could not be ruled out for sepsis in 1 subject.

#### 7.2.2.6 Foreign phase II study (CTD 5.3.5.1.4, Study 1028 [November 2008 - August 2014])

An open-label, randomized, comparative study was conducted at 47 foreign study sites to compare the efficacy and safety between dacomitinib and erlotinib in patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy (target sample size, 160 subjects).

A total of 187 subjects enrolled and treated with the study drug (93 in the dacomitinib group and 94 in the erlotinib group) were included in the safety analysis population.

Safety results included deaths reported in 23 of 93 subjects (24.7%) in the dacomitinib group and 21 of 94 subjects (22.3%) in the erlotinib group during the treatment period or within 28 days after the end of treatment. The causes of these deaths, except for deaths due to disease progression (14 subjects in the dacomitinib group and 16 subjects in the erlotinib group), were pneumonia (2 subjects), and gastrointestinal haemorrhage, pneumonia bacterial, lung neoplasm malignant, pneumonitis, pulmonary embolism, pulmonary haemorrhage, and respiratory failure (1 subject each) in the dacomitinib group; and pneumonia (2 subjects) and cachexia, dyspnoea, and pulmonary embolism (1 subject each) in the erlotinib group. A causal relationship to the study drug could not be ruled out for pneumonia and pneumonitis in 1 subject each in the dacomitinib group and pneumonia and pulmonary embolism in 1 subject each in the erlotinib group.

#### 7.2.2.7 Foreign phase II study (CTD 5.3.5.2.4, Study 1042 [December 2011 - May 2015])

An open-label, randomized study was conducted at 41 foreign study sites to investigate the safety and PK, etc. of dacomitinib in patients with unresectable advanced or recurrent NSCLC (target sample size, 156 subjects in Cohorts 1 and 2, 28 subjects in Cohort 3).

Patients previously treated with chemotherapy were enrolled in Cohorts 1 and 2, and chemotherapy-naïve patients with HER1- or HER2-mutant or HER2-amplified NSCLC were enrolled in Cohort 3.

A total of 231 subjects enrolled and treated with the study drug (139 in Cohort 1, 67 in Cohort 2, and 25 in Cohort 3) were included in the safety analysis population.

Safety results included deaths reported in 26 of 139 subjects (18.7%) in Cohort 1, 10 of 67 subjects (14.9%) in Cohort 2, and 2 of 25 subjects (8.0%) in Cohort 3 during the treatment period or within 28 days after the end of treatment. The causes of these deaths, except for deaths due to disease progression (14 subjects in Cohort 1, 8 subjects in Cohort 2, and 1 subject in Cohort 3), were septic shock and lung cancer metastatic (2

subjects each), and pneumothorax, toxicity to various agents, hypovolaemic shock, cardiogenic shock, respiratory failure, NSCLC metastatic, cardiac arrest, and intra-abdominal haemorrhage (1 subject each) in Cohort 1, pneumonia and cardiac arrest (1 subject each) in Cohort 2, and embolism (1 subject) in Cohort 3. A causal relationship to the study drug could not be ruled out for pneumonia in 1 subject in Cohort 2.

#### 7.2.2.8 Foreign phase II study (CTD 5.3.5.4.1, Study 1047 [July 2013 - September 2015])

An open-label, uncontrolled study was conducted at 7 foreign study sites to investigate the efficacy and safety of dacomitinib in patients with unresectable advanced or recurrent NSCLC (target sample size, 15 subjects in Cohort A[46)] and 20 subjects in Cohort B[47)]).

A total of 38 subjects enrolled and treated with dacomitinib (16 in Cohort A and 22 in Cohort B) were included in the safety analysis population.

Safety results included deaths reported in 3 of 16 subjects (18.8%) in Cohort A and 4 of 22 subjects (18.2%) in Cohort B during the treatment period or within 28 days after the end of treatment. The causes of these deaths were NSCLC, malignant neoplasm progression, and cardio-respiratory arrest (1 subject each) in Cohort A and NSCLC, dyspnoea, respiratory failure, and sepsis (1 subject each) in Cohort B. The causal relationship to dacomitinib was ruled out for all these events.

#### 7.2.2.9 Foreign phase III study (CTD 5.3.5.1.3, Study 1011 [December 2009 to June 2015])

A double-blind, randomized, comparative study was conducted at 91 foreign study sites to compare efficacy and safety between dacomitinib and placebo in patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy[48)] (target sample size, 720 subjects).

A total of 720 subjects enrolled and treated with study drug (480 in the dacomitinib group and 240 in the placebo group) were included in the ITT population. Of the subjects included in the ITT population, 716 subjects (477 in the dacomitinib group and 239 in the placebo group), excluding 4 subjects not treated with the study drug (3 in the dacomitinib group and 1 in the placebo group), were included in the safety analysis population.

Safety results included deaths reported in 95 of 477 subjects (19.9%) in the dacomitinib group and 48 of 239 subjects (20.1%) in the placebo group during the treatment period or within 30 days after the end of treatment. The causes of these deaths were NSCLC (75 subjects), lung infection (9 subjects), death, and respiratory failure (2 subjects each), and cardiac arrest, sudden death, lung cancer metastatic, NSCLC metastatic, dyspnoea, pulmonary haemorrhage, and pulmonary oedema (1 subject each) in the dacomitinib group, and NSCLC (37 subjects), lung infection (4 subjects), sudden death (2 subjects), and sepsis, neoplasm progression, cerebrovascular accident, haemorrhage intracranial, and respiratory failure (1 subject each) in the placebo

46) Patients with EGFR T790M mutation-positive NSCLC were enrolled.
47) Patients with EGFR T790M mutation-negative or -unknown NSCLC were enrolled.
48) Including previous treatment with gefitinib or erlotinib

group. A causal relationship to dacomitinib could not be ruled out for respiratory failure in 2 subjects and death in 1 subject in the dacomitinib group.

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Data for review

PMDA considers that pivotal clinical study evaluating the efficacy and safety of dacomitinib in the submitted evaluation data was the global phase III study (Study 1050) in chemotherapy-naïve patients with EGFR activating mutation-positive, unresectable advanced or recurrent NSCLC, and has determined to evaluate this application with a main focus on this study.

PMDA has determined to use the data from the global phase III study (Study 1009) in patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy to confirm primarily the safety of dacomitinib because this study was performed in patients with NSCLC with no regard to EGFR activating mutation status.

PMDA has determined to evaluate the efficacy of dacomitinib in Japanese patients in light of data consistency between the overall study population and the Japanese subgroup in Study 1050 in accordance with “Basic Principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010 dated September 28, 2007 issued by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare) and “Basic Principles on Global Clinical Trials (Reference Cases)” (PFSB/ELD Administrative Notice, dated September 5, 2012).

### 7.R.2 Efficacy

As a result of the following review, PMDA has concluded that the submitted data has demonstrated the efficacy of dacomitinib in chemotherapy-naïve patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC.

#### 7.R.2.1 Selection of control group

The applicant provided the rationale for the control group in Study 1050 as follows:
National Comprehensive Cancer Network (NCCN) Guideline (ver. 2. 2012) available at the time of designing Study 1050 recommended gefitinib based on a report (*Lancet Oncol.* 2010;11:121-8), etc. demonstrating the high efficacy of gefitinib compared with platinum-based chemotherapy in patients eligible for Study 1050. In consideration of the above, gefitinib was selected as the control treatment in Study 1050.

PMDA accepted the applicant’s explanation.

### 7.R.2.2 Efficacy endpoint

The applicant explained the appropriateness of selecting PFS as the primary endpoint in Study 1050 as follows: In patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC, prolongation of time to disease progression is expected to slow down the worsening of clinical symptoms associated with disease progression. Prolongation of PFS in these patients is therefore considered of clinical significance. In light of the above, it was appropriate to select PFS as the primary endpoint in the study.

PMDA's view:

Given that treatment of EGFR mutation-positive, unresectable advanced or recurrent NSCLC is generally performed with the purpose of prolonging the patient's life, overall survival (OS) should have been used as the primary endpoint in Study 1050. However, prolongation of PFS in these patients has a certain level of clinical significance depending on the degree of improvement. Therefore, PMDA has concluded that the efficacy of dacomitinib should be evaluated in a comprehensive manner based on the data on PFS, the primary endpoint of Study 1050, as well as data on OS.

### 7.R.2.3 Efficacy evaluation results

In Study 1050, the superiority of dacomitinib over gefitinib was demonstrated in terms of the primary endpoint, PFS, as determined by IRC review according to RECIST ver. 1.1 [see Section 7.1.3.3]. The study was designed so that hypothetical tests of secondary endpoints, in the order of response rate and OS, could be performed if a statistically significant difference was observed in the primary endpoint. Since no statistically significant difference was observed in the above analysis of response rates (stratified Cochran-Mantel-Haenazel test; *P*-value [one-sided], 0.1942), the test for OS was not performed.

The results of the final analysis of OS, a secondary endpoint, (data cut-off on February 17, 2017) and Kaplan-Meier curves are shown in Table 26 and Figure 4, respectively.

**Table 26. Results of final analysis of OS (ITT population, data cut-off on February 17, 2017)**

| | Dacomitinib | Gefitinib |
|---|---|---|
| N | 227 | 225 |
| Number of events (%) | 103 (45.4) | 117 (52.0) |
| Median [95% CI] (months) | 34.1 [29.5, 37.7] | 26.8 [23.7, 32.1] |
| Hazard ratio [95% CI][*1] | 0.760 [0.582, 0.993] | |
| *P*-value (one-sided)[*2] | 0.0219 | |

[*1], Stratified Cox regression with race (Japanese, non-Japanese East-Asian, non-Asian) and EGFR genotype (Ex19del, L858R) as stratification factors
[*2], Stratified log-rank test with race (Japanese, non-Japanese East-Asian, non-Asian) and EGFR genotype (Ex19del, L858R) as stratification factors

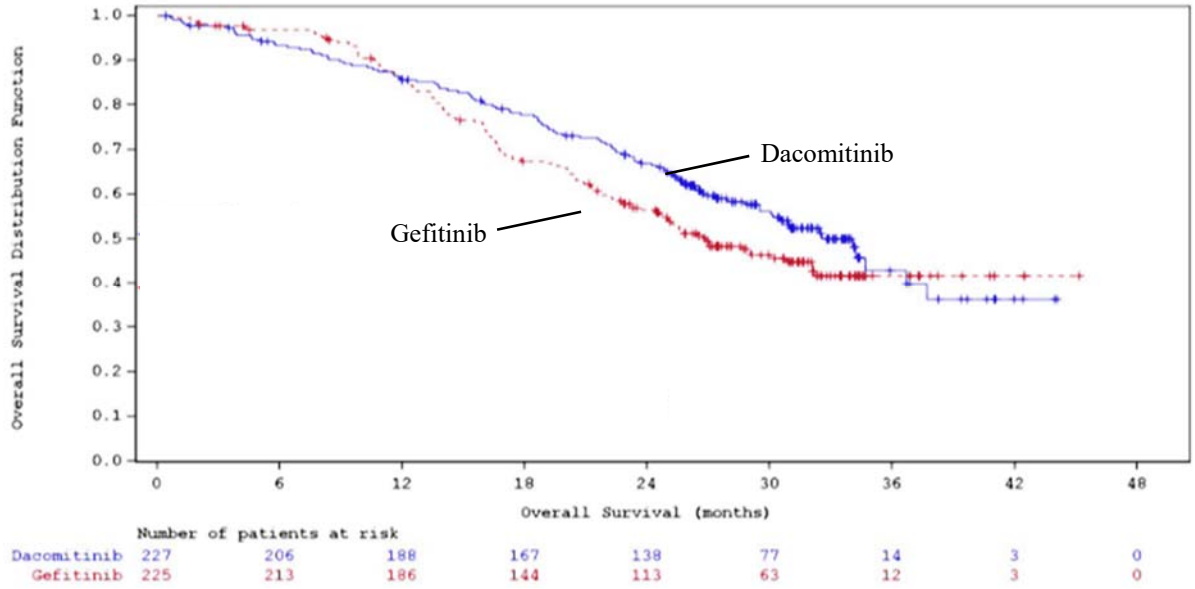


**Figure 4. Kaplan-Meier curves for OS at the final analysis (ITT population, data cut-off on February 17, 2017)**

The results of analysis of PFS in the Japanese subjects in Study 1050 as determined by IRC review and Kaplan-Meier curves are shown in Table 27 and Figure 5, respectively.

**Table 27. Results of final analysis of PFS in Japanese subjects (determined by IRC review, ITT population, data cut-off on July 29, 2016)**

| | Dacomitinib | Gefitinib |
|---|---|---|
| N | 40 | 41 |
| Number of events (%) | 22 (55.0) | 31 (75.6) |
| Median [95% CI] (months) | 18.2 [11.0, 31.3] | 9.3 [7.4, 14.7] |
| Hazard ratio [95% CI][*1] | 0.544 [0.307, 0.961] | |
| *P*-value (one-sided)[*2] | 0.0163 | |

[*1], Stratified Cox regression with EGFR mutation type (Ex19del, L858R) as the stratification factor
[*2], Stratified log-rank test with EGFR mutation type (Ex19del, L858R) as the stratification factor

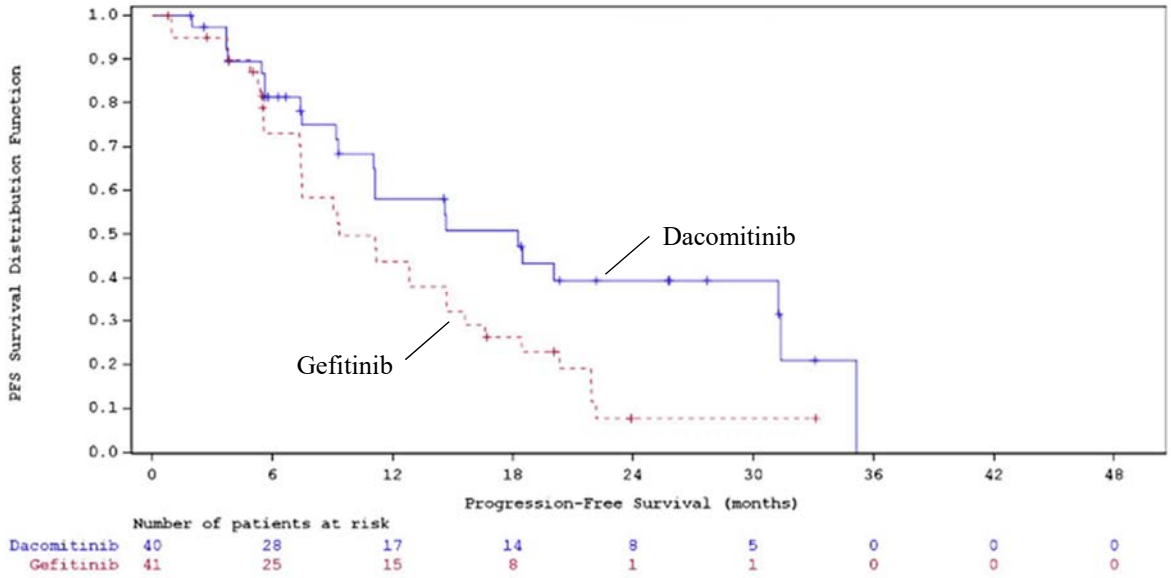


**Figure 5. Kaplan-Meier curves for PFS in Japanese subjects at the final analysis (IRC review, ITT population, data cut-off on July 29, 2016)**

PMDA's view:

PMDA has concluded that the efficacy of dacomitinib in patients of Study 1050 has been demonstrated for the following reasons:

- The superiority of dacomitinib to gefitinib was demonstrated in terms of PFS, the primary endpoint, and a clinically significant level of beneficial effect was observed. In addition, results from the Japanese subgroup were consistent to those from the overall study population.
- No tendency for OS, a secondary endpoint, to be decreased in subjects treated with dacomitinib compared to those treated with gefitinib was observed.

### 7.R.3 Safety [for adverse events, see Section "7.3 Adverse events reported in clinical studies"]

Based on the assessment of safety data presented below, PMDA has reached the following conclusion:

Adverse events requiring special attention during treatment with dacomitinib in patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC are ILD, skin disorders, diarrhoea, hepatic function disorders, gastrointestinal disorders (excluding diarrhoea), nail abnormality, and hypokalaemia. Patients on dacomitinib should be monitored for the above adverse events.

Although due attention should be paid to the occurrence of the above adverse events in patients on dacomitinib, the tolerability profile of dacomitinib is acceptable if appropriate measures, such as monitoring and management of adverse events and dose adjustment, are taken by physicians with sufficient knowledge and experience in cancer chemotherapy.

### 7.R.3.1 Safety profile of dacomitinib and differences in safety between Japanese and non-Japanese patients

Based on the safety data from Study 1050 and Study 1009, the applicant explained the safety profile of dacomitinib and differences in safety between Japanese and non-Japanese patients as follows:

(a) Safety profile of dacomitinib

The safety data from Study 1050 and Study 1009 are summarized in Table 28.

**Table 28. Summary of safety data (Study 1050 and Study 1009)**

| | n (%) | | | |
|---|---|---|---|---|
| | Study 1050 | | Study 1009 | |
| | Dacomitinib N = 227 | Gefitinib N = 224 | Dacomitinib N = 436 | Erlotinib N = 436 |
| All adverse events | 226 (99.6) | 220 (98.2) | 431 (98.9) | 428 (98.2) |
| Grade ≥3 adverse events | 143 (63.0) | 92 (41.1) | 254 (58.3) | 234 (53.7) |
| Adverse events leading to death | 22 (9.7) | 20 (8.9) | 85 (19.5) | 73 (16.7) |
| Serious adverse events | 62 (27.3) | 50 (22.3) | 178 (40.8) | 170 (39.0) |
| Adverse events leading to treatment discontinuation | 40 (17.6) | 27 (12.1) | 87 (20.0) | 80 (18.3) |
| Adverse events leading to treatment interruption | 130 (57.3) | 60 (26.8) | 213 (48.9) | 145 (33.3) |
| Adverse events leading to dose reduction | 150 (66.1) | 18 (8.0) | 41 (9.4) | 21 (4.8) |

In Study 1050, the adverse events of any grade with an incidence higher in the dacomitinib group than in the gefitinib group by ≥15% were diarrhoea (198 subjects [87.2%] in the dacomitinib group and 125 subjects [55.8%] in the gefitinib group), paronychia (140 [61.7%], 45 [20.1%]), dermatitis acneiform (111 [48.9%], 64 [28.6%]), and stomatitis (99 [43.6%], 40 [17.9%]). The Grade ≥3 adverse events with an incidence higher in the dacomitinib group than in the gefitinib group by ≥5% were dermatitis acneiform (31 [13.7%], 0), diarrhoea (20 [8.8%], 2 [0.9%]), and paronychia (17 [7.5%], 3 [1.3%]). There were no serious adverse events or adverse events leading to treatment discontinuation that occurred with an incidence higher in the dacomitinib group than in the gefitinib group by ≥5%. The adverse events leading to treatment interruption with an incidence higher in the dacomitinib group than in the gefitinib group by ≥5% were dermatitis acneiform (32 [14.1%], 4 [1.8%]), paronychia (28 [12.3%], 2 [0.9%]), and diarrhoea (22 [9.7%], 1 [0.4%]). The adverse events leading to dose reduction with an incidence higher in the dacomitinib group than in the gefitinib group by ≥5% were dermatitis acneiform (46 [20.3%], 3 [1.3%]), paronychia (38 [16.7%], 2 [0.9%]), and diarrhoea (19 [8.4%], 3 [1.3%]). There were no adverse events leading to death that occurred with an incidence higher in the dacomitinib group than in the gefitinib group by ≥2%.

In Study 1009, the adverse event of any grade with an incidence higher in the dacomitinib group than in the erlotinib group by ≥15% was diarrhoea (324 subjects [74.3%] in the dacomitinib group and 218 subjects [50.0%] in the erlotinib group). The Grade ≥3 adverse event with an incidence higher in the dacomitinib group than in the erlotinib group by ≥5% was diarrhoea (49 [11.2%], 11 [2.5%]). There were no serious adverse events or adverse events leading to treatment discontinuation that occurred with an incidence higher in the dacomitinib group than in the erlotinib group by ≥5%. The adverse event leading to treatment interruption with an incidence higher in the dacomitinib group than in the erlotinib group by ≥5% was diarrhoea (87 [20.0%],

21 [4.8%]). There were no adverse events leading to dose reduction with an incidence higher in the dacomitinib group than in the erlotinib group by ≥5% or adverse events leading to death that occurred with an incidence higher in the dacomitinib group than in the erlotinib group by ≥2%.

No clear difference was observed in the safety profile of dacomitinib between Study 1050 and Study 1009.

(b) Differences in safety between Japanese and non-Japanese patients

A summary of safety in Japanese patients and non-Japanese patients in Study 1050 and Study 1009 is shown in Table 29.

**Table 29. Summary of safety (dacomitinib group in Study 1050 and Study 1009)**

| | n (%) | | | |
|---|---|---|---|---|
| | Study 1050 | | Study 1009 | |
| | Japanese N = 40 | Non-Japanese N = 187 | Japanese N = 53 | Non-Japanese N = 383 |
| All adverse events | 40 (100) | 186 (99.5) | 52 (98.1) | 379 (99.0) |
| Grade ≥3 adverse events | 19 (47.5) | 124 (66.3) | 31 (58.5) | 223 (58.2) |
| Adverse events leading to death | 0 | 22 (11.8) | 4 (7.5) | 81 (21.1) |
| Serious adverse events | 6 (15.0) | 56 (29.9) | 18 (34.0) | 160 (41.8) |
| Adverse events leading to treatment discontinuation | 10 (25.0) | 30 (16.0) | 9 (17.0) | 78 (20.4) |
| Adverse events leading to treatment interruption | 27 (67.5) | 103 (55.1) | 30 (56.6) | 183 (47.8) |
| Adverse events leading to dose reduction | 34 (85.0) | 116 (62.0) | 5 (9.4) | 36 (9.4) |

In Study 1050, the adverse events of any grade with an incidence higher in Japanese subjects than in non-Japanese subjects by ≥20% were dermatitis acneiform (39 Japanese subjects [97.5%] and 72 non-Japanese subjects [38.5%]), paronychia (38 [95.0%], 102 [54.5%]), stomatitis (32 [80.0%], 67 [35.8%]), dry skin (24 [60.0%], 39 [20.9%]), pruritus (17 [42.5%], 28 [15.0%]), and dysgeusia (14 [35.0%], 2 [1.1%]). The Grade ≥3 adverse events with an incidence higher in Japanese subjects than in non-Japanese subjects by ≥10% were dermatitis acneiform (11 [27.5%], 20 [10.7%]) and paronychia (9 [22.5%], 8 [4.3%]). The adverse events leading to treatment interruption with an incidence higher in Japanese subjects than in non-Japanese subjects by ≥10% were dermatitis acneiform (15 [37.5%], 17 [9.1%]) and paronychia (15 [37.5%], 13 [7.0%]). The adverse events leading to dose reduction with an incidence higher in Japanese subjects than in non-Japanese subjects by ≥10% were dermatitis acneiform (21 [52.5%], 25 [13.4%]), paronychia (16 [40.0%], 22 [11.8%]), diarrhoea (7 [17.5%], 12 [6.4%]), and dry skin (6 [15.0%], 1 [0.5%]). There were no serious adverse events or adverse events leading to treatment discontinuation that occurred with an incidence higher in Japanese subjects than in non-Japanese subjects by ≥5% or adverse events leading to death that occurred with an incidence higher in Japanese subjects than in non-Japanese subjects by ≥2%.

In Study 1009, the adverse events of any grade with an incidence higher in Japanese subjects than in non-Japanese subjects by ≥20% were dermatitis acneiform (32 Japanese subjects [60.4%] and 49 non-Japanese subjects [12.8%]), stomatitis (31 [58.5%], 50 [13.1%]), paronychia (30 [56.6%], 64 [16.7%]), dry skin (26 [49.1%], 60 [15.7%]), pruritus (16 [30.2%], 33 [8.6%]), and dysgeusia (15 [28.3%], 19 [5.0%]). The adverse event leading to treatment interruption with an incidence higher in Japanese subjects than in non-Japanese

subjects by ≥10% was dermatitis acneiform (7 [13.2%], 5 [1.3%]). There were no Grade ≥3 adverse events with an incidence higher in Japanese subjects than in non-Japanese subjects by ≥10%, serious adverse events or adverse events leading to treatment discontinuation or dose reduction with an incidence higher in Japanese subjects than in non-Japanese subjects by ≥5%, or adverse events leading to death that occurred with an incidence higher in Japanese subjects than in non-Japanese subjects by ≥2%.

PMDA's view:
Adverse events that occurred with an incidence higher in the dacomitinib group than in the control group in Study 1050 or Study 1009 require special attention as events occurring during treatment with dacomitinib. Information regarding these adverse events should be provided to healthcare professionals appropriately through the package insert and relevant materials. It is difficult to determine apparent differences in the safety of dacomitinib between Japanese and non-Japanese patients due to limited clinical experience with dacomitinib in Japanese patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC. However, given that there have been no serious adverse events reported with an incidence higher in Japanese patients than in non-Japanese patients, no apparent differences have been observed in the safety of dacomitinib between Japanese and non-Japanese patients at present. Because information on the safety of dacomitinib in Japanese patients is limited, the applicant should collect relevant information in the post-marketing setting, and new safety findings should be appropriately provided to healthcare professionals.

The sections below present, based mainly on safety data from Study 1050, a review of the adverse events with an incidence higher in the dacomitinib group than in the control group in Study 1050 or Study 1009 as well as events requiring special attention during treatment with existing EGFR-TKIs, namely, gefitinib, erlotinib, afatinib, and osimertinib.

### 7.R.3.2 ILD

The applicant's explanation of ILD in patients treated with dacomitinib:
Adverse events included in the narrow term of the Standardised MedDRA Queries (SMQ) "interstitial lung disease" were tabulated as ILD.

The incidence of ILD in Study 1050 and Study 1009 is shown in Table 30.

**Table 30. Incidence of ILD (Study 1050 and Study 1009)**

| Preferred term (MedDRA ver.19.1) | n (%) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Study 1050 | | | | Study 1009 | | | |
| | Dacomitinib N = 227 | | Gefitinib N = 224 | | Dacomitinib N = 436 | | Erlotinib N = 436 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| ILD | 6 (2.6) | 2 (0.9) | 3 (1.3) | 1 (0.4) | 7 (1.6) | 2 (0.5) | 7 (1.6) | 2 (0.5) |
| ILD | 3 (1.3) | 0 | 1 (0.4) | 0 | 3 (0.7) | 1 (0.2) | 4 (0.9) | 1 (0.2) |
| Pneumonitis | 3 (1.3) | 2 (0.9) | 2 (0.9) | 1 (0.4) | 3 (0.7) | 0 | 1 (0.2) | 1 (0.2) |
| Pulmonary fibrosis | 0 | 0 | 0 | 0 | 1 (0.2) | 1 (0.2) | 0 | 0 |
| Alveolitis | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.2) | 0 |
| Lung infiltration | 0 | 0 | 0 | 0 | 0 | 0 | 1 (0.2) | 0 |

In Study 1050, ILD leading to death occurred in 1 of 227 subjects (0.4%; pneumonitis in 1 subject) in the dacomitinib group, and a causal relationship to dacomitinib was denied. Serious ILD occurred in 3 of 227 subjects (1.3%; pneumonitis in 2 and ILD in 1) in the dacomitinib group and 2 of 224 subjects (0.9%; ILD and pneumonitis in 1 each) in the gefitinib group. For events in 2 of 227 subjects (0.9%; ILD and pneumonitis in 1 each) in the dacomitinib group and 2 of 224 subjects (0.9%; ILD and pneumonitis in 1 each) in the gefitinib group from among these serious events, a causal relationship to the study drug could not be ruled out. ILD leading to treatment discontinuation occurred in 4 of 227 subjects (1.8%; ILD and pneumonitis in 2 each) in the dacomitinib group and 3 of 224 subjects (1.3%; pneumonitis in 2 and ILD in 1) in the gefitinib group. ILD leading to treatment interruption occurred in 2 of 227 subjects (0.9%; pneumonitis in 2) in the dacomitinib group and no subjects in the gefitinib group. There were no reports of ILD leading to dose reduction in any subjects.

In Study 1009, ILD leading to death occurred in 1 of 436 subjects (0.2%; ILD in 1) in the dacomitinib group, and a causal relationship to dacomitinib could not be ruled out. Serious ILD occurred in 3 of 436 subjects (0.7%; ILD in 2 and pulmonary fibrosis in 1) in the dacomitinib group and 4 of 436 subjects (0.9%; ILD in 3 and pneumonitis in 1) in the erlotinib group. A causal relationship to the study drug could not be ruled out for any of these serious events. ILD leading to treatment discontinuation occurred in 3 of 436 subjects (0.7%; ILD in 2 and pneumonitis in 1) in the dacomitinib group and 3 of 436 subjects (0.7%; ILD in 3) in the erlotinib group. ILD leading to treatment interruption occurred in no subjects in the dacomitinib group and 2 of 436 subjects (0.5%; ILD and pneumonitis in 1 each) in the erlotinib group. There were no reports of ILD leading to dose reduction in any subjects.

The median time to the first onset of ILD (range) in the dacomitinib group was 112 (55-238) days in Study 1050 and 80 (6-227) days in Study 1009.

In Japanese subjects in the dacomitinib group in clinical studies[49)] in patients with NSCLC, ILD occurred in 6 of 101 subjects (5.9%; ILD in 4 and pneumonitis in 2), and serious ILD or ILD leading to death occurred in 3 of 101 subjects (3.0%; ILD in 3).

Detailed data on subjects treated with dacomitinib who experienced serious ILD in clinical studies[50)] of dacomitinib are shown in Table 31.

49) Studies 1001, 1002, 1003, 1005, 1009, 1011, 1014, 1017, 1028, and 1050 (Japanese subjects were enrolled in Studies 1005, 1009, 1017, and 1050).
50) Studies 1001, 1002, 1003, 1004, 1005, 1006, 1009, 1011, 1014, 1015, 1018, 1017, 1020, 1021, 1022, 1027, 1028, 1031, 1039, 1042, 1046, 1047, 1050, and 1051

**Table 31. List of subjects experiencing serious ILD in clinical studies of dacomitinib (dacomitinib group)**

| Study | Sex | Age | Race | PT (MedDRA ver.19.1) | Grade | Time to onset (days) | Duration (days) | Action on dacomitinib | Causal relation-ship | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|
| 1009 | Male | 67 | Japanese | ILD | 3 | 80 | 16 | Discontinued | Yes | Unresolved |
| | | | | | 5 | 96 | 1 | Discontinued | Yes | Death |
| | Male | 69 | Japanese | ILD | 2 | 31 | 91 | Continued | Yes | Resolved |
| | Male | 82 | Non-Japanese | Pulmonary fibrosis | 3 | 227 | 35 | Continued | Yes | Resolved |
| 1017 | Male | 58 | Non-Japanese | Pneumonitis | 3 | 106 | Unknown | Continued | No | Unresolved |
| 1028 | Male | 61 | Non-Japanese | Pneumonitis | 2 | 76 | 12 | Discontinued | Yes | Unresolved |
| | | | | | 5 | 88 | 1 | Discontinued | Yes | Death |
| 1042 | Female | 61 | Non-Japanese | Pneumonitis | 4 | 41 | 6 | Discontinued | Yes | Unresolved |
| | Female | 56 | Non-Japanese | Pneumonitis | 3 | 80 | 25 | Continued | Yes | Unresolved |
| | Male | 57 | Non-Japanese | Pneumonitis | 3 | 99 | 9 | Discontinued | Yes | Resolved |
| 1011 | Female | 56 | Non-Japanese | Pneumonitis | 3 | 21 | 14 | Discontinued | Yes | Resolved |
| | Male | 60 | Non-Japanese | Pneumonitis | 4 | 195 | Unknown | Discontinued | No | Unresolved |
| 1050 | Female | 62 | Non-Japanese | Pneumonitis | 4 | 142 | 13 | Discontinued | No | Unresolved |
| | | | | | 5 | 154 | 1 | Discontinued | No | Death |
| | Male | 68 | Japanese | ILD | 2 | 111 | 89 | Discontinued | Yes | Resolved |
| | Male | 70 | Non-Japanese | Pneumonitis | 3 | 68 | 7 | Discontinued | Yes | Resolved |

PMDA's view:

Given that ILD is an adverse event known to occur in patients treated with EGFR-TKIs and that serious ILD occurred in subjects treated with dacomitinib in Study 1050, patients on dacomitinib should be monitored for ILD, and the applicant should provide information regarding ILD reported in clinical studies to healthcare professionals appropriately through the package insert and relevant materials. Due to a limited number of patients who have experienced ILD during treatment with dacomitinib, characteristics of the onset of ILD or risk factors for the event remain unknown. However, the incidence of ILD reported in clinical studies of dacomitinib did not appear to be higher than that reported in clinical studies of existing EGFR-TKIs, namely, gefitinib, erlotinib, afatinib, and osimertinib (see "Review Report of Iressa Tablets 250 mg dated November 16, 2011," "Review Report of Tarceva Tablets 25, 100, and 150 mg dated May 7, 2013," "Review Report of Giotrif Tablets 20, 30, 40, and 50 mg dated October 31, 2013," and "Review Report of Tagrisso Tablets 40 and 80 mg dated February 17, 2016"). In consideration of the above, the tolerability profile of dacomitinib is acceptable if patients eligible for dacomitinib therapy are carefully selected based on the presence or absence of any complication or history of ILD and are monitored based on clinical symptoms and imaging data, and if appropriate measures such as treatment interruption are taken when any clinical symptoms suggestive of ILD are observed.

In light of these findings, the applicant should provide information of ILD reported in clinical studies to healthcare professionals and include appropriate precautions in the package insert and relevant materials to ensure that physicians take the above measures adequately. The applicant should also investigate risk factors for ILD in the post-marketing setting.

### 7.R.3.3 Skin disorders

The applicant's explanation of skin disorders in patients treated with dacomitinib:

As skin disorders, the following adverse events were tabulated: adverse events included in the narrow SMQ term "severe cutaneous adverse reactions"; adverse events coded to a MedDRA high-level term (HLT) "acnes"; and MedDRA preferred term (PT) "exfoliative rash," "skin exfoliation," "acne pustular," "drug eruption," "rash," "rash erythematous," "rash generalised," "rash maculo-papular," "rash pruritic," "dry skin," "palmar-plantar erythrodysaesthesia syndrome," "skin fissures," "skin ulcer," and "xerosis."

The incidence of skin disorders in Study 1050 is shown in Table 32.

**Table 32. Incidence of skin disorders (Study 1050)**

| PT (MedDRA ver.19.1) | n (%) | | | |
|---|---|---|---|---|
| | Dacomitinib N = 227 | | Gefitinib N = 224 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Skin disorder | 190 (83.7) | 59 (26.0) | 134 (59.8) | 2 (0.9) |
| Dermatitis acneiform | 111 (48.9) | 31 (13.7) | 64 (28.6) | 0 |
| Dry skin | 63 (27.8) | 3 (1.3) | 38 (17.0) | 0 |
| Rash | 40 (17.6) | 10 (4.4) | 24 (10.7) | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | 33 (14.5) | 2 (0.9) | 7 (3.1) | 0 |
| Rash maculo-papular | 28 (12.3) | 10 (4.4) | 27 (12.1) | 1 (0.4) |
| Skin fissures | 21 (9.3) | 0 | 6 (2.7) | 0 |
| Acne | 20 (8.8) | 2 (0.9) | 13 (5.8) | 0 |
| Drug eruption | 9 (4.0) | 2 (0.9) | 4 (1.8) | 0 |
| Skin exfoliation | 7 (3.1) | 0 | 8 (3.6) | 0 |
| Xerosis | 5 (2.2) | 1 (0.4) | 4 (1.8) | 1 (0.4) |
| Rash erythematous | 5 (2.2) | 1 (0.4) | 0 | 0 |
| Skin ulcer | 5 (2.2) | 0 | 1 (0.4) | 0 |
| Rash pruritic | 2 (0.9) | 1 (0.4) | 0 | 0 |
| Rash generalised | 2 (0.9) | 0 | 0 | 0 |
| Acne pustular | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Exfoliative rash | 1 (0.4) | 0 | 0 | 0 |

In Study 1050, there were no skin disorders leading to death. Serious skin disorders occurred in 3 of 227 subjects (1.3%; dermatitis acneiform, drug eruption, and rash maculo-papular in 1 each) in the dacomitinib group, and a causal relationship to dacomitinib could not be ruled out for any of these events. Skin disorders leading to treatment discontinuation occurred in 6 of 227 subjects (2.6%; dermatitis acneiform in 3, rash maculo-papular in 2, and rash in 1) in the dacomitinib group and no subjects in the gefitinib group. Skin disorders leading to treatment interruption occurred in 58 of 227 subjects (25.6%; dermatitis acneiform in 32, rash in 11, rash maculo-papular in 9, acne and dry skin in 5 each, drug eruption in 2, and rash erythematous, palmar-plantar erythrodysaesthesia syndrome, and acne pustular in 1 each [some subjects were counted for more than 1 event]) in the dacomitinib group and 6 of 224 subjects (2.7%; dermatitis acneiform in 4, rash maculo-papular in 2, and rash in 1) in the gefitinib group. Skin disorders leading to dose reduction occurred in 77 of 227 subjects (33.9%; dermatitis acneiform in 46, rash maculo-papular in 11, rash in 10, dry skin in 7, palmar-plantar erythrodysaesthesia syndrome in 5, acne in 4, skin fissures in 2, and rash erythematous, acne

pustular, and xerosis in 1 each [some subjects were counted for more than 1 event]) in the dacomitinib group and 3 of 224 subjects (1.3%; dermatitis acneiform in 3) in the gefitinib group.

The median time to the first onset of a skin disorder (range) in Study 1050 was 13 (2-355) days.

PMDA's view:
Although most of the skin disorders observed in Study 1050 were Grade ≤2 in severity, patients treated with dacomitinib should be monitored for skin disorders in consideration of the following results: (a) The incidence of skin disorders was higher in the dacomitinib group than in the gefitinib group; and (b) Serious skin disorders for which a causal relationship to dacomitinib cannot be ruled out occurred. Information regarding skin disorders reported in clinical studies should be appropriately provided to healthcare professionals. The applicant should also appropriately provide healthcare professionals with criteria for dose adjustment employed in clinical studies and measures to take if skin disorders occur through the package insert and relevant materials.

### 7.R.3.4 Diarrhoea

The applicant's explanation of diarrhoea in patients treated with dacomitinib:
As diarrhoea, the following adverse events were tabulated: adverse events coded to MedDRA PT, "acute prerenal failure," "azotaemia," "dehydration," "diarrhoea," "blood urea nitrogen/creatinine ratio increased," "electrolyte imbalance," "hypovolaemia," and "prerenal failure."

The incidence of diarrhoea in Study 1050 is shown in Table 33.

**Table 33. Incidence of diarrhoea (Study 1050)**

| PT (MedDRA ver.19.1) | n (%) | | | |
|---|---|---|---|---|
| | Dacomitinib N = 227 | | Gefitinib N = 224 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Diarrhoea | 198 (87.2) | 22 (9.7) | 126 (56.3) | 2 (0.9) |
| Diarrhoea | 198 (87.2) | 20 (8.8) | 125 (55.8) | 2 (0.9) |
| Dehydration | 3 (1.3) | 1 (0.4) | 1 (0.4) | 0 |
| Electrolyte imbalance | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Azotaemia | 1 (0.4) | 0 | 0 | 0 |

In Study 1050, diarrhoea leading to death occurred in 1 of 227 subjects (0.4%; diarrhoea in 1) in the dacomitinib group, and a causal relationship to dacomitinib could not be ruled out. Serious diarrhoea occurred in 6 of 227 subjects (2.6%; diarrhoea in 5 and dehydration in 1) in the dacomitinib group, and a causal relationship to dacomitinib could not be ruled out for any of these events. Diarrhoea leading to treatment discontinuation occurred in 2 of 227 subjects (0.9%; diarrhoea in 2) in the dacomitinib group and no subjects in the gefitinib group. Diarrhoea leading to treatment interruption occurred in 23 of 227 subjects (10.1%; diarrhoea in 22, and dehydration and azotaemia in 1 each [some subjects were counted for more than 1 event]) in the dacomitinib group and 1 of 224 subjects (0.4%; diarrhoea in 1) in the gefitinib group. Diarrhoea leading

to dose reduction occurred in 21 of 227 subjects (9.3%; diarrhoea in 19, and dehydration and azotaemia in 1 each) in the dacomitinib group and 3 of 224 subjects (1.3%; diarrhoea in 3) in the gefitinib group.

The median time to the first onset of diarrhoea (range) in Study 1050 was 7.0 (1-578) days.

PMDA's view:
Although most of the diarrhoea observed in Study 1050 were Grade ≤2 in severity, patients treated with dacomitinib should be monitored for diarrhoea, taking into account that diarrhoea with acute renal failure leading to death and serious diarrhoea for which a causal relationship to dacomitinib cannot be ruled out were reported. Information regarding diarrhoea reported in clinical studies should be appropriately provided to healthcare professionals. The applicant should also appropriately provide healthcare professionals with criteria for dose adjustment employed in clinical studies and measures to take if diarrhoea occurs through the package insert and relevant materials.

### 7.R.3.5 Hepatic function disorders

The applicant's explanation of hepatic function disorders in patients treated with dacomitinib:
As hepatic function disorders, the following adverse events were tabulated: adverse events included in the narrow SMQ term, "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions"; and adverse events coded to MedDRA PT "alanine aminotransferase abnormal," "alanine aminotransferase increased," "aspartate aminotransferase abnormal," "aspartate aminotransferase increased," "bilirubin conjugated abnormal," "bilirubin conjugated increased," "blood bilirubin abnormal," "blood bilirubin increased," "hepatic enzyme abnormal," "hepatic enzyme increased," "hyperbilirubinaemia," "hypertransaminasemia," "liver function test abnormal," "transaminases abnormal," and "transaminases increased."

The incidence of hepatic function disorders in Study 1050 is shown in Table 34.

**Table 34. Incidence of hepatic function disorders (Study1050)**

| PT (MedDRA ver.19.1) | n (%) | | | |
|---|---|---|---|---|
| | Study 1050 | | | |
| | Dacomitinib N = 227 | | Gefitinib N = 224 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Hepatic function disorder | 69 (30.4) | 5 (2.2) | 102 (45.5) | 27 (12.1) |
| ALT increased | 44 (19.4) | 2 (0.9) | 88 (39.3) | 19 (8.5) |
| AST increased | 42 (18.5) | 0 | 81 (36.2) | 9 (4.0) |
| Blood bilirubin increased | 20 (8.8) | 0 | 19 (8.5) | 0 |
| Bilirubin conjugated increased | 3 (1.3) | 0 | 8 (3.6) | 0 |
| Liver injury | 2 (0.9) | 1 (0.4) | 3 (1.3) | 3 (1.3) |
| Drug-induced liver injury | 2 (0.9) | 1 (0.4) | 1 (0.4) | 1 (0.4) |
| Ascites | 1 (0.4) | 1 (0.4) | 0 | 0 |
| Hyperbilirubinaemia | 1 (0.4) | 0 | 0 | 0 |
| Transaminases increased | 1 (0.4) | 0 | 1 (0.4) | 0 |

In Study 1050, no hepatic function disorders leading to death occurred. Serious hepatic function disorders occurred in 3 of 227 subjects (1.3%; liver injury in 2 and drug-induced liver injury in 1) in the dacomitinib group and 5 of 224 subjects (2.2%; hepatic enzyme increased in 2, and ALT increased, AST increased, liver injury, and drug-induced liver injury in 1 each [some subjects were counted for more than 1 event]) in the gefitinib group. A causal relationship to the study drug could not be ruled out for any of these serious adverse events. Hepatic function disorders leading to treatment discontinuation occurred in 1 of 227 subjects (0.4%; liver injury in 1) in the dacomitinib group and 7 of 224 subjects (3.1%; ALT increased in 4, AST increased and hepatic enzyme increased in 2 each, and drug-induced liver injury in 1 [some subjects were counted for more than 1 event]) in the gefitinib group. Hepatic function disorders leading to treatment interruption occurred in 4 of 227 subjects (1.8%; ALT increased in 2, and liver injury, drug-induced liver injury, and AST increased in 1 each [some subjects were counted for more than 1 event]) in the dacomitinib group and 26 of 224 subjects (11.6%; ALT increased in 19, AST increased in 14, liver injury in 3, blood bilirubin increased in 2, and hepatic failure and hepatic enzyme increased in 1 each [some subjects were counted for more than 1 event]) in the gefitinib group. Hepatic function disorders leading to dose reduction occurred in 2 of 227 subjects (0.9%; liver injury and blood bilirubin increased in 1 each) in the dacomitinib group and 9 of 224 subjects (4.0%; ALT increased in 6, AST increased in 5, and hepatic failure and liver injury in 1 each [some subjects were counted for more than 1 event]) in the gefitinib group.

The median time to the first onset of a hepatic function disorder (range) in Study 1050 was 79.0 (8-702) days.

In Study 1050, hepatic function disorders meeting the Hy's law criteria[51)] for which a causal relationship to dacomitinib was denied occurred in 1 of 227 subjects (0.4%). The subject experiencing this event discontinued the study treatment on Day 55, when a hepatic function disorder meeting the Hy's law criteria (AST of >3-fold upper limit of normal [ULN], ALT of >5-fold ULN, and total bilirubin of >2-fold ULN) was detected. Resolution of these liver function-related laboratory values to reference values was not confirmed.

PMDA's view:

Although the incidences of any grade and Grade ≥3 hepatic function disorder were low in the dacomitinib group compared with the gefitinib group in Study 1050, patients treated with dacomitinib should be closely monitored for hepatic function disorders in consideration of the following points. Information regarding hepatic function disorders reported in clinical studies should be provided to healthcare professionals appropriately via the package insert and other relevant materials.

- Hepatic function disorders occurred with a certain incidence in patients treated with dacomitinib.
- Serious hepatic function disorders for which a causal relationship to dacomitinib cannot be ruled out occurred.
- Hepatic function disorders have been specified as adverse events requiring special attention based on data from clinical studies of existing EGFR-TKIs, namely, gefitinib, erlotinib, afatinib, and osimertinib (see

51) Defined based on "Guidance for industry. Drug-Induced Liver Injury: premarketing Clinical Evaluation" issued by the U.S. Department of Health and Human Services, Food and Drug Administration in July 2009.

"Review Report of Iressa Tablets 250 mg dated November 16, 2011," "Review Report of Tarceva Tablets 25, 100, and 150 mg dated May 7, 2013," "Review Report of Giotrif Tablets 20, 30, 40, and 50 mg dated October 31, 2013," and "Review Report of Tagrisso Tablets 40 and 80 mg dated February 17, 2016").

### 7.R.3.6 Gastrointestinal disorders (excluding diarrhoea)

The applicant's explanation of gastrointestinal disorders (excluding diarrhoea) in patients treated with dacomitinib:

As gastrointestinal disorders (excluding diarrhoea), the following adverse events were tabulated: adverse events included in the narrow SMQ terms, "gastrointestinal perforation," "gastrointestinal haemorrhage," "gastrointestinal obstruction," and "gastrointestinal ulceration"; adverse events included in the narrow or broad SMQ terms, "gastrointestinal nonspecific dysfunction," "gastrointestinal nonspecific inflammation," "gastrointestinal nonspecific symptoms and therapeutic procedures," and "gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/procedures"; and adverse events coded to MedDRA HLT, "stomatitis and ulceration"; and MedDRA PT, "cheilitis," "oral pain," "oropharyngeal discomfort," "oropharyngeal pain," and "mucosal inflammation."

The incidence of gastrointestinal disorders (excluding diarrhoea) in Study 1050 is shown in Table 35.

**Table 35. Incidence of gastrointestinal disorders (excluding diarrhoea) reported with an incidence of ≥3 % in either group (Study 1050)**

| PT (MedDRA ver.19.1) | n (%) | | | |
|---|---|---|---|---|
| | Dacomitinib N = 227 | | Gefitinib N = 224 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| Gastrointestinal disorder | 183 (80.6) | 23 (10.1) | 140 (62.5) | 4 (1.8) |
| Stomatitis | 99 (43.6) | 8 (3.5) | 40 (17.9) | 1 (0.4) |
| Nausea | 43 (18.9) | 3 (1.3) | 49 (21.9) | 1 (0.4) |
| Constipation | 30 (13.2) | 0 | 31 (13.8) | 0 |
| Mouth ulceration | 28 (12.3) | 0 | 13 (5.8) | 0 |
| Chest pain | 22 (9.7) | 0 | 32 (14.3) | 0 |
| Mucosal inflammation | 21 (9.3) | 3 (1.3) | 8 (3.6) | 0 |
| Vomiting | 20 (8.8) | 2 (0.9) | 29 (12.9) | 0 |
| Aphthous ulcer | 13 (5.7) | 0 | 6 (2.7) | 0 |
| Abdominal pain | 12 (5.3) | 2 (0.9) | 12 (5.4) | 1 (0.4) |
| Oral pain | 12 (5.3) | 0 | 1 (0.4) | 0 |
| Dysphagia | 10 (4.4) | 0 | 12 (5.4) | 0 |
| Cheilitis | 10 (4.4) | 0 | 5 (2.2) | 0 |
| Abdominal pain upper | 9 (4.0) | 0 | 14 (6.3) | 0 |
| Oropharyngeal pain | 9 (4.0) | 0 | 8 (3.6) | 0 |
| Dyspepsia | 8 (3.5) | 0 | 11 (4.9) | 1 (0.4) |

In Study 1050, no gastrointestinal disorders (excluding diarrhoea) leading to death occurred. Serious gastrointestinal disorders (excluding diarrhoea) occurred in 10 of 227 subjects (4.4%; abdominal pain in 2, and gastric ulcer haemorrhage, ileus, rectal haemorrhage, stomatitis, vomiting, non-cardiac chest pain, diverticulitis, and abdominal distension in 1 each) in the dacomitinib group and 3 of 224 subjects (1.3%; dyspepsia, haematochezia, and large intestinal obstruction in 1 each) in the gefitinib group. A causal

relationship to dacomitinib could not be ruled out for the events in 5 of 227 subjects (2.2%; abdominal pain in 2, and ileus, vomiting, and stomatitis in 1 each) in the dacomitinib group. Gastrointestinal disorders (excluding diarrhoea) leading to treatment discontinuation occurred in 2 of 227 subjects (0.9%; stomatitis in 2) in the dacomitinib group and 3 of 224 subjects (1.3%; vomiting in 2 and dysphagia in 1) in the gefitinib group. Gastrointestinal disorders (excluding diarrhoea) leading to treatment interruption occurred in 35 of 227 subjects (15.4%; stomatitis in 10, vomiting and mucosal inflammation in 5 each, abdominal pain in 4, nausea in 3, cheilitis and ileus in 2 each, and gastric ulcer haemorrhage, abdominal pain upper, aphthous ulcer, mouth ulceration, oral pain, haemorrhoidal haemorrhage, anorectal discomfort, oesophageal irritation, and diverticulitis in 1 each [some subjects were counted for more than 1 event]) in the dacomitinib group and 5 of 224 subjects (2.2%; abdominal discomfort, dyspepsia, gastritis, vomiting, and large intestinal obstruction in 1 each) in the gefitinib group. Gastrointestinal disorders (excluding diarrhoea) leading to dose reduction occurred in 13 of 227 subjects (5.7%; stomatitis in 6, mouth ulceration and nausea in 2 each, and abdominal pain, vomiting, mucosal inflammation, and oropharyngeal pain in 1 each [some subjects were counted for more than 1 event]) in the dacomitinib group and no subjects in the gefitinib group.

PMDA's view:
Although most of the gastrointestinal disorder cases (excluding diarrhoea) reported in Study 1050 were Grade ≤2 in severity, patients treated with dacomitinib should be closely monitored for gastrointestinal disorders (excluding diarrhoea), taking into account that its incidence was high in the dacomitinib group compared with the gefitinib group in the study. Information regarding gastrointestinal disorders (excluding diarrhoea) reported in clinical studies should be provided to healthcare professionals appropriately via the package insert and other relevant materials.

### 7.R.3.7 Nail abnormalities

The applicant's explanation of nail abnormalities in patients treated with dacomitinib:
As nail abnormalities, adverse events coded to MedDRA PT, "nail disorder" and "paronychia" were tabulated.

In Study 1050, nail abnormalities occurred in 142 of 227 subjects (62.6%; paronychia in 140 and nail disorder in 5 [some subjects were counted for more than 1 event]) in the dacomitinib group and 46 of 224 subjects (20.5%; paronychia in 45 and nail disorder in 1) in the gefitinib group. Grade ≥3 nail abnormalities occurred in 18 of 227 subjects (7.9%; paronychia in 17 and nail disorder in 1) in the dacomitinib group and 3 of 224 subjects (1.3%; paronychia in 3) in the gefitinib group. No nail abnormality leading to death, serious nail abnormality, or nail abnormality leading to treatment discontinuation occurred. Nail abnormalities leading to treatment interruption occurred in 28 of 227 subjects (12.3%; paronychia in 28) in the dacomitinib group and 2 of 224 subjects (0.9%; paronychia in 2) in the gefitinib group. Nail abnormalities leading to dose reduction occurred in 39 of 227 subjects (17.2%; paronychia in 38 and nail disorder in 1) in the dacomitinib group and 2 of 224 subjects (0.9%; paronychia in 2) in the gefitinib group.

PMDA's view:

Although most of the nail abnormality reported in Study 1050 were Grade ≤2 in severity, patients treated with dacomitinib should be closely monitored for nail abnormalities, taking into account that their incidence was high in the dacomitinib group compared with the gefitinib group in the study. Information regarding nail abnormalities reported in clinical studies should be provided to healthcare professionals appropriately via the package insert and other relevant materials.

### 7.R.3.8 Hypokalaemia

The applicant's explanation of hypokalaemia in patients treated with dacomitinib:

As hypokalaemia, adverse events coded to MedDRA PT, "blood potassium decreased" and "hypokalaemia" were tabulated.

In Study 1050, hypokalaemia occurred in 23 of 227 subjects (10.1%; hypokalaemia in 22 [9.7%] and blood potassium decreased in 2 [0.9%] [some subjects were counted for more than 1 event]) in the dacomitinib group and 13 of 224 subjects (5.8%; hypokalaemia in 13 [5.8%] and blood potassium decreased in 1 [0.4%]) in the gefitinib group. Grade ≥3 hypokalaemia occurred in 11 of 227 subjects (4.8%; hypokalaemia in 11) in the dacomitinib group and 4 of 224 subjects (1.8%; hypokalaemia in 4) in the gefitinib group. No hypokalaemia leading to death, serious hypokalaemia, or hypokalaemia leading to treatment discontinuation occurred. Hypokalaemia leading to treatment interruption occurred in 3 of 227 subjects (1.3%; hypokalaemia in 3) in the dacomitinib group. Hypokalaemia leading to dose reduction occurred in 1 of 227 subjects (0.4%; hypokalaemia in 1) in the dacomitinib group.

The median time to the first onset of hypokalaemia (range) in the dacomitinib group in Study 1050 was 91.0 (15-564) days.

The details of the patient who experienced serious hypokalaemia in a clinical study of dacomitinib[51)] are shown in Table 36.

**Table 36. List of patients who experienced serious hypokalaemia in clinical studies of dacomitinib (dacomitinib group)**

| Study | Sex | Age | PT (MedDRA ver.19.1) | Grade | Time to onset (days) | Duration (days) | Action on dacomitinib | Causal relation-ship | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1011 | Female | 70 | Hypokalaemia | 4 | 42 | Unknown | Discontinued | Yes | Resolved |

PMDA's view:

Patients treated with dacomitinib should be closely monitored for hypokalaemia in consideration of the following points: (a) Hypokalaemia occurred with a certain incidence in patients treated with dacomitinib in Study 1050; and (b) Serious hypokalaemia for which a causal relationship to dacomitinib cannot be ruled out occurred in a clinical study. Therefore, information regarding hypokalaemia reported in clinical studies should be provided to healthcare professionals appropriately via the package insert and other relevant materials.

### 7.R.4 Clinical positioning and indication

The proposed indication of dacomitinib is "EGFR mutation-positive, unresectable advanced or recurrent non-small cell lung cancer," and the "Precautions Concerning Indications" section includes the following:

- Dacomitinib should be administered to patients with EGFR mutation-positive NSCLC confirmed by testing performed by pathologists or at testing facilities with sufficient experience. Testing should be performed using approved *in vitro* diagnostics.
- Physicians should select patients eligible for dacomitinib therapy after closely reading the "Clinical Studies" section to ensure they fully understand the characteristics of the patients enrolled in clinical studies as well as the efficacy and safety of dacomitinib.

On the basis of the review presented in Sections "7.R.2 Efficacy" and "7.R.3 Safety" as well as the following considerations described in the sections below, PMDA has concluded that the proposed indication is acceptable if the following precautionary statement is included in the "Precautions Concerning Indications" section of the package insert:

- EGFR mutation testing should be performed. Dacomitinib should be administered to patients with EGFR mutation-positive NSCLC confirmed by testing performed by pathologists or at testing facilities with sufficient experience, using approved *in vitro* diagnostics.
- Physicians should select patients eligible for dacomitinib therapy after closely reading the "Clinical Studies" section to ensure they fully understand the efficacy and safety of dacomitinib.
- The efficacy and safety of dacomitinib in adjuvant chemotherapy have not been established.

#### 7.R.4.1 Clinical positioning of dacomitinib

No description about dacomitinib was found in any clinical practice guidelines or representative textbooks of clinical oncology published within or outside of Japan.

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

Study 1050 demonstrated the clinical usefulness of dacomitinib in chemotherapy-naïve patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC compared with existing gefitinib therapy. On the basis of the above and the following points, dacomitinib is considered to be one of the standard treatments to be selected preferentially over existing EGFR-TKIs, namely, gefitinib, erlotinib, and afatinib, for chemotherapy-naïve patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC:

- At present, there are no available data from confirmatory clinical studies performed to compare dacomitinib and erlotinib in terms of efficacy and safety in chemotherapy-naïve patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC. However, in a foreign phase III study in patients with Stage IIIB or IV NSCLC with no prior EGFR-TKI therapy (the CTONG 0901 study), the hazard ratio [95% CI] for PFS of the erlotinib group vs. gefitinib group was 0.81 [0.62, 1.05], showing no clear difference between these groups (*Br J Cancer*. 2017;116:568-74). In addition, in Study 1009 in patients with unresectable advanced or recurrent NSCLC previously treated with chemotherapy, subgroup analysis of data from patients with EGFR mutation-positive NSCLC (37 subjects in the dacomitinib group

and 39 subjects in the erlotinib group) showed that the duration of PFS in the dacomitinib group tended to increase compared with the erlotinib group (median, 14.6 months in the dacomitinib group and 9.6 months in the erlotinib group; hazard ratio [95% CI], 0.67 [0.37, 1.22]). Based on the above results etc., dacomitinib is expected to be clinically more useful than erlotinib.

- At present, there are no available data from confirmatory clinical studies performed to compare dacomitinib and afatinib in terms of efficacy and safety. However, in a foreign phase IIb study in chemotherapy-naïve patients with Stage IIIB or IV NSCLC (the LUX-Lung 7 study), the hazard ratio [95% CI] for PFS in the afatinib group vs. gefitinib group was 0.73 [0.57, 0.95], showing no clear difference between these groups (*Lancet Oncol.* 2016;17:577-89). Based on the above results etc., dacomitinib is expected to be clinically more useful than afatinib.

Considering that no clinical studies have compared dacomitinib and osimertinib in terms of efficacy and safety and that the hazard ratio [95% CI] for PFS in the osimertinib group vs. gefitinib or erlotinib group was 0.46 [0.37, 0.57] in a global phase III study in chemotherapy-naïve patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC (the FLAURA study) (*N Engl J Med.* 2018;378:113-25), it remains unclear which of dacomitinib and osimertinib should be selected over the other for this patient population at present.

PMDA's view:

The applicant's explanation of the clinical positioning of dacomitinib compared to gefitinib or osimertinib is acceptable. Meanwhile, the clinical positioning of dacomitinib compared with erlotinib or afatinib is unclear at present because there are no available data from clinical studies performed to compare dacomitinib and erlotinib or afatinib in terms of efficacy and safety in chemotherapy-naïve patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC. On the basis of the above review, PMDA has concluded that dacomitinib is positioned as one of the standard therapeutic options for chemotherapy-naïve patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC.

### 7.R.4.2 Intended patient population and indication of dacomitinib

Out of chemotherapy-naïve patients with EGFR mutation-positive NSCLC, patients with adenocarcinoma harboring EGFR activating mutation Ex19del or L858R were enrolled in Study 1050. PMDA asked the applicant to explain the clinical usefulness and other traits of dacomitinib in (a) patients with NSCLC harboring EGFR activating mutation excluding Ex19del and L858R, (b) patients with NSCLC classified as any histological type other than adenocarcinoma, and (c) patients with EGFR mutation-positive NSCLC who were previously treated with chemotherapy.

The applicant's response:

(a) In Study 1009, Study 1017, and Study 1028, dacomitinib was administered to 7 patients with NSCLC harboring EGFR activating mutation other than Ex19del and L858R (G719X in 3 and S768I and L861Q in 2 each), and 6 of the 7 patients achieved clinical response (all were assessed as PR) and tolerated the

dacomitinib therapy. Therefore, dacomitinib is expected to be clinically useful irrespective of the type of EGFR mutation.

(b) In Study 1009 and Study 1028, dacomitinib was administered to 6 patients with NSCLC classified as non-adenocarcinoma histological types (squamous cell carcinoma in 5 and mucoepidermoid carcinoma in 1), and 3 patients achieved clinical response (CR for 1 and PR for 2) and tolerated the dacomitinib therapy. Therefore, dacomitinib is also expected to be clinically useful for patients with NSCLC classified as any histological type other than adenocarcinoma.

(c) Because subgroup analysis of data from patients with EGFR mutation-positive NSCLC in Study 1009 showed that the duration of PFS in the dacomitinib group tended to increase compared with the erlotinib group [see Section 7.R.4.1] etc., dacomitinib is also expected to be clinically useful for patients who have received chemotherapy. However, the clinical usefulness of dacomitinib is unclear in patients with EGFR T790M mutation-positive NSCLC whose condition aggravated after EGFR-TKI therapy because of extremely limited clinical experience with this patient population in clinical studies.

Based on the above, the indication of dacomitinib has been proposed as "EGFR mutation-positive, unresectable or recurrent non-small cell lung cancer" with the following precautionary statement included in the "Precautions Concerning Indications" section:

- Physicians should select patients eligible for dacomitinib therapy after closely reading the "Clinical Studies" section to ensure they fully understand the efficacy and safety of dacomitinib.

PMDA's view:

The results from the above clinical studies in (a) patients with NSCLC harboring EGFR activating mutation excluding Ex19del and L858R, (b) patients with NSCLC classified as any histological type other than adenocarcinoma, and (c) patients with NSCLC who were previously treated with chemotherapy were only exploratory data. Therefore, it is difficult to determine the clinical usefulness of dacomitinib in these patient populations. However, considering that dacomitinib is used by physicians with sufficient knowledge and experience in cancer chemotherapy, the proposed indication of dacomitinib is acceptable if the "Clinical Studies" section of the package insert includes information regarding EGFR mutation types and histological types of NSCLC in patients enrolled in Study 1050 and if the "Precautions Concerning Indications" section includes a precautionary statement that physicians should select patients eligible for dacomitinib therapy after closely reading the "Clinical Studies" section to ensure they fully understand the efficacy and safety of dacomitinib.

At present, there are no available data from clinical studies performed to evaluate the efficacy and safety of dacomitinib as adjuvant therapy. This information should be included in the "Precautions Concerning Indications" section.

### 7.R.4.3 EGFR mutation testing

The applicant's explanation:

Based on the following points, it is appropriate to select patients eligible for dacomitinib therapy using "therascreen EGFR mutation detection kit RGQ 'Qiagen'" manufactured by QIAGEN K.K., and this information will be included in the "Precautions Concerning Indications" section of the package insert.

- Study 1050, in which the clinical usefulness of dacomitinib was demonstrated, enrolled patients with NSCLC assessed as EGFR mutation-positive based on the results of testing performed at either the central testing facility or study sites. The "therascreen EGFR mutation detection kit RGQ 'Qiagen'" manufactured by QIAGEN K.K. was used for testing at the central facility [see Section 6.1.1]. Later, using samples collected from patients enrolled in Study 1050 after their eligibility had been confirmed at study sites with a standard EGFR mutation detection kit, "Clinical Trial Assay (CTA)," the substantial equivalence of this kit to "therascreen EGFR mutation detection kit RGQ 'Qiagen'" was investigated. The results showed that the positive agreement rate was 96.1%, and the positive agreement rate for Ex19del and L858R mutations was 96.9% and 95.0%, respectively.

PMDA's view:

The applicant's explanation is generally accepted. PMDA has concluded that the precautionary statement in the "Precautions Concerning Indications" section should be modified as follows:

- EGFR mutation testing should be performed. Dacomitinib should be administered to patients with EGFR mutation-positive NSCLC confirmed by testing performed by pathologists or at testing facilities with sufficient experience, using approved *in vitro* diagnostics.

### 7.R.5 Dosage and administration

The proposed "Dosage and Administration" statement is as follows: "The usual adult dosage is 45 mg of dacomitinib administered orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition." The "Precautions Concerning Dosage and Administration" section includes the following precautionary statements:

- At present, data available from patients with severe hepatic or renal impairment treated with dacomitinib are limited. Therefore, these patient populations should be particularly closely monitored for adverse events when treated with dacomitinib, and dose reduction should be considered.
- Criteria for dose interruption, dose reduction, or discontinuation of dacomitinib due to adverse drug reactions

On the basis of the review presented in Sections "6.R.1 Use of dacomitinib in patients with hepatic impairment," "6.R.2 Use of dacomitinib in patients with renal impairment," "7.R.2 Efficacy," and "7.R.3 Safety" as well as the following considerations described in sections below, PMDA has concluded that the proposed "Dosage and Administration" statement is acceptable provided that the following precautionary statements are included in the "Precautions Concerning Dosage and Administration" section of the package insert:

- Criteria for dose interruption, dose reduction, or discontinuation of dacomitinib due to adverse drug reactions
- Efficacy and safety of dacomitinib used in combination with other antineoplastic agents have not been established.

### 7.R.5.1 Dosage and administration of dacomitinib

The applicant's justification for the proposed dosage and administration statement:
On the basis of the results of the following clinical studies, the dosage regimen for Study 1050 was determined to be 45 mg QD administered orally. This dosage regimen was used in Study 1050, which demonstrated the clinical usefulness of dacomitinib in patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC. Based on the dosage regimen used in the study, the proposed dosage regimen of dacomitinib was selected.

- In the dose-escalation part of the foreign phase I study (Study 1001), subjects received dacomitinib orally either at (a) 0.5, 1, 2, 4, 8, 16, 30, 45, or 60 mg QD or (b) 45 mg BID from Days 1 to 3 and QD from Day 4 onward. On the basis of the results of the study, the maximum tolerated dose (MTD) of dacomitinib was determined to be 45 mg QD administered orally, at which level the treatment was well-tolerated.
- In the phase I part of the foreign phase I/II study (Study 1003), subjects received dacomitinib orally at 30 or 45 mg QD as a single dose and, after an interval of ≥10 days, at 30 or 45 mg QD under fasting conditions. Based on the results of the study, the recommended phase II dosage regimen was determined to be dacomitinib 45 mg QD administered orally, at which level the treatment was well-tolerated.
- In the Japanese phase I study (Study 1005), subjects received dacomitinib orally at 15, 30, or 45 mg QD. During the study, no DLTs occurred, and dacomitinib was well-tolerated when administered orally at 45 mg QD.

PMDA asked the applicant to explain coadministration of dacomitinib with other antineoplastic agents.

The applicant's response:
Considering that there are no available data from clinical studies performed to evaluate the efficacy and safety of dacomitinib in combination with other antineoplastic agents in patients with NSCLC, the concomitant use of dacomitinib with other antineoplastic agents is not recommended.

PMDA's view:
The applicant's explanation is generally accepted. However, considering that there are no data available from clinical studies performed to evaluate the efficacy and safety of dacomitinib in combination with other antineoplastic agents in patients with NSCLC, the "Precautions Concerning Dosage and Administration" section of the package insert should include a precautionary statement that the efficacy and safety of dacomitinib used in combination with other antineoplastic agents have not been established.

### 7.R.5.2 Dose adjustment of dacomitinib

The applicant's explanation of dose adjustment of dacomitinib:

The protocol of Study 1050 specified criteria for dose interruption, reduction, and discontinuation of dacomitinib. The study demonstrated the clinical usefulness of dacomitinib, which was administered in accordance with the criteria. On the basis of the above, the dose adjustment criteria employed in Study 1050 are included in the "Precautions Concerning Dosage and Administration" section after making the following modifications:

- As a skin toxicity-related dose adjustment, no criteria were specified for treatment resumption in patients experiencing dose interruption due to a Grade 2 adverse event in Study 1050. In the study, subjects experiencing dose interruption due to a Grade ≥3 adverse event were allowed to resume dacomitinib at the previous dose level or a dose reduced by 1 dose level after resolution of the event to Grade 2 or baseline. Considering that various types of adverse events occurred in clinical studies including Study 1050, the proposed criteria for skin toxicity-related dose adjustment state that patients experiencing dose interruption due to an adverse event are allowed to resume dacomitinib after resolution of the event to Grade ≤1 and that a dose should be reduced by 1 dose level when dacomitinib is resumed after dose interruption due to a Grade ≥3 adverse event.
- As a dose adjustment related to adverse reactions other than ILD, diarrhoea, or skin toxicity, the dose adjustment criteria employed in Study 1050 required that treatment should be interrupted when an intolerable Grade 2 or Grade ≥3 adverse event occurred. However, since few Grade 2 adverse events requiring dose interruption, reduction, or discontinuation of dacomitinib occurred in any clinical studies including Study 1050, the proposed dose adjustment criteria do not require dose adjustment for patients experiencing Grade 2 adverse events. In Study 1050, dacomitinib was administered at the previous dose level or a dose reduced by 1 dose level when treatment was resumed after interruption due to Grade 2 or 3 adverse events. Considering that various types of adverse events occurred in clinical studies including Study 1050, the proposed criteria for dose adjustment state that a dose should be reduced by 1 dose level when dacomitinib is resumed after interruption due to Grade ≥3 adverse events.

PMDA's view:

The applicant's explanation is generally accepted. However, the precautionary statement related to dose adjustment to be included in the "Precautions Concerning Dosage and Administration" section should be modified as follows:

- If any adverse drug reaction occurs, dose interruption, dose reduction, or discontinuation of dacomitinib should be considered in accordance with the criteria below.

**Dose reduction level of dacomitinib**

| Dose reduction level | Dose |
|---|---|
| Usual dose | 45 mg/day |
| Dose reduced by 1 dose level | 30 mg/day |
| Dose reduced by 2 dose levels | 15 mg/day |

**Criteria for dose interruption, dose reduction, or discontinuation due to adverse drug reactions**

| Adverse drug reaction | Severity* | Measures |
|---|---|---|
| ILD | Any Grade | Discontinue dacomitinib. |
| Diarrhoea | Grade 2 | Withhold dacomitinib until resolution to Grade ≤1. After resolution, resume dacomitinib at the previous dose level or a dose reduced by 1 dose level. |
| | Grade 3 or 4 | Withhold dacomitinib until resolution to Grade ≤1. After resolution, resume dacomitinib at a dose reduced by 1 dose level. |
| Skin toxicity (skin symptoms with rash, erythema, or exfoliation) | Grade 2 | Withhold dacomitinib until resolution to Grade ≤1. After resolution, resume dacomitinib at the previous dose level or a dose reduced by 1 dose level. |
| | Grade 3 or 4 | Withhold dacomitinib until resolution to Grade ≤1. After resolution, resume dacomitinib at a dose reduced by 1 dose level. |
| Other adverse drug reactions | Grade 3 or 4 | Withhold dacomitinib until resolution to Grade ≤2. After resolution, resume dacomitinib at a dose reduced by 1 dose level. |

*: Severity grade according to NCI-CTCAE ver. 4.03

### 7.R.6 Post-marketing investigations

The applicant's explanation of the proposed post-marketing surveillance plan for dacomitinib:

The applicant plans a post-marketing surveillance of patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC treated with dacomitinib to monitor the safety of dacomitinib in the post-marketing clinical setting.

It has been proposed that ILD should be a safety specification, taking into account that the incidence of ILD was high in Japanese subjects in clinical studies conducted in patients with NSCLC [see Section 7.R.3.2] and that ILD has also been specified as an adverse event requiring special attention among patients treated with EGFR-TKIs other than dacomitinib.

The planned sample size of 799 patients has been set as the number needed to evaluate risk factors for ILD based on the incidence of ILD in Japanese subjects in clinical studies[50)] conducted in patients with NSCLC [see Section 7.R.3.2].

The observation period of 52 weeks has been set based on the facts that ILD occurred during the first 52 weeks of treatment with dacomitinib in clinical studies[50)] in patients with NSCLC and that there was no trend toward an increase in the incidence of ILD with an increase in the administration period of dacomitinib.

PMDA's view:

On the basis of the applicant's explanation above and the fact that serious ILD and ILD leading to death for which a causal relationship to dacomitinib could not be ruled out were reported [see Section 7.R.3.2] etc., the applicant's proposal that the post-marketing surveillance will be performed with the focus on ILD is acceptable. PMDA has concluded that there is no specific problem with the proposed plan for post-marketing surveillance.

### 7.3 Adverse events reported in clinical studies

Deaths reported in the clinical studies in data submitted for safety evaluation are described in Sections "7.1 Evaluation data" and "7.2 Reference data." Common adverse events other than death are summarized in the sections below.

### 7.3.1 Japanese phase I study (Study 1005)

Adverse events occurred in 3 of 3 subjects (100%) in the 15 mg group, 3 of 3 subjects (100%) in the 30 mg group, and 7 of 7 subjects (100%) in the 45 mg group. Adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in all subjects. Adverse events with an incidence of ≥40% in any group are shown in Table 37.

**Table 37. Adverse events with an incidence of ≥40% in any group**

| SOC<br>PT<br>(MedDRA/J ver.19.1) | n (%) | | | | | |
|---|---|---|---|---|---|---|
| | 15 mg<br>N = 3 | | 30 mg<br>N = 3 | | 45 mg<br>N = 7 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| All adverse events | 3 (100) | 2 (66.7) | 3 (100) | 0 | 7 (100) | 4 (57.1) |
| Blood and lymphatic system disorders | | | | | | |
| Leukopenia | 0 | 0 | 0 | 0 | 3 (42.9) | 0 |
| Gastrointestinal disorders | | | | | | |
| Diarrhoea | 2 (66.7) | 0 | 3 (100) | 0 | 7 (100) | 0 |
| Nausea | 1 (33.3) | 0 | 1 (33.3) | 0 | 4 (57.1) | 0 |
| Stomatitis | 1 (33.3) | 0 | 2 (66.7) | 0 | 5 (71.4) | 0 |
| General disorders and administration site conditions | | | | | | |
| Fatigue | 0 | 0 | 1 (33.3) | 0 | 5 (71.4) | 0 |
| Oedema | 0 | 0 | 0 | 0 | 3 (42.9) | 0 |
| Infections and infestations | | | | | | |
| Angular cheilitis | 2 (66.7) | 0 | 1 (33.3) | 0 | 2 (28.6) | 0 |
| Conjunctivitis | 0 | 0 | 1 (33.3) | 0 | 3 (42.9) | 0 |
| Paronychia | 1 (33.3) | 0 | 2 (66.7) | 0 | 6 (85.7) | 0 |
| Investigations | | | | | | |
| Electrocardiogram QT prolonged | 2 (66.7) | 0 | 0 | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | | | | |
| Decreased appetite | 0 | 0 | 1 (33.3) | 0 | 3 (42.9) | 1 (14.3) |
| Renal and urinary disorders | | | | | | |
| Proteinuria | 0 | 0 | 0 | 0 | 3 (42.9) | 0 |
| Skin and subcutaneous tissue disorders | | | | | | |
| Dry skin | 2 (66.7) | 0 | 1 (33.3) | 0 | 5 (71.4) | 0 |
| Palmar-plantar erythrodysaesthesia syndrome | 1 (33.3) | 0 | 2 (66.7) | 0 | 2 (28.6) | 0 |
| Rash | 3 (100) | 0 | 3 (100) | 0 | 7 (100) | 2 (28.6) |

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the 15 mg group and 2 of 7 subjects (28.6%) in the 45 mg group. These serious adverse events were disease progression in 1 subject (33.3%) in the 15 mg group, and haemobilia and device related infection in 1 subject (14.3%) each in the 45 mg group. A causal relationship to dacomitinib could not be ruled out for haemobilia and device related infection in 1 subject each in the 45 mg group.

An adverse event leading to treatment discontinuation occurred in 1 of 7 subjects (14.3%) in the 45 mg group. The adverse event leading to treatment discontinuation reported was rash in 1 subject (14.3%), and a causal relationship to dacomitinib could not be ruled out.

### 7.3.2 Global phase II study (Study 1017)

#### 7.3.2.1 Cohort A

Adverse events occurred in 30 of 30 subjects (100%) in the 30 mg group and 59 of 59 subjects in the 45 mg group. Adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in all subjects. Adverse events with an incidence of ≥25% in either group are shown in Table 38.

**Table 38. Adverse events with an incidence of ≥25% in either group**

| SOC<br>PT<br>(MedDRA/J ver.19.1) | n (%) | | | |
|---|---|---|---|---|
| | 30 mg<br>N = 30 | | 45 mg<br>N = 59 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| All adverse events | 30 (100) | 15 (50.0) | 59 (100) | 41 (69.5) |
| Gastrointestinal disorders | | | | |
| Diarrhoea | 27 (90.0) | 3 (10.0) | 58 (98.3) | 11 (18.6) |
| Nausea | 8 (26.7) | 1 (3.3) | 17 (28.8) | 2 (3.4) |
| Stomatitis | 6 (20.0) | 1 (3.3) | 30 (50.8) | 3 (5.1) |
| Vomiting | 6 (20.0) | 1 (3.3) | 15 (25.4) | 2 (3.4) |
| General disorders and administration site conditions | | | | |
| Fatigue | 13 (43.3) | 0 | 23 (39.0) | 1 (1.7) |
| Mucosal inflammation | 13 (43.3) | 0 | 15 (25.4) | 2 (3.4) |
| Infections and infestations | | | | |
| Paronychia | 15 (50.0) | 1 (3.3) | 20 (33.9) | 3 (5.1) |
| Metabolism and nutrition disorders | | | | |
| Decreased appetite | 8 (26.7) | 0 | 20 (33.9) | 0 |
| Musculoskeletal and connective tissue disorders | | | | |
| Muscle spasms | 8 (26.7) | 0 | 7 (11.9) | 0 |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Cough | 10 (33.3) | 1 (3.3) | 18 (30.5) | 0 |
| Dyspnoea | 8 (26.7) | 1 (3.3) | 9 (15.3) | 2 (3.4) |
| Epistaxis | 9 (30.0) | 0 | 12 (20.3) | 0 |
| Skin and subcutaneous tissue disorders | | | | |
| Acne | 2 (6.7) | 0 | 16 (27.1) | 2 (3.4) |
| Dermatitis acneiform | 26 (86.7) | 2 (6.7) | 43 (72.9) | 14 (23.7) |
| Dry skin | 15 (50.0) | 0 | 25 (42.4) | 0 |
| Nail disorder | 9 (30.0) | 0 | 10 (16.9) | 1 (1.7) |
| Palmar-plantar erythrodysaesthesia | 3 (10.0) | 0 | 16 (27.1) | 3 (5.1) |
| Pruritus | 8 (26.7) | 0 | 15 (25.4) | 0 |
| Skin fissures | 9 (30.0) | 0 | 11 (18.6) | 1 (1.7) |

Serious adverse events occurred in 9 of 30 subjects (30.0%) in the 30 mg group and 20 of 59 subjects (33.9%) in the 45 mg group. Serious adverse events reported in ≥2 subjects in each group were pneumothorax in 2 subjects (6.7%) in the 30 mg group; and diarrhoea in 3 subjects (5.1%), vomiting, asthenia, disease progression, dehydration, confusional state, and dermatitis acneiform in 2 subjects (3.4%) each in the 45 mg group. A causal relationship to dacomitinib could not be ruled out for diarrhoea in 3 subjects, asthenia, dehydration, and dermatitis acneiform in 2 subjects each, and vomiting in 1 subject in the 45 mg group.

Adverse event leading to treatment discontinuation occurred in 2 of 30 subjects (6.7%) in the 30 mg group and 10 of 59 subjects (16.9%) in the 45 mg group. The adverse event leading to treatment discontinuation reported

in ≥2 subjects in each group was disease progression in 2 subjects (3.4%) in the 45 mg group, and a causal relationship to dacomitinib was denied for both cases.

#### 7.3.2.2 Cohort B

Adverse events occurred in 26 of 26 subjects (100%) in the HER2-mutant NSCLC group and 4 of 4 subjects (100%) in the HER2-amplified NSCLC group. Adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in all subjects. Adverse events with an incidence of ≥40% in each group were diarrhoea in 26 subjects (100%), dermatitis acneiform in 19 subjects (73.1%), fatigue in 15 subjects (57.7%), dry skin in 14 subjects (53.8%), and pruritus in 11 subjects (42.3%) in the HER2-mutant NSCLC group; and diarrhoea, nausea, vomiting, fatigue, dehydration, and dermatitis acneiform in 3 subjects (75.0%) each, mucosal inflammation, cough, gastrooesophageal reflux disease, and paronychia in 2 subjects (50.0%) each in the HER2-amplified NSCLC group.

Serious adverse events occurred in 9 of 26 subjects (34.6%) in the HER2-mutant NSCLC group and 1 of 4 subjects (25.0%) in the HER2-amplified NSCLC group. Serious adverse events reported in ≥2 subjects in each group were disease progression in 3 subjects (11.5%), and diarrhoea and pneumothorax in 2 subjects (7.7%) each in the HER2-mutant NSCLC group. A causal relationship to dacomitinib could not be ruled out for diarrhoea in 1 subject.

Adverse events leading to treatment discontinuation occurred in 3 of 26 subjects (11.5%) in the HER2-mutant NSCLC group. There were no adverse events leading to treatment discontinuation reported in ≥2 subjects in either group.

### 7.3.3 Global phase III study (Study 1009)

Adverse events occurred in 431 of 436 subjects (98.9%) in the dacomitinib group and 428 of 436 subjects (98.2%) in the erlotinib group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 410 of 436 subjects (94.0%) in the dacomitinib group and 391 of 436 subjects (89.7%) in the erlotinib group. Adverse events with an incidence of ≥15% in either group are shown in Table 39.

**Table 39. Adverse events with an incidence of ≥15% in either group**

| SOC<br>PT<br>(MedDRA/J ver.19.1) | n (%) | | | |
|---|---|---|---|---|
| | Dacomitinib N = 436 | | Erlotinib N = 436 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| All adverse events | 431 (98.9) | 254 (58.3) | 428 (98.2) | 234 (53.7) |
| Gastrointestinal disorders | | | | |
| Diarrhoea | 324 (74.3) | 49 (11.2) | 218 (50.0) | 11 (2.5) |
| Nausea | 91 (20.9) | 7 (1.6) | 83 (19.0) | 6 (1.4) |
| Stomatitis | 81 (18.6) | 7 (1.6) | 52 (11.9) | 1 (0.2) |
| Vomiting | 74 (17.0) | 5 (1.1) | 70 (16.1) | 3 (0.7) |
| General disorders and administration site conditions | | | | |
| Fatigue | 78 (17.9) | 14 (3.2) | 94 (21.6) | 15 (3.4) |
| Asthenia | 68 (15.6) | 15 (3.4) | 59 (13.5) | 19 (4.4) |
| Mucosal inflammation | 67 (15.4) | 7 (1.6) | 28 (6.4) | 1 (0.2) |
| Infections and infestations | | | | |
| Paronychia | 94 (21.6) | 5 (1.1) | 44 (10.1) | 3 (0.7) |
| Metabolism and nutrition disorders | | | | |
| Decreased appetite | 139 (31.9) | 14 (3.2) | 120 (27.5) | 18 (4.1) |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Cough | 54 (12.4) | 1 (0.2) | 73 (16.7) | 3 (0.7) |
| Dyspnoea | 81 (18.6) | 23 (5.3) | 87 (20.0) | 20 (4.6) |
| Skin and subcutaneous tissue disorders | | | | |
| Dermatitis acneiform | 81 (18.6) | 5 (1.1) | 88 (20.2) | 7 (1.6) |
| Dry skin | 86 (19.7) | 3 (0.7) | 84 (19.3) | 0 |
| Rash | 218 (50.0) | 28 (6.4) | 203 (46.6) | 11 (2.5) |

Serious adverse events occurred in 178 of 436 subjects (40.8%) in the dacomitinib group and 170 of 436 subjects (39.0%) in the erlotinib group. Serious adverse events reported in ≥3 subjects in each group were disease progression in 53 subjects (12.2%), diarrhoea in 20 subjects (4.6%), pneumonia in 15 subjects (3.4%), dehydration in 13 subjects (3.0%), dyspnoea in 8 subjects (1.8%), vomiting, death, pyrexia, and haemoptysis in 5 subjects (1.1%) each, febrile neutropenia, nausea, general physical health deterioration, renal failure, acute kidney injury, pulmonary embolism, and respiratory failure in 4 subjects (0.9%) each, and anaemia, asthenia, condition aggravated, oedema peripheral, femoral neck fracture, acute respiratory failure, and pneumothorax in 3 subjects (0.7%) each in the dacomitinib group; and disease progression in 50 subjects (11.5%), pneumonia in 15 subjects (3.4%), general physical health deterioration in 10 subjects (2.3%), anaemia and dyspnoea in 8 subjects (1.8%) each, diarrhoea in 7 subjects (1.6%), dehydration in 6 subjects (1.4%), respiratory failure in 5 subjects (1.1%), nausea, fatigue, and decreased appetite in 4 subjects (0.9%) each, and atrial fibrillation, myocardial infarction, vomiting, bronchitis, sepsis, lung infection, respiratory tract infection, ILD, and pulmonary embolism in 3 subjects (0.7%) each in the erlotinib group. A causal relationship to the study drug could not be ruled out for diarrhoea in 18 subjects, dehydration in 9 subjects, vomiting in 4 subjects, nausea in 3 subjects, acute kidney injury and ILD in 2 subjects each, and asthenia, oedema peripheral, pneumonia, renal failure, and pulmonary embolism in 1 subject each in the dacomitinib group; and diarrhoea in 6 subjects, nausea and decreased appetite in 4 subjects each, dehydration and ILD in 3 subjects each, vomiting and fatigue in 2 subjects each, and anaemia, atrial fibrillation, and dyspnoea in 1 subject each in the erlotinib group.

Adverse events leading to treatment discontinuation occurred in 87 of 436 subjects (20.0%) in the dacomitinib group and 80 of 436 subjects (18.3%) in the erlotinib group. Adverse events leading to treatment discontinuation reported in ≥3 subjects in each group were disease progression in 13 subjects (3.0%), pneumonia in 6 subjects (1.4%), asthenia in 5 subjects (1.1%), diarrhoea, death, and rash in 4 subjects (0.9%) each, and stomatitis and dyspnoea in 3 subjects (0.7%) each in the dacomitinib group; and disease progression in 20 subjects (4.6%), general physical health deterioration in 6 subjects (1.4%), respiratory failure in 4 subjects (0.9%), and ILD and rash in 3 subjects (0.7%) each in the erlotinib group. A causal relationship to the study drug could not be ruled out for asthenia in 5 subjects, diarrhoea and rash in 4 subjects each, stomatitis in 3 subjects, and pneumonia in 2 subjects in the dacomitinib group; and ILD and rash in 3 subjects each in the erlotinib group.

### 7.3.4 Global phase III study (Study 1050)

Adverse events occurred in 226 of 227 subjects (99.6%) in the dacomitinib group and 220 of 224 subjects (98.2%) in the gefitinib group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 220 of 227 subjects (96.9%) in the dacomitinib group and 213 of 224 subjects (95.1%) in the gefitinib group. Adverse events with an incidence of ≥15% in either group are shown in Table 40.

**Table 40. Adverse events with an incidence of ≥15% in either group**

| SOC<br>PT<br>(MedDRA/J ver.19.1) | n (%) | | | |
|---|---|---|---|---|
| | Dacomitinib N = 227 | | Gefitinib N = 224 | |
| | All Grades | Grade ≥3 | All Grades | Grade ≥3 |
| All adverse events | 226 (99.6) | 143 (63.0) | 220 (98.2) | 92 (41.1) |
| Gastrointestinal disorders | | | | |
| Diarrhoea | 198 (87.2) | 20 (8.8) | 125 (55.8) | 2 (0.9) |
| Nausea | 43 (18.9) | 3 (1.3) | 49 (21.9) | 1 (0.4) |
| Stomatitis | 99 (43.6) | 8 (3.5) | 40 (17.9) | 1 (0.4) |
| Infections and infestations | | | | |
| Conjunctivitis | 43 (18.9) | 0 | 9 (4.0) | 0 |
| Paronychia | 140 (61.7) | 17 (7.5) | 45 (20.1) | 3 (1.3) |
| Investigations | | | | |
| ALT increased | 44 (19.4) | 2 (0.9) | 88 (39.3) | 19 (8.5) |
| AST increased | 42 (18.5) | 0 | 81 (36.2) | 9 (4.0) |
| Weight decreased | 58 (25.6) | 5 (2.2) | 37 (16.5) | 1 (0.4) |
| Metabolism and nutrition disorders | | | | |
| Decreased appetite | 70 (30.8) | 7 (3.1) | 56 (25.0) | 1 (0.4) |
| Musculoskeletal and connective tissue disorders | | | | |
| Back pain | 18 (7.9) | 0 | 35 (15.6) | 1 (0.4) |
| Respiratory, thoracic and mediastinal disorders | | | | |
| Cough | 48 (21.1) | 0 | 42 (18.8) | 1 (0.4) |
| Skin and subcutaneous tissue disorders | | | | |
| Alopecia | 53 (23.3) | 1 (0.4) | 28 (12.5) | 0 |
| Dermatitis acneiform | 111 (48.9) | 31 (13.7) | 64 (28.6) | 0 |
| Dry skin | 63 (27.8) | 3 (1.3) | 38 (17.0) | 0 |
| Pruritus | 45 (19.8) | 1 (0.4) | 32 (14.3) | 3 (1.3) |
| Rash | 40 (17.6) | 10 (4.4) | 24 (10.7) | 0 |

Serious adverse events occurred in 62 of 227 subjects (27.3%) in the dacomitinib group and 50 of 224 subjects (22.3%) in the gefitinib group. Serious adverse events reported in ≥2 subjects in each group were disease progression in 8 subjects (3.5%), diarrhoea, pneumonia, and pleural effusion in 5 subjects (2.2%) each, and abdominal pain, liver injury, urinary tract infection, respiratory tract infection, decreased appetite, haemoptysis, pneumonitis, pneumothorax, and respiratory failure in 2 subjects (0.9%) each in the dacomitinib group; and disease progression in 11 subjects (4.9%), dyspnoea in 4 subjects (1.8%), and pneumonia, subdural haematoma, hepatic enzyme increased, hyponatraemia, cerebral infarction, and pleural effusion in 2 subjects (0.9%) each in the gefitinib group. A causal relationship to the study drug could not be ruled out for diarrhoea in 5 subjects, abdominal pain and liver injury in 2 subjects each, and pneumonia, decreased appetite, and pneumonitis in 1 subject each in the dacomitinib group; and hepatic enzyme increased in 2 subjects and pneumonia in 1 subject in the gefitinib group.

Adverse events leading to treatment discontinuation occurred in 40 of 227 subjects (17.6%) in the dacomitinib group and 27 of 224 subjects (12.1%) in the gefitinib group. Adverse event leading to treatment discontinuation reported in ≥2 subjects in each group were disease progression in 6 subjects (2.6%), pneumonia in 5 subjects (2.2%), dermatitis acneiform in 3 subjects (1.3%), and diarrhoea, stomatitis, ILD, pneumonitis, and rash maculo-papular in 2 subjects (0.9%) each in the dacomitinib group; and ALT increased in 4 subjects (1.8%) and vomiting, AST increased, hepatic enzyme increased, dyspnoea, and pneumonitis in 2 subjects (0.9%) each in the gefitinib group. A causal relationship to the study drug could not be ruled out for dermatitis acneiform in 3 subjects, diarrhoea, stomatitis, pneumonia, ILD, and rash maculo-papular in 2 subjects each, and pneumonitis in 1 subject in the dacomitinib group; and ALT increased in 4 subjects, AST increased, hepatic enzyme increased, and pneumonitis in 2 subjects each, and vomiting in 1 subject in the gefitinib group.

### 7.3.5 Foreign phase I study (Study 1001)

#### 7.3.5.1 Schedule A

Adverse events occurred in 3 of 3 subjects (100%) in the 0.5 mg group, 3 of 3 subjects (100%) in the 1 mg group, 3 of 3 subjects (100%) in the 2 mg group, 5 of 5 subjects (100%) in the 4 mg group, 3 of 3 subjects (100%) in the 8 mg group, 4 of 4 subjects (100%) in the 16 mg group, 13 of 13 subjects (100%) in the 30 mg group, 52 of 52 subjects (100%) in the 45 mg group, 19 of 19 subjects (100%) in the 45 mg LD group, and 6 of 6 subjects (100%) in the 60 mg group. Adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in 2 of 3 subjects (66.7%) in the 0.5 mg group, 1 of 3 subjects (33.3%) in the 1 mg group, 2 of 3 subjects (66.7%) in the 2 mg group, 5 of 5 subjects (100%) in the 4 mg group, 1 of 3 subjects (33.3%) in the 8 mg group, 4 of 4 subjects (100%) in the 16 mg group, 13 of 13 subjects (100%) in the 30 mg group, 50 of 52 subjects (96.2%) in the 45 mg group, 18 of 19 subjects (94.7%) in the 45 mg LD group, and 6 of 6 subjects (100%) in the 60 mg group. Adverse events with an incidence of ≥60% in each group were abdominal pain, dyspepsia, fatigue, dizziness, and pruritus in 2 subjects (66.7%) in the 0.5 mg group; fatigue, pyrexia, and pruritus in 2 subjects (66.7%) each in the 1 mg group; abdominal pain upper, dry mouth, fatigue, and dry skin in 2 subjects (66.7%) each in the 2 mg group; abdominal pain upper, diarrhoea, and nausea in 3 subjects (60.0%) each in the 4 mg group; abdominal pain in 3 subjects (100%) and vomiting, decreased appetite,

and myalgia in 2 subjects (66.7%) each in the 8 mg group; diarrhoea and vomiting in 3 subjects (75.0%) each in the 16 mg group; decreased appetite in 8 subjects (61.5%) and diarrhoea in 10 subjects (76.9%) in the 30 mg group; diarrhoea in 41 subjects (78.8%) in the 45 mg group; diarrhoea in 19 subjects (100%) and rash in 13 subjects (68.4%) in the 45 mg LD group; and diarrhoea in 6 subjects (100%), fatigue in 5 subjects (83.3%), and nausea and dry skin in 4 subjects (66.7%) each in the 60 mg group.

Serious adverse events occurred in 1 of 3 subjects (33.3%) in the 1 mg group, 1 of 3 subjects (33.3%) in the 2 mg group, 2 of 5 subjects (40.0%) in the 4 mg group, 3 of 3 subjects (100%) in the 8 mg group, 1 of 4 subjects (25.0%) in the 16 mg group, 1 of 13 subjects (7.7%) in the 30 mg group, 12 of 52 subjects (23.1%) in the 45 mg group, 5 of 19 subjects (26.3%) in the 45 mg LD group, and 3 of 6 subjects (50.0%) in the 60 mg group. Serious adverse events that occurred in ≥2 subjects in each group were disease progression in 5 subjects (9.6%), and nausea, vomiting, pneumonia, and mental status changes in 2 subjects (3.8%) each in the 45 mg group. A causal relationship to dacomitinib was denied for all of these serious adverse events.

Adverse events leading to treatment discontinuation occurred in 1 of 3 subjects (33.3%) in the 2 mg group, 1 of 3 subjects (33.3%) in the 8 mg group, 1 of 4 subjects (25.0%) in the 16 mg group, 1 of 13 subjects (7.7%) in the 30 mg group, 6 of 52 subjects (11.5%) in the 45 mg group, 3 of 19 subjects (15.8%) in the 45 mg LD group, and 2 of 6 subjects (33.3%) in the 60 mg group. There were no adverse events leading to treatment discontinuation reported in ≥2 subjects in any group.

#### 7.3.5.2 Schedule B

Adverse events occurred in 10 of 10 subjects (100%), and adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in 9 of 10 subjects (90.0%). Adverse events with an incidence of ≥30% were diarrhoea in 9 subjects (90.0%), fatigue and rash in 6 subjects (60.0%) each, vomiting and nausea in 5 subjects (50.0%) each, decreased appetite in 4 subjects (40.0%), and dry eye, abdominal pain, stomatitis, dehydration, dermatitis acneiform, dry skin, and skin fissures in 3 subjects (30.0%) each.

Serious adverse events occurred in 3 of 10 subjects (30.0%). The serious adverse event that occurred in ≥2 subjects was dehydration in 2 subjects (20.0%). A causal relationship to dacomitinib could not be ruled out for dehydration in 1 subject.

Adverse events leading to treatment discontinuation occurred in 2 of 10 subjects (20.0%). There were no adverse events leading to treatment discontinuation reported in ≥2 subjects.

### 7.3.6 Foreign phase I study (Study 1014)

Adverse events occurred in 11 of 11 subjects (100%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in all subjects. Adverse events that occurred in ≥3 subjects were diarrhoea in 8 subjects (72.7%), decreased appetite and dry skin in 7 subjects (63.6%) each, nausea, mucosal

inflammation, dysgeusia, and dermatitis acneiform in 5 subjects (45.5%) each, and chest pain, fatigue, weight decreased, back pain, rash, and rash pruritic in 3 subjects (27.3%) each.

Serious adverse events occurred in 3 of 11 subjects (27.3%). The serious adverse event that occurred in ≥2 subjects was disease progression in 2 subjects (18.2%). A causal relationship to dacomitinib was denied for both cases.

There were no adverse events leading to treatment discontinuation.

### 7.3.7 Foreign phase I study (Study 1015)

Adverse events occurred in 11 of 24 subjects (45.8%) during (a) treatment with dacomitinib 45 mg + rabeprazole in the fasted state, 7 of 24 subjects (29.2%) during (b) treatment with dacomitinib 45 mg in the fasted state, and 7 of 24 subjects (29.2%) during (c) treatment with dacomitinib 45 mg in the fed state. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 7 of 24 subjects (29.2%) during (a), 3 of 24 subjects (12.5%) during (b), and 3 of 24 subjects (12.5%) during (c). Adverse events that occurred in ≥2 subjects in each period were diarrhoea and headache in 4 subjects (36.4%) each and oropharyngeal pain in 2 subjects (8.3%) during (a); acne in 2 subjects (8.3%) during (b); and headache in 3 subjects (12.5%) and oropharyngeal pain in 2 subjects (8.3%) during (c).

No serious adverse events or adverse events leading to treatment discontinuation occurred.

### 7.3.8 Foreign phase I study (Study 1018)

Adverse events occurred in 1 of 9 subjects with moderate hepatic impairment (11.1%), and a causal relationship to the study drug was denied.

The serious adverse event which also led to treatment discontinuation occurred in 1 of 9 subjects with moderate hepatic impairment (11.1%). The serious adverse event which also led to treatment discontinuation was road traffic accident in 1 subject (11.1%), and a causal relationship to the study drug was denied for the event.

### 7.3.9 Foreign phase I study (Study 1020)

Adverse events occurred in 2 of 6 subjects (33.3%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 2 of 6 subjects (33.3%). The adverse events reported were dermatitis acneiform in 2 subjects (33.3%), and photophobia, constipation, dizziness, and insomnia in 1 subject (16.7%) each.

No serious adverse events or adverse events leading to treatment discontinuation occurred.

### 7.3.10 Foreign phase I study (Study 1021)

Adverse events occurred in 6 of 14 subjects (42.9%) during (a) treatment with dacomitinib alone and 11 of 14 subjects (78.6%) during (b) treatment with dacomitinib + paroxetine. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 3 of 14 subjects (21.4%) during (a) and 11 of 14 subjects (78.6%) during (b). Adverse events that occurred in ≥2 subjects during each period were headache in 3 subjects (21.4%) and flushing in 2 subjects (14.3%) during (a); and headache in 5 subjects (35.7%), vision blurred and constipation in 3 subjects (21.4%) each, and abdominal pain, diarrhoea, fatigue, and dizziness in 2 subjects (14.3%) each during (b).

No serious adverse events or adverse events leading to treatment discontinuation occurred.

### 7.3.11 Foreign phase I study (Study 1022)

Adverse events occurred in 17 of 32 subjects (53.1%) during (a) treatment with 15 mg tablets (a formulation for clinical study) and 17 of 32 subjects (53.1%) during (b) treatment with 45 mg tablets (the proposed commercial formulation). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 8 of 32 subjects (25.0%) during (a) and 11 of 32 subjects (34.4%) during (b). Adverse events that occurred in ≥3 subjects during each period were diarrhoea and nasopharyngitis in 5 subjects (15.6%) each and headache in 3 subjects (9.4%) during (a); and diarrhoea in 7 subjects (21.9%), headache in 6 subjects (18.8%), and nasopharyngitis in 3 subjects (9.4%) during (b).

No serious adverse events or adverse events leading to treatment discontinuation occurred.

### 7.3.12 Foreign phase I study (Study 1039)

Adverse events occurred in 6 of 14 subjects (42.9%) during (a) treatment with DXM alone and 9 of 14 subjects (64.3%) during (b) treatment with dacomitinib + DXM. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 5 of 14 subjects (35.7%) during (a) and 7 of 14 subjects (50.0%) during (b). Adverse events that occurred in ≥2 subjects during each period were diarrhoea in 5 subjects (35.7%) and gastrointestinal sounds abnormal in 2 subjects (14.3%) during (a); and diarrhoea in 6 subjects (42.9%), and abdominal pain, gastrointestinal sounds abnormal, and headache in 2 subjects (14.3%) each during (b).

No serious adverse events or adverse events leading to treatment discontinuation occurred.

### 7.3.13 Foreign phase I study (Study 1046)

Adverse events occurred in 6 of 14 subjects (42.9%) during (a) treatment with a single oral dose of dacomitinib 45 mg and 2 of 13 subjects (15.4%) during (b) treatment with a single intravenous dose of dacomitinib 20 mg. Adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in 5 of 14 subjects (35.7%) during (a) and 1 of 13 subjects (7.7%) during (b). Adverse events that occurred in ≥2 subjects during each period were headache in 4 subjects (28.6%) and folliculitis in 2 subjects (14.3%) during (a).

No serious adverse events occurred.

Adverse events leading to treatment discontinuation occurred in 1 of 14 subjects (7.1%) during (a). The adverse events leading to treatment discontinuation reported were rash papular and ALT increased in 1 subject (7.1%) each. A causal relationship to dacomitinib could not be ruled out for either event.

### 7.3.14 Foreign phase I study (Study 1051)

Adverse events occurred in 2 of 14 subjects (14.3%), and adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in 2 of 14 subjects (14.3%). The adverse events reported were rhinitis and blood bilirubin increased in 1 subject (7.1%) each.

No serious adverse events or adverse events leading to treatment discontinuation occurred.

### 7.3.15 Foreign phase I study (Study 1004)

Adverse events occurred in 24 of 24 subjects (100%) in (a) the dacomitinib 10 mg + FIG 20 mg/kg group, 25 of 25 subjects (100%) in (b) the dacomitinib 15 mg + FIG 20 mg/kg group, 7 of 7 subjects (100%) in (c) the dacomitinib 20 mg + FIG 10 mg/kg group, 10 of 10 subjects (100%) in (d) the dacomitinib 20 mg + FIG 20 mg/kg group, and 5 of 5 subjects (100%) in (e) the dacomitinib 30 mg + FIG 20 mg/kg group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 23 of 24 subjects (95.8%) in (a), 25 of 25 subjects (100%) in (b), 6 of 7 subjects (85.7%) in (c), 10 of 10 subjects (100%) in (d), and 5 of 5 subjects (100%) in (e). Adverse events with an incidence of ≥40% in each group were fatigue and decreased appetite in 12 subjects (50.0%) each and diarrhoea in 11 subjects (45.8%) in (a); diarrhoea in 18 subjects (72.0%), fatigue in 16 subjects (64.0%), dermatitis acneiform and decreased appetite in 15 subjects (60.0%) each, mucosal inflammation in 12 subjects (48.0%), and asthenia in 11 subjects (44.0%) in (b); mucosal inflammation in 5 subjects (71.4%), diarrhoea in 4 subjects (57.1%), and fatigue, dermatitis acneiform, and dry skin in 3 subjects (42.9%) each in (c); mucosal inflammation and dry skin in 8 subjects (80.0%) each, diarrhoea in 7 subjects (70.0%), asthenia and decreased appetite in 5 subjects (50.0%) each, and disease progression, fatigue, dermatitis acneiform, and exfoliative rash in 4 subjects (40.0%) each in (d); and mucosal inflammation in 4 subjects (80.0%), diarrhoea, fatigue, and dermatitis acneiform in 3 subjects (60.0%) each, and dysphagia and dehydration in 2 subjects (40.0%) each in (e).

Serious adverse events occurred in 9 of 24 subjects (37.5%) in (a), 9 of 25 subjects (36.0%) in (b), 2 of 7 subjects (28.6%) in (c), 7 of 10 subjects (70.0%) in (d), and 2 of 5 subjects (40.0%) in (e). The serious adverse event that occurred in ≥2 subjects in each group was disease progression in 8 subjects (33.3%) in (a), 3 subjects (12.0%) in (b), 2 subjects (28.6%) in (c), and 4 subjects (40.0%) in (d), and a causal relationship to the study drug was denied for all of these events.

Adverse events leading to treatment discontinuation occurred in 9 of 24 subjects (37.5%) in (a), 8 of 25 subjects (32.0%) in (b), 3 of 7 subjects (42.9%) in (c), 5 of 10 subjects (50.0%) in (d), and 2 of 5 subjects (40.0%) in

(e). Adverse event leading to treatment discontinuation that occurred in ≥2 subjects in each group was disease progression in 8 subjects (33.3%) in (a), 3 subjects (12.0%) in (b), 2 subjects (28.6%) in (c), and 4 subjects (40.0%) in (d), and a causal relationship to the study drug was denied for all of these events.

### 7.3.16 Foreign phase I study (Study 1006)

#### 7.3.16.1 Dose escalation part

Adverse events occurred in 14 of 14 subjects (100%) in (a) the dacomitinib 30 mg QD + crizotinib 200 mg BID group, 6 of 6 subjects (100%) in (b) the dacomitinib 45 mg QD + crizotinib 200 mg BID group, 7 of 7 subjects (100%) in (c) the dacomitinib 30 mg QD + crizotinib 250 mg BID group, and 6 of 6 subjects (100%) in (d) the dacomitinib 45 mg QD + crizotinib 250 mg QD group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in all subjects. Adverse events with an incidence of ≥40% in each group were diarrhoea in 12 subjects (85.7%), nausea in 10 subjects (71.4%), rash and vomiting in 9 subjects (64.3%) each, dry skin, fatigue, oedema peripheral, and decreased appetite in 7 subjects (50.0%) each, and paronychia in 6 subjects (42.9%) in (a); diarrhoea in 6 subjects (100%), nausea and decreased appetite in 4 subjects (66.7%) each, and rash, fatigue, and epistaxis in 3 subjects (50.0%) each in (b); diarrhoea in 6 subjects (85.7%), nausea in 5 subjects (71.4%), and rash, fatigue, oedema peripheral, mucosal inflammation, decreased appetite, and visual impairment in 3 subjects (42.9%) each in (c); and diarrhoea and nausea in 6 subjects (100%) each, vomiting in 5 subjects (83.3%), and rash, dry skin, dermatitis acneiform, fatigue, decreased appetite, and paronychia in 3 subjects (50.0%) each in (d).

Serious adverse events occurred in 6 of 14 subjects (42.9%) in (a), 2 of 6 subjects (33.3%) in (b), 1 of 7 subjects (14.3%) in (c), and 4 of 6 subjects (66.7%) in (d). There were no serious adverse events that occurred in ≥2 subjects in any group.

Adverse events leading to treatment discontinuation occurred in 5 of 14 subjects (35.7%) in (a) and 2 of 6 subjects (33.3%) in (b). There were no adverse events leading to treatment discontinuation that occurred in ≥2 subjects in any group.

#### 7.3.16.2 Expansion part

Adverse events occurred in 22 of 25 subjects (88.0%) in expansion cohort 1 and 11 of 12 subjects (91.7%) in expansion cohort 2. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 22 of 25 subjects (88.0%) in expansion cohort 1 and 11 of 12 subjects (91.7%) in expansion cohort 2. Adverse events with an incidence of ≥30% in each cohort were diarrhoea in 16 subjects (64.0%), dermatitis acneiform and fatigue in 10 subjects (40.0%) each, nausea in 9 subjects (36.0%), and vomiting, dyspepsia, decreased appetite, and paronychia in 8 subjects (32.0%) each in expansion cohort 1; and nausea in 8 subjects (66.7%), diarrhoea in 6 subjects (50.0%), vomiting in 5 subjects(41.7%), and oedema peripheral in 4 subjects (33.3%) in expansion cohort 2.

Serious adverse events occurred in 8 of 25 subjects (32.0%) in expansion cohort 1 and 8 of 12 subjects (66.7%) in expansion cohort 2. Serious adverse events that occurred in ≥2 subjects in each cohort were hypoxia and diarrhoea in 2 subjects (8.0%) each in expansion cohort 1; and diarrhoea and disease progression in 2 subjects (16.7%) each in expansion cohort 2. A causal relationship to the study drug could not be ruled out for diarrhoea in 2 subjects in expansion cohort 1 and diarrhoea in 2 subjects in expansion cohort 2.

Adverse events leading to treatment discontinuation occurred in 6 of 25 subjects (24.0%) in expansion cohort 1 and 5 of 12 subjects (41.7%) in expansion cohort 2. The adverse event leading to treatment discontinuation that occurred in ≥2 subjects in each cohort was hypoxia in 2 subjects (8.0%) in expansion cohort 1, and a causal relationship to the study drug could not be ruled out for either case.

#### 7.3.17 Foreign phase Ib study (Study 1031)

Adverse events occurred in 17 of 19 subjects (89.5%), and adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in 14 of 19 subjects (73.7%). Adverse events with an incidence of ≥20% were diarrhoea in 13 subjects (68.4%), rash in 5 subjects (26.3%), and atrial fibrillation in 4 subjects (21.1%).

Serious adverse events occurred in 5 of 19 subjects (26.3%). The serious adverse events reported were respiratory distress in 4 subjects (21.1%), subcutaneous emphysema in 2 subjects (10.5%), and acute kidney injury, bronchopleural fistula, delirium, myocardial infarction, and pneumonia in 1 subject (5.3%) each. A causal relationship to dacomitinib was denied for all of these serious adverse events.

An adverse event leading to treatment discontinuation occurred in 1 of 19 subjects (5.3%). The adverse event leading to treatment discontinuation reported was diarrhoea in 1 subject (5.3%), and a causal relationship to the study drug could not be ruled out.

#### 7.3.18 Foreign phase I/II study (Study 1003)

##### 7.3.18.1 Phase I part

Adverse events occurred in 6 of 6 subjects (100%) in the 30 mg group and 6 of 6 subjects (100%) in the 45 mg group. Adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in all subjects. Adverse events that occurred in ≥2 subjects were dermatitis acneiform in 5 subjects (83.3%), paronychia and cough in 3 subjects (50.0%) each, and diarrhoea, stomatitis, mucosal inflammation, musculoskeletal pain, haemoptysis, palmar-plantar erythrodysaesthesia syndrome, and pruritus in 2 subjects (33.3%) each in the 30 mg group; and diarrhoea and dermatitis acneiform in 6 subjects (100%) each, stomatitis, paronychia, mucosal inflammation, and palmar-plantar erythrodysaesthesia syndrome in 3 subjects (50.0%) each, and nausea, decreased appetite, and dyspnoea in 2 subjects (33.3%) each in the 45 mg group.

A serious adverse event occurred in 1 of 6 subjects (16.7%) in the 30 mg group. The serious adverse event reported was pleural effusion in 1 subject (16.7%), and a causal relationship to dacomitinib was denied.

No adverse events leading to treatment discontinuation occurred.

#### 7.3.18.2 Phase II part

Adverse events occurred in 43 of 43 subjects (100%), and adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in 41 of 43 subjects (95.3%). Adverse events with an incidence of ≥30% were diarrhoea in 36 subjects (83.7%), dermatitis acneiform in 35 subjects (81.4%), paronychia in 29 subjects (67.4%), stomatitis in 20 subjects (46.5%), dry skin in 16 subjects (37.2%), pruritus in 15 subjects (34.9%), decreased appetite in 14 subjects (32.6%), and palmar-plantar erythrodysaesthesia syndrome in 13 subjects (30.2%).

Serious adverse events occurred in 9 of 43 subjects (20.9%). The serious adverse event that occurred in ≥2 subjects was disease progression in 5 subjects (11.6%), and a causal relationship to dacomitinib was ruled out.

Adverse events leading to treatment discontinuation occurred in 2 of 43 subjects (4.7%). There were no adverse events leading to treatment discontinuation that occurred in ≥2 subjects.

### 7.3.19 Foreign phase II study (Study 1002)

Adverse events occurred in 50 of 50 subjects (100%) in Group A (patients with adenocarcinoma NSCLC) and 16 of 16 subjects (100%) in Group B (patients with non-adenocarcinoma NSCLC). Adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in 50 of 50 subjects (100%) in Group A, and 15 of 16 subjects (93.8%) in Group B. Adverse events with an incidence of ≥30% in each group were diarrhoea in 44 subjects (88.0%), dermatitis acneiform in 33 subjects (66.0%), fatigue in 31 subjects (62.0%), dry skin in 18 subjects (36.0%), and decreased appetite in 15 subjects (30.0%) in Group A; and diarrhoea in 13 subjects (81.3%), dermatitis acneiform in 12 subjects (75.0%), dry skin and fatigue in 7 subjects (43.8%) each, and nausea and decreased appetite in 6 subjects (37.5%) each in Group B.

Serious adverse events occurred in 9 of 50 subjects (18.0%) in Group A and 6 of 16 subjects (37.5%) in Group B. Serious adverse events that occurred in ≥2 subjects in each group were disease progression and respiratory failure in 3 subjects (6.0%) each and pulmonary embolism in 2 subjects (4.0%) in Group A; and abdominal pain and constipation in 2 subjects (12.5%) each in Group B. A causal relationship to dacomitinib could not be ruled out for pulmonary embolism in 1 subject in Group A.

Adverse events leading to treatment discontinuation occurred in 11 of 50 subjects (22.0%) in Group A and 2 of 16 subjects (12.5%) in Group B. Adverse events leading to treatment discontinuation that occurred in ≥2 subjects in each group were fatigue and pulmonary embolism in 2 subjects (4.0%) each in Group A, and a causal relationship to dacomitinib could not be ruled out for any of these cases.

### 7.3.20 Foreign phase II study (Study 1027)

Adverse events occurred in 68 of 69 subjects (98.6%), and adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in 67 of 69 subjects (97.1%). Adverse events with an incidence of ≥30% were diarrhoea in 59 subjects (85.5%), dermatitis acneiform in 52 subjects (75.4%), fatigue in 35 subjects (50.7%), dry skin in 34 subjects (49.3%), palmar-plantar erythrodysaesthesia syndrome in 24 subjects (34.8%), and stomatitis in 23 subjects (33.3%).

Serious adverse events occurred in 20 of 69 subjects (29.0%). Serious adverse events that occurred in ≥2 subjects were diarrhoea and disease progression in 4 subjects (5.8%) each, and pneumonia aspiration, vomiting, and dehydration in 2 subjects (2.9%) each. A causal relationship to dacomitinib could not be ruled out for diarrhoea in 3 subjects, vomiting in 2 subjects, and dehydration and pneumonia aspiration in 1 subject each.

Adverse events leading to treatment discontinuation occurred in 19 of 69 subjects (27.5%). Adverse events leading to treatment discontinuation that occurred in ≥2 subjects were disease progression in 4 subjects (5.8%), dermatitis acneiform in 3 subjects (4.3%), and fatigue in 2 subjects (2.9%). A causal relationship to dacomitinib could not be ruled out for dermatitis acneiform in 3 subjects and fatigue in 2 subjects.

### 7.3.21 Foreign phase II study (Study 1028)

Adverse events occurred in 94 of 94 subjects (100%) in the dacomitinib group and 93 of 93 subjects (100%) in the erlotinib group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 89 of 93 subjects (95.7%) in the dacomitinib group and 88 of 94 subjects (93.6%) in the erlotinib group. Adverse events with an incidence of ≥30% in each group were diarrhoea in 68 subjects (73.1%) and dermatitis acneiform in 60 subjects (64.5%) in the dacomitinib group; and dermatitis acneiform in 54 subjects (57.4%), diarrhoea in 47 subjects (50.0%), fatigue in 33 subjects (35.1%), and decreased appetite in 29 subjects (30.9%) in the erlotinib group.

Serious adverse events occurred in 35 of 93 subjects (37.6%) in the dacomitinib group and 31 of 94 subjects (33.0%) in the erlotinib group. Serious adverse events that occurred in ≥2 subjects in each group were disease progression in 10 subjects (10.8%), dyspnoea in 8 subjects (8.6%), pneumonia in 6 subjects (6.5%), and diarrhoea, vomiting, and confusional state in 2 subjects (2.2%) each in the dacomitinib group; and disease progression in 13 subjects (13.8%), pneumonia and dyspnoea in 4 subjects (4.3%) each, pulmonary embolism in 3 subjects (3.2%), and abdominal pain and diarrhoea in 2 subjects (2.1%) each in the erlotinib group. A causal relationship to the study drug could not be ruled out for diarrhoea in 2 subjects, and vomiting and pneumonia in 1 subject each in the dacomitinib group; and diarrhoea and pneumonia in 2 subjects each, and pulmonary embolism in 1 subject in the erlotinib group.

Adverse events leading to treatment discontinuation occurred in 22 of 93 subjects (23.7%) in the dacomitinib group and 16 of 94 subjects (17.0%) in the erlotinib group. Adverse events leading to treatment discontinuation that occurred in ≥2 subjects in each group were pneumonia, dyspnoea, and dermatitis acneiform in 2 subjects

(2.2%) each in the dacomitinib group; and disease progression in 4 subjects (4.3%), and pneumonia, dyspnoea, and pulmonary embolism in 2 subjects (2.1%) each in the erlotinib group. A causal relationship to the study drug could not be ruled out for dermatitis acneiform in 2 subjects in the dacomitinib group; and pneumonia and pulmonary embolism in 1 subject each in the erlotinib group.

### 7.3.22 Foreign phase II study (Study 1042)

#### 7.3.22.1 Cohort 1

Adverse events occurred in 66 of 66 subjects (100%) in Group A (coadministration with placebo), 66 of 66 subjects (100%) in Group B (coadministration with doxycycline), and 7 of 7 subjects (100%) in Group C (coadministration with alclometasone dipropionate 0.05% cream). Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 62 of 66 subjects (93.9%) in Group A, 65 of 66 subjects (98.5%) in Group B, and 7 of 7 subjects (100%) in Group C. Adverse events with an incidence of ≥40% in each group were diarrhoea in 54 subjects (81.8%), nausea and rash in 28 subjects (42.4%) each, and dry skin in 27 subjects (40.9%) in Group A; diarrhoea in 52 subjects (78.8%), nausea in 33 subjects (50.0%), rash in 29 subjects (43.9%), and fatigue in 27 subjects (40.9%) in Group B; and diarrhoea in 7 subjects (100%), rash in 5 subjects (71.4%), chills in 4 subjects (57.1%), and anaemia, paronychia, stomatitis, vomiting, fatigue, decreased appetite, cough, dyspnoea, and pruritus in 3 subjects (42.9%) each in Group C.

Serious adverse events occurred in 25 of 66 subjects (37.9%) in Group A, 27 of 66 subjects (40.9%) in Group B, and 3 of 7 subjects (42.9%) in Group C. Serious adverse events that occurred in ≥2 subjects in each group were disease progression in 7 subjects (10.6%), dehydration in 5 subjects (7.6%), acute kidney injury in 3 subjects (4.5%), and pain, asthenia, septic shock, pneumonia and pneumothorax in 2 subjects (3.0%) each in Group A; and disease progression in 7 subjects (10.6%), nausea in 4 subjects (6.1%), dehydration and vomiting in 3 subjects (4.5%) each, and pneumothorax, dyspnoea, respiratory failure, pneumonitis, supraventricular tachycardia, and diarrhoea in 2 subjects (3.0%) each in Group B. A causal relationship to the study drug could not be ruled out for dehydration in 3 subjects and asthenia in 2 subjects in Group A; and dehydration, diarrhoea, nausea, and pneumonitis in 2 subjects each in Group B.

Adverse events leading to treatment discontinuation occurred in 15 of 66 subjects (22.7%) in Group A, 12 of 66 subjects (18.2%) in Group B, and 1 of 7 subjects (14.3%) in Group C. Adverse events leading to treatment discontinuation that occurred in ≥2 subjects in each group were diarrhoea in 4 subjects (6.1%) and disease progression in 2 subjects (3.0%) in Group A and disease progression in 2 subjects (3.0%) in Group B. A causal relationship to the study drug could not be ruled out for diarrhoea in 4 subjects in Group A.

#### 7.3.22.2 Cohort 2

Adverse events occurred in 66 of 67 subjects (98.5%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 63 of 67 subjects (94.0%). Adverse events with an incidence of ≥30% were diarrhoea in 54 subjects (80.6%), decreased appetite and rash in 25 subjects (37.3%), and nausea in 21 subjects (31.3%).

Serious adverse events occurred in 22 of 67 subjects (32.8%). Serious adverse events that occurred in ≥2 subjects were disease progression in 8 subjects (11.9%), pneumonia in 5 subjects (7.5%), and vomiting in 2 subjects (3.0%). A causal relationship to the study drug could not be ruled out for vomiting and pneumonia in 1 subject each.

Adverse events leading to treatment discontinuation occurred in 10 of 67 subjects (14.9%). The adverse event leading to treatment discontinuation that occurred in ≥2 subjects was disease progression in 2 subjects (3.0%), and a causal relationship to the study drug was denied for both cases.

#### 7.3.22.3 Cohort 3

Adverse events occurred in 25 of 25 subjects (100%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in all subjects. Adverse events with an incidence of ≥40% were diarrhoea in 23 subjects (92.0%), dermatitis acneiform in 18 subjects (72.0%), pruritus in 17 subjects (68.0%), stomatitis and paronychia in 16 subjects (64.0%) each, and decreased appetite and dry skin in 14 subjects (56.0%) each.

Serious adverse events occurred in 6 of 25 subjects (24.0%). There were no serious adverse events that occurred in ≥2 subjects. Adverse events leading to treatment discontinuation occurred in 3 of 25 subjects (12.0%). There were no adverse events leading to treatment discontinuation that occurred in ≥2 subjects.

### 7.3.23 Foreign phase II study (Study 1047)

Adverse events occurred in 16 of 16 subjects (100%) in Cohort A and 22 of 22 subjects (100%) in Cohort B. Adverse events for which a causal relationship to dacomitinib could not be ruled out occurred in all subjects. Adverse events with an incidence of ≥40% in each cohort were diarrhoea in 14 subjects (87.5%), rash in 8 subjects (50.0%), and nausea, stomatitis, and dry skin in 7 subjects (43.8%) each in Cohort A; and diarrhoea in 16 subjects (72.7%), rash in 12 subjects (54.5%), and nausea in 9 subjects (40.9%) in Cohort B.

Serious adverse events occurred in 7 of 16 subjects (43.8%) in Cohort A and 8 of 22 subjects (36.4%) in Cohort B. Serious adverse events that occurred in ≥2 subjects in each cohort were diarrhoea in 3 subjects (13.6%) and dyspnoea in 2 subjects (9.1%) in Cohort B. A causal relationship to dacomitinib could not be ruled out for diarrhoea in 2 subjects.

Adverse events leading to treatment discontinuation occurred in 3 of 16 subjects (18.8%) in Cohort A and 3 of 22 subjects (13.6%) in Cohort B. There were no adverse events leading to treatment discontinuation that occurred in ≥2 subjects in either cohort.

#### 7.3.24 Foreign phase III study (Study 1011)

Adverse events occurred in 474 of 477 subjects (99.4%) in the dacomitinib group and 212 of 239 subjects (88.7%) in the placebo group. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 445 of 477 subjects (93.3%) in the dacomitinib group and 100 of 239 subjects (41.8%) in the placebo group. Adverse events with an incidence of ≥40% in each group were diarrhoea in 375 subjects (78.6%), dermatitis acneiform in 271 subjects (56.8%), and stomatitis in 205 subjects (43.0%) in the dacomitinib group.

Serious adverse events occurred in 191 of 477 subjects (40.0%) in the dacomitinib group and 87 of 239 subjects (36.4%) in the placebo group. Serious adverse events that occurred in ≥5 subjects in each group were NSCLC in 76 subjects (15.9%), lung infection in 31 subjects (6.5%), dyspnoea in 26 subjects (5.5%), diarrhoea in 17 subjects (3.6%), dehydration in 16 subjects (3.4%), embolism in 12 subjects (2.5%), vomiting and pleural effusion in 8 subjects (1.7%) each, pyrexia in 7 subjects (1.5%), acute kidney injury, pulmonary haemorrhage, and respiratory failure in 6 subjects (1.3%) each, and stomatitis in 5 subjects (1.0%) in the dacomitinib group; and NSCLC in 42 subjects (17.6%), dyspnoea in 14 subjects (5.9%), and lung infection in 12 subjects (5.0%) in the placebo group. A causal relationship to dacomitinib could not be ruled out for diarrhoea in 16 subjects, dehydration in 9 subjects, vomiting in 7 subjects, stomatitis in 5 subjects, acute kidney injury in 4 subjects, embolism in 3 subjects, lung infection and respiratory failure in 2 subjects each, and pyrexia in 1 subject in the dacomitinib group.

Adverse events leading to treatment discontinuation occurred in 53 of 477 subjects (11.1%) in the dacomitinib group and 24 of 239 subjects (10.0%) in the placebo group. Adverse event leading to treatment discontinuation that occurred in ≥3 subjects in each group were NSCLC in 23 subjects (4.8%), lung infection in 9 subjects (1.9%), and diarrhoea and acute kidney injury in 3 subjects (0.6%) each in the dacomitinib group; and NSCLC in 14 subjects (5.9%) in the placebo group. A causal relationship to dacomitinib could not be ruled out for diarrhoea and acute kidney injury in 3 subjects each and lung infection in 1 subject in the dacomitinib group.

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

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

The assessments are currently underway. The results and PMDA's conclusion will be reported in Review Report (2).

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

The assessments are currently underway. The results and PMDA's conclusion will be reported in Review Report (2).

## 9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that dacomitinib has efficacy in the treatment of EGFR mutation-positive, unresectable or recurrent non-small cell lung cancer, and that dacomitinib has acceptable safety in view of its benefits. Dacomitinib is a drug with a new active ingredient and is thought to suppress the growth of EGFR mutation-positive non-small cell lung cancer by inhibiting the phosphorylation of EGFR tyrosine kinases. Dacomitinib is considered of clinical significance as an option for the treatment of EGFR mutation-positive, unresectable or recurrent non-small cell lung cancer. PMDA considers that further discussion is needed regarding the clinical positioning, indications, and post-marketing investigations of dacomitinib.

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

**Review Report (2)**

November 9, 2018

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Vizimpro Tablets 15 mg |
| | Vizimpro Tablets 45 mg |
| **Non-proprietary Name** | Dacomitinib Hydrate |
| **Applicant** | Pfizer Japan Inc. |
| **Date of Application** | May 28, 2018 |

**List of Abbreviations**

See Appendix.

## 1. Content of the Review

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

### 1.1 Efficacy

On the basis of the review presented in "7.R.2 Efficacy" of the Review Report (1), PMDA has concluded that dacomitinib shows efficacy in chemotherapy-naïve patients with EGFR activating mutation-positive,[52] unresectable advanced or recurrent non-small cell lung cancer (NSCLC)[53] based on the data from the global phase III study in EGFR mutation-positive, unresectable advanced or recurrent NSCLC (Study 1050), in which the superiority of dacomitinib over gefitinib was demonstrated in terms of PFS determined by IRC review, the primary endpoint of the study.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

### 1.2 Safety

On the basis of the review presented in "7.R.3 Safety" of the Review Report (1), PMDA has concluded that the adverse events requiring special attention for treatment of chemotherapy-naïve patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC with dacomitinib are interstitial lung disease

52) The study enrolled patients with NSCLC, from whom tumor tissue samples were collected and the presence of Ex19del or L858R, out of EGFR activating mutations, was confirmed in the samples. Patients harboring T790M mutation in their tumor tissue samples were also enrolled in the study.

53) Of patients with NSCLC, those with confirmed adenocarcinoma or tumors categorized in an adenocarcinoma-specific histological type were enrolled in the study.

(ILD), skin disorder, diarrhoea, hepatic function disorder, gastrointestinal disorder (excluding diarrhoea), nail abnormality, and hypokalaemia.

In addition, PMDA has concluded that, although patients on dacomitinib should be closely monitored for the above adverse events, the tolerability profile of dacomitinib is acceptable if appropriate measures such as monitoring and management of adverse events and dose adjustment of dacomitinib are taken by physicians with sufficient knowledge and experience in cancer chemotherapy.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

### 1.3 Clinical positioning and indication

On the basis of the review presented in "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA has concluded that the indication of dacomitinib should be "EGFR mutation-positive, unresectable or recurrent non-small cell lung cancer" as proposed; provided that information on patients eligible for Study 1050, such as EGFR mutation types and histological types of NSCLC, is included in the "Clinical Studies" section and the following precautionary statement is included in the "Precautions Concerning Indications" section of the package insert.

[Precautions Concerning Indication]

- EGFR mutation testing should be performed. Dacomitinib should be administered to patients with EGFR mutation-positive NSCLC confirmed by testing performed by pathologists or at testing facilities with sufficient experience, using approved *in vitro* diagnostics.
- Physicians should select patients eligible for dacomitinib therapy after closely reading the "Clinical Studies" section to ensure they fully understand the efficacy and safety of dacomitinib.
- The efficacy and safety of dacomitinib in adjuvant chemotherapy have not been established.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comment was made by the expert advisors:

- Patients with brain metastases were excluded from Study 1050. This information should be adequately provided to healthcare professionals.

Based on the above, PMDA instructed the applicant to include not only the information on patients eligible for Study 1050 such as EGFR mutation types and histological types of NSCLC but also the information that patients with brain metastases were excluded from Study 1050 in the "Clinical Studies" section of the package insert and to include the above statements in the "Indications" and "Precautions Concerning Indication" sections, and the applicant responded that it would duly follow the instruction.

### 1.4 Dosage and administration

On the basis of the review presented in "7.R.5 Dosage and administration" of the Review Report (1), PMDA has concluded that the "Dosage and Administration" section should include the statement, "The usual adult dosage is 45 mg of dacomitinib administered orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition," as proposed; provided that the following precautionary statement is included in the "Precautions Concerning Dosage and Administration" section of the package insert.

[Precautions Concerning Dosage and Administration]

- Criteria for dose interruption, dose reduction, or discontinuation of dacomitinib due to adverse drug reactions
- Efficacy and safety of dacomitinib used in combination with other antineoplastic agents have not been established.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

PMDA instructed the applicant to include the above statements in the "Dosage and Administration" and "Precautions Concerning Dosage and Administration" sections, and the applicant responded that it would duly follow the instruction.

### 1.5 Risk management plan (draft)

The applicant has proposed ILD as a safety specification and plans to conduct a post-marketing surveillance with a planned sample size of 799 patients and an observation period of 52 weeks to investigate risk factors for ILD.

In view of the discussions presented in "7.R.6 Post-marketing investigations" of the Review Report (1), PMDA has concluded that the post-marketing surveillance may be conducted as proposed by the applicant.

In the Expert Discussion, the expert advisors supported the above conclusion of PMDA including its decision that no materials for healthcare professionals or patients will be prepared or provided as additional risk minimization activities.

On the basis of the discussion above, PMDA has concluded that the risk management plan (draft) for dacomitinib should include the safety specifications presented in Table 41 and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Tables 42 and 43.

**Table 41. Safety and efficacy specifications in the risk management plan (draft)**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • ILD<br>• Severe diarrhoea<br>• Severe skin disorder | • Hepatic function disorder<br>• Reproductive and developmental toxicity<br>• Hypokalaemia<br>• Corneal disorder | • Safety in patients with hepatic impairment |
| Efficacy specification | | |
| None | | |

**Table 42. Summary of additional pharmacovigilance activities, efficacy-related investigations, and additional risk minimization activities included under the risk management plan (draft)**

| Additional pharmacovigilance activities | Efficacy-related investigations | Additional risk minimization activities |
|---|---|---|
| • Early post-marketing phase vigilance<br>• Specified drug use-results survey | None | • Disseminate data gathered during early post-marketing phase vigilance |

**Table 43. Outline of post-marketing surveillance (draft)**

| | |
|---|---|
| Objective | To investigate risk factors for ILD in patients treated with dacomitinib |
| Survey method | Central registration system |
| Population | Patients with EGFR mutation-positive, unresectable advanced or recurrent NSCLC treated with dacomitinib |
| Observation period | 52 weeks |
| Planned sample size | 799 patients |
| Main survey items | Safety specification: ILD<br>Main survey items other than above: patient characteristics (e.g., age, ECOG PS, smoking history, history of exposure to asbestos, history of supplemental oxygen administration for treatment of respiratory disease, prior treatment of the primary disease, medical history, complications), and use status of dacomitinib |

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1.1 and CTD 5.3.5.1.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, PMDA confirmed that the studies were generally conducted in compliance with GCP. Thus, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. Although overall evaluation of the studies is not significantly affected, the inspection revealed the following findings at some of the sponsors. PMDA informed the applicant (sponsor) of these matters as findings requiring corrective action.

[Findings requiring corrective action]

Sponsor

Delay in periodic reporting of safety information to the investigators and the heads of study sites

## 3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below with the following conditions, provided that appropriate precautions are included in the package insert, information on the proper use of the product is disseminated adequately in the post-marketing setting, and the product is properly used by physicians with sufficient knowledge and experience in cancer chemotherapy at medical institutions capable of responding to medical emergencies. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not categorized as a biological product or specified biological product. The drug substance and drug product are classified as a powerful drug.

**Indication**

EGFR mutation-positive, unresectable or recurrent non-small cell lung cancer

**Dosage and Administration**

The usual adult dosage is 45 mg of dacomitinib administered orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition.

**Approval Conditions**

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

**Warnings**

1. Dacomitinib should be administered only to patients who are eligible for treatment with dacomitinib, under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy, at a medical institution with adequate facilities that can respond to medical emergencies. Patients or their family members should be fully informed of the benefits and risks of dacomitinib (in particular, early symptoms of interstitial lung disease, precautions on treatment with dacomitinib, and information on fatal cases that occurred during treatment), and informed consent should be obtained prior to the start of therapy.
2. Interstitial lung disease may occur in patients on dacomitinib, and fatal cases have been reported. Patients should therefore be monitored carefully for early symptoms of the disease (e.g., dyspnoea, cough, and pyrexia) and should undergo chest imaging examinations on a regular basis. If any abnormality is observed, treatment with dacomitinib should be discontinued and appropriate measures should be taken. In the initial treatment phase, patients should be hospitalized or supervised under equivalent conditions so they can be carefully monitored for serious adverse drug reactions such as interstitial lung disease.

**Contraindication**

Patients with a history of hypersensitivity to any components of the product

**Precautions Concerning Indication**

- EGFR mutation testing should be performed. Dacomitinib should be administered to patients with EGFR mutation-positive NSCLC confirmed by testing performed by pathologists or at testing facilities with sufficient experience, using approved *in vitro* diagnostics.
- Physicians should select patients eligible for dacomitinib therapy after closely reading the "Clinical Studies" section to ensure they fully understand the efficacy and safety of dacomitinib.
- The efficacy and safety of dacomitinib in adjuvant chemotherapy have not been established.

**Precautions Concerning Dosage and Administration**

1. Efficacy and safety of dacomitinib used in combination with other antineoplastic agents have not been established.
2. Dose interruption, dose reduction, or treatment discontinuation of dacomitinib due to adverse drug reactions should be considered based on the criteria shown below.

**Dose reduction level of dacomitinib**

| Dose reduction level | Dose |
|---|---|
| Usual dose | 45 mg/day |
| Dose reduced by 1 dose level | 30 mg/day |
| Dose reduced by 2 dose levels | 15 mg/day |

**Criteria for dose interruption, dose reduction, or discontinuation due to adverse drug reactions**

| Adverse drug reaction | Severity* | Measures |
|---|---|---|
| ILD | Any Grade | Discontinue dacomitinib. |
| Diarrhoea | Grade 2 | Withhold dacomitinib until resolution to Grade ≤1. After resolution, resume dacomitinib at the previous dose level or a dose reduced by 1 dose level. |
| | Grade 3 or 4 | Withhold dacomitinib until resolution to Grade ≤1. After resolution, resume dacomitinib at a dose reduced by 1 dose level. |
| Skin toxicity (skin symptoms with rash, erythema, or exfoliation) | Grade 2 | Withhold dacomitinib until resolution to Grade ≤1. After resolution, resume dacomitinib at the previous dose level or a dose reduced by 1 dose level. |
| | Grade 3 or 4 | Withhold dacomitinib until resolution to Grade ≤1. After resolution, resume dacomitinib at a dose reduced by 1 dose level. |
| Other adverse drug reactions | Grade 3 or 4 | Withhold dacomitinib until resolution to Grade ≤2. After resolution, resume dacomitinib at a dose reduced by 1 dose level. |

*: Severity grade according to NCI-CTCAE ver. 4.03

**Appendix**

**List of Abbreviations**

| | |
|---|---|
| ABL | abelson murine leukemia virus oncogene |
| afatinib | afatinib maleate |
| A/G ratio | albumin/globulin ratio |
| ALP | alkaline phosphatase |
| ALT | alanine aminotransferase |
| APA | action potential amplitude |
| $APD_{50}$ | action potential duration at 50% repolarization |
| $APD_{90}$ | action potential duration at 90% repolarization |
| application | application for marketing approval |
| AST | aspartate aminotransferase |
| ATP | adenosine triphosphate |
| BA | bioavailability |
| BCRP | breast cancer resistance protein |
| BID | bis in die |
| BLK | B lymphoid tyrosine kinase |
| BRAF | B-Raf proto-oncogene, serine/threonine kinase |
| BSA | bovine serum albumin |
| BSEP | bile salt export pump |
| BTK | Bruton's tyrosine kinase |
| BUN | blood urea nitrogen |
| $C_{avg}$ | average plasma concentration |
| CHO cell line | Chinese hamster ovary cell line |
| CI | confidence interval |
| $CL_{int}$ | intrinsic clearance |
| CPP | critical process parameter |
| CQA | critical quality attribute |
| CrCL | creatinine clearance |
| CYP | cytochrome P450 |
| $^{14}$C-dacomitinib | $^{14}$C-labeled dacomitinib |
| dacomitinib | dacomitinib hydrate |
| dacomitinib 10 mg + FIG 20 mg/kg | dacomitinib 10 mg in combination with FIG 20 mg/kg |
| dacomitinib 15 mg + FIG 20 mg/kg | dacomitinib 15 mg in combination with FIG 20 mg/kg |
| dacomitinib 20 mg + FIG 10 mg/kg | dacomitinib 20 mg in combination with FIG 10 mg/kg |
| dacomitinib 20 mg + FIG 20 mg/kg | dacomitinib 20 mg in combination with FIG 20 mg/kg |
| dacomitinib 30 mg + FIG 20 mg/kg | dacomitinib 30 mg in combination with FIG 20 mg/kg |
| dacomitinib 30 mg QD + crizotinib 200 mg BID | dacomitinib 30 mg QD in combination with crizotinib 200 mg BID |
| dacomitinib 45 mg QD + crizotinib 200 mg BID | dacomitinib 45 mg QD in combination with crizotinib 200 mg BID |

| | |
|---|---|
| dacomitinib 30 mg QD + crizotinib 250 mg BID | dacomitinib 30 mg QD in combination with crizotinib 250 mg BID |
| dacomitinib 45 mg QD + crizotinib 250 mg QD | dacomitinib 45 mg QD in combination with crizotinib 250 mg QD |
| dacomitinib + DXM | dacomitinib in combination with DXM |
| dacomitinib + paroxetine | dacomitinib in combination with paroxetine |
| DLT | dose limiting toxicity |
| DMSO | dimethyl sulfoxide |
| DXM | dextromethorphan hydrobromide hydrate |
| ECOG | Eastern Cooperative Oncology Group |
| efflux ratio | ratio of the secretory permeability to the absorptive permeability |
| EGFR | epidermal growth factor receptor |
| EGFR-TKI | epidermal growth factor receptor-tyrosine kinase inhibitor |
| ELISA | enzyme-linked immunosorbent assay |
| EM | extensive metabolizer |
| EPHB4 | ephrin type-B receptor 4 |
| erlotinib | erlotinib hydrochloride |
| Ex19del | exon 19 deletion |
| Ex19del/T790M | Ex19del and T790M |
| FC | film coating |
| FGR | feline Gardner-Rasheed sarcoma viral oncogene homolog |
| FIG | figitumumab (unapproved in Japan) |
| FLT3 | FMS-like tyrosine kinase 3 |
| FRET | fluorescence resonance energy transfer |
| FYN | tyrosine-protein kinase Fyn |
| GC | gas chromatography |
| GGT | gamma-glutamyl transferase |
| μ-GST | μ glutathione-S transferase |
| G719X | Substitution of a glycine (G) at position 719 in exon 18 with a serine (S) or alanine (A) |
| HDPE | high density polyethylene |
| HER | human epidermal growth factor receptor |
| hERG | human *ether-a-go-go* related gene |
| ICH | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| ICH Q3A Guidelines | “Revision of Guidelines on Impurities in New Drug Substances” (PMSB/ELD Notification No. 1216001 dated December 16, 2002) |
| ICH Q3B Guidelines | “Revision of Guidelines on Impurities in New Drug Products” (PMSB/ELD Notification No. 0624001 dated June 24, 2003) |
| ICH Q1D Guidelines | “Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products” (PMSB/ELD Notification No. 0731004 dated July 31, 2002) |
| ILD | interstitial lung disease |
| IM | intermediate metabolizer |
| IR | infrared absorption spectrum |
| IRC | independent radiologic central |
| ITT | intention-to-treat |

| | |
|---|---|
| Japanese treatment guideline | Guideline for Diagnosis and Treatment of Lung Cancer 2017, Stage IV Non-small Cell Lung Cancer, edited by the Japan Lung Cancer Society |
| $K_a$ | absorption rate constant |
| Ki | inhibition constant |
| KRAS | Kirsten rat sarcoma viral oncogene homolog |
| KRAS-WT population | KRAS wild type population |
| LC | liquid chromatography |
| LC-MS/MS | liquid chromatography-tandem mass spectrometry |
| LCK | T-lymphocyte specific protein tyrosine kinase |
| LDPE | low density polyethylene |
| L861Q | Substitution of a leucine (L) at position 861 in exon 21 with a glutamine (Q) |
| L858R | Substitution of a leucine (L) at position 858 in exon 21 with an arginine (R) |
| L858R/T790M | L858R and T790M |
| LYN | tyrosine protein kinase Lyn |
| MAPK | mitogen-activated protein kinase |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mRNA | messenger ribonucleic acid |
| NADPH | nicotinamide adenine dinucleotide phosphate hydrogen |
| NAG | N-acetyl-β-D-glucosaminidase |
| NCCN Guidelines | National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer |
| NCI-CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |
| NCI-ODWG | National Cancer Institute Organ Dysfunction Working Group |
| NMR | nuclear magnetic resonance spectrum |
| NSCLC | non-small cell lung cancer |
| NZW | New Zealand White |
| OAT | organic anion transporter |
| OATP | organic anion transporting polypeptide |
| OCT | organic cation transporter |
| OS | overall survival |
| osimertinib | osimertinib mesilate |
| $P_{app\ A \rightarrow B}$ | apparent permeability in apical to basolateral direction |
| paroxetine | paroxetine hydrochloride hydrate |
| PCR | polymerase chain reaction |
| PFS | progression free survival |
| P-gp | P-glycoprotein |
| PK | pharmacokinetics |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PPK | population pharmacokinetics |
| PS | performance status |
| PTK6 | protein tyrosine kinase 6 |
| PTP | press through packaging |
| QbD | quality by design |
| QD | quaque die |
| QTcF | QT interval corrected for heart rate using the Fridericia formula |
| ΔQTcF | change in QTcF from baseline |

| | |
|---|---|
| rabeprazole | rabeprazole sodium |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RET | rearranged during transfection |
| RP2D | recommended Phase II dose |
| SCID mouse | severe combined immunodeficient mouse |
| S768I | Substitution of a serine (S) at position 768 in exon 20 with an isoleucine (I) |
| SRC | proto-oncogene tyrosine-protein kinase Src |
| Study 1001 | Study A7471001 |
| Study 1002 | Study A7471002 |
| Study 1003 | Study A7471003 |
| Study 1004 | Study A7471004 |
| Study 1005 | Study A7471005 |
| Study 1006 | Study A8081006 |
| Study 1009 | Study A7471009 |
| Study 1011 | Study A7471011 |
| Study 1014 | Study A7471014 |
| Study 1015 | Study A7471015 |
| Study 1017 | Study A7471017 |
| Study 1018 | Study A7471018 |
| Study 1020 | Study A7471020 |
| Study 1021 | Study A7471021 |
| Study 1022 | Study A7471022 |
| Study 1027 | Study A7471027 |
| Study 1028 | Study A7471028 |
| Study 1031 | Study A7471031 |
| Study 1039 | Study A7471039 |
| Study 1042 | Study A7471042 |
| Study 1046 | Study A7471046 |
| Study 1047 | Study A7471047 |
| Study 1050 | Study A7471050 |
| Study 1051 | Study A7471051 |
| TK | toxicokinetics |
| T790M | Substitution of a threonine (T) at position 790 in EGFR exon 20 with a methionine (M) |
| UDPGA | uridine diphosphate glucuronic acid |
| UGT | uridine diphosphate glucuronosyl transferase |
| UM | ultra-rapid metabolizer |
| UV/VIS | ultraviolet/visible spectrum |
| VEGFR2 | vascular endothelial growth factor receptor 2 |
| $V_{max}$ | maximum rate of depolarization |
| V2 | volume of distribution of the central compartment |
| YES1 | Yamaguchi sarcoma viral oncogene homolog |