Report on the Deliberation Results

November 26, 2013

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

[Brand name]	Giotrif Tablets 20 mg, 30 mg, 40 mg, and 50 mg
[Non-proprietary name]	Afatinib Maleate (JAN*)
[Applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	November 30, 2012

[Results of deliberation]
In the meeting held on November 18, 2013, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

**Japanese Accepted Name (modified INN)*

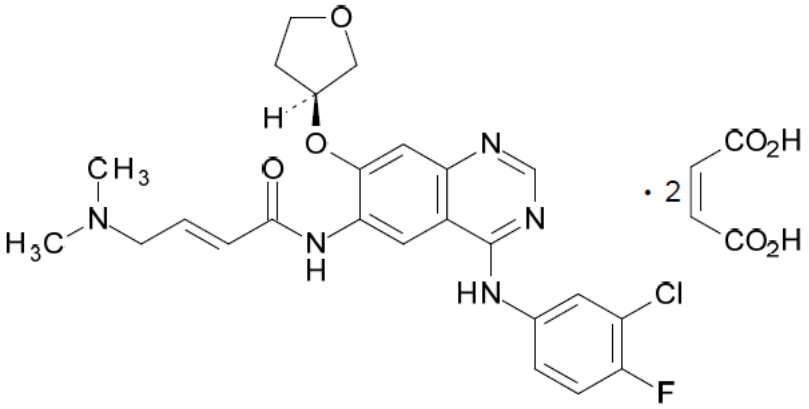
Review Report

October 31, 2013
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Giotrif Tablets 20 mg, 30 mg, 40 mg, and 50 mg
[Non-proprietary name]	Afatinib Maleate
[Name of applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	November 30, 2012
[Dosage form/Strength]	A tablet containing 29.56, 44.34, 59.12, or 73.9 mg of afatinib maleate (20, 30, 40, or 50 mg as afatinib, respectively)
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula:	$C_{24}H_{25}ClFN_5O_3 \cdot 2C_4H_4O_4$
Molecular weight:	718.08
Chemical name:	(*2E*)-*N*-[4-(3-Chloro-4-fluoroanilino)-7-{[(3*S*)-oxolan-3-yl]oxy}quinazolin-6-yl]-4-(dimethylamino)but-2-enamide dimaleate

[Items warranting special mention]
None

[Reviewing office] Office of New Drug V

Review Results

October 31, 2013

[Brand name]	Giotrif Tablets 20 mg, 30 mg, 40 mg, and 50 mg
[Non-proprietary name]	Afatinib Maleate
[Name of applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	November 30, 2012

[Results of review]
Based on the submitted data, it is concluded that the efficacy of the product in patients with epidermal growth factor receptor (*EGFR*) mutation-positive inoperable or recurrent non-small cell lung cancer (NSNLC) has been demonstrated, and its safety is acceptable in view of its observed benefits. Events such as interstitial lung disease, diarrhoea (including dehydration and renal function disorder due to diarrhoea), skin disorder, hepatic function disorder, gastrointestinal ulceration, gastrointestinal haemorrhage, left ventricular ejection fraction (LVEF) decreased, and cardiac failure, etc. need to be further investigated via post-marketing surveillance.

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

[Indication]	*EGFR* mutation-positive inoperable or recurrent non-small cell lung cancer
[Dosage and administration]	The usual adult dosage is 40 mg of afatinib orally administered once daily in the fasted state. The dose may be adjusted according to the conditions of the patient as appropriate. The dose may be increased up to 50 mg once daily.

Review Report (1)

September 19, 2013

I. Product Submitted for Registration

[Brand name]	Giotrif Tablets 20 mg, 30 mg, 40 mg, and 50 mg
[Non-proprietary name]	Afatinib Maleate
[Name of applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	November 30, 2012
[Dosage form/Strength]	A tablet containing 29.56, 44.34, 59.12, or 73.9 mg of afatinib maleate (20, 30, 40, or 50 mg as afatinib, respectively)
[Proposed indication]	*EGFR* mutation-positive inoperable or recurrent non-small cell lung cancer
[Proposed dosage and administration]	The usual adult dosage is 40 mg of afatinib orally administered once daily in the fasted state. The dose may be adjusted according to the conditions of the patient as appropriate, but should not exceed 50 mg once daily.

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

A summary of the submitted data and an outline of the review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

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

1.(1) Drug overview

The epidermal growth factor receptor (EGFR) forms its homodimer or heterodimer with human epidermal growth factor receptor 2 or 4 (HER2 or HER4, respectively), molecular of the EGFR family, and thereby activates its downstream signal transduction pathway, which regulates cell proliferation and differentiation.

Afatinib maleate (hereinafter referred to as afatinib) is a tyrosine kinase inhibitor discovered by Boehringer Ingelheim GmbH (Germany) and is considered to suppress tumor growth by inhibiting phosphorylation of tyrosine kinases (TKs) such as EGFR, HER2, and HER4. Antineoplastic drugs that have the inhibitory effect on the phosphorylation of EGFR-TK as with afatinib include gefitinib and erlotinib hydrochloride which have both been approved for the same indication of treatment of *EGFR* mutation-positive non-small cell lung cancer (NSCLC) in Japan as the proposed one for afatinib.

1.(2) Development history etc.

A foreign phase I study (Study 1200.1) was conducted in patients with advanced solid tumor from [redacted], 20[redacted] by Boehringer Ingelheim GmbH, and a phase II study (Study 1200.22) was conducted in patients with *EGFR* mutation-positive NSCLC who were chemotherapy-naive or had received 1 regimen of chemotherapy (except for EGFR TK inhibitors [EGFR-TKIs]) from [redacted], 20[redacted]. Then, a phase III study (Study 1200.32) in chemotherapy-naive patients with *EGFR* mutation-positive NSCLC was conducted from [redacted], 20[redacted] as a global clinical study involving Japan. Another phase III study (Study 1200.23) in NSCLC patients previously treated with EGFR-TKIs was conducted from [redacted], 20[redacted].

In Europe and the US, an application for afatinib using the results from Study 1200.32 as the pivotal data was submitted in [redacted], 20[redacted] by Boehringer Ingelheim GmbH and in [redacted], 20[redacted] by Boehringer Ingelheim Pharmaceuticals, Inc. (US), respectively. In the U.S, afatinib was approved in July, 2013; "GILOTRIF is indicated for the first-line treatment of patients with metastatic NSCLC whose tumors have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations as detected by an FDA-approved test. Limitation of Use: Safety and efficacy of GILOTRIF have not been established in patients whose tumors have other EGFR mutations." Afatinib is currently under review in the EU.

As of the end of August, 2013, afatinib is approved in 2 countries with the indication of *EGFR* mutation-positive NSCLC.

In Japan, a phase I/II study (Study 1200.33) in NSCLC patients who had received EGFR-TKIs was conducted from [redacted], 20[redacted], and then patient enrollment in Study 1200.32 was started in [redacted], 20[redacted].

An application for afatinib was submitted in [redacted], 20[redacted] based on the results from Study 1200.32 as the pivotal data.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

The drug substance occurs as a white to yellow-brown powder, and its description, solubility, hygroscopicity, melting point, dissociation constant, partition coefficient, and crystalline polymorphism have been determined. [redacted].

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

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

[redacted].

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

[redacted].

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

Stability studies on the drug substance are as shown in the table below. The photostability study showed that the drug substance was unstable to light.

Stability studies of the drug substance

Study type	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term testing	Commercial-scale: 3 batches	25° C	60%RH	Low-density polyethylene bag + dampproof aluminum-laminated bag (heat seal)	24 months
Accelerated testing	Commercial-scale: 3 batches	40° C	75%RH		6 months

Based on the above stability data, the retest period of 24 months has been proposed for the drug substance filled in a low-density polyethylene bag, which is packaged in a dampproof aluminum-laminated bag followed by heat sealing, and stored at room temperature. The long-term testing is planned to be continued up to [redacted] months.

2.A.(2) Drug product

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

The drug product is an immediate-release film-coated tablet containing 29.56, 44.34, 59.12, or 73.9 mg of afatinib maleate (20, 30, 40, or 50 mg as afatinib, respectively). The drug product contains lactose hydrate, microcrystalline cellulose, light anhydrous silicic acid, crospovidone, magnesium stearate, hypromellose, macrogol 400, titanium dioxide, talc, FD & C Blue No. 2 aluminum lake (not contained in 20 mg tablets), and polysorbate 80 as excipients.

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

[redacted].

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

[redacted].

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

Stability studies conducted for the drug product are as shown in the table below. For the 30 and 40 mg drug products, the study was conducted in a reduced design by bracketing. The results of photostability study showed that the drug product is unstable to light.

Stability studies of the drug product

Study type	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term testing	Commercial-scale: 3 batches*	25° C	60%RH	PTP package	36 months
Accelerated testing	Commercial-scale: 3 batches*	40° C	75%RH	PTP package	6 months

*Data from 3 batches each of the 20 and 50 mg drug products and from 1 batch each of the 30 and 40 mg drug products have been submitted.

Based on the above stability data, a shelf-life of 36 months has been proposed for the drug product when packaged with polyvinyl chloride/polyvinylidene chloride/aluminum foil (PTP), which are packed in a light-resistant aluminum pillow bag with a desiccant, and stored at room temperature.

2.B Outline of the review by PMDA

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

3. Non-clinical data

In this section, the dose and concentration of the test drug and comparator are all described on a free-base equivalent.

3.(i) Summary of pharmacology studies

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

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

3.(i).A.(1).1) Growth inhibitory effect on EGFR mutation-positive NSCLC cells (Report U[redacted]-1338)

Anchorage-independent growth inhibitory effect of afatinib and antineoplastic drugs (gefitinib, erlotinib hydrochloride [erlotinib], canertinib [unapproved in Japan]), both of which are inhibitors of TK phosphorylation of EGFR-TKIs, were investigated in human NSCLC cell lines expressing wild-type and mutant (L858R in Exon 21 [active mutant], T790M in Exon 20 [resistant mutant]) EGFR, i.e., NCI-H1666, NCI-H3255 and NCI-H1975 cells, using absorbance with a redox dye as an indicator. The IC_{50} values are as shown in the table below.

Inhibitory effects on anchorage-independent growth of human NSCLC cell lines

Cell line	Expressed EGFR	IC_{50} (nmol/L)			
		Afatinib	Gefitinib	Erlotinib	Canertinib
NCI-H1666	Wild-type	60, 37	157, 232	110, 344	198, 361
NCI-H3255	Mutant (L858R)	0.7, 0.08	4.7, 1.2	40, 31	1.2, 1.7
NCI-H1975	Mutant (L858R/T790M)	99, 116	>4000, >4000	>4000, >4000	101, 115

n = 2 (replications for each assay)

3.(i).A.(1).2) Mechanism of action

i) Phosphorylation-inhibiting effect

(a) Study using enzymes (recombinant proteins) (Report U[redacted]-1351, U[redacted]-2645, U[redacted]-1265, U[redacted]-1338)

Inhibitory effects of afatinib, gefitinib, and canertinib on phosphorylation of various TKs in EGFR, HER2 and HER4, which belong to the EGFR family, as well as vascular endothelial growth factor receptor (VEGFR)-2 were investigated by the enzyme-linked immunoassay (ELISA) with recombinant proteins or using [γ-^{33}P] ATP uptake as an indicator. The IC_{50} values are as shown in the table below. A total of 27 serine/threonine kinases were included in a similar investigation, but afatinib had no obvious effect on phosphorylation.

Inhibitory effect on phosphorylation of various TKs (recombinant proteins)

TK	IC_{50} (nmol/L)		
	Afatinib	Gefitinib	Canertinib
EGFR	0.465, 0.230	1.02, 3.91	0.307, 1.39
HER2	13.8, 28.3	1830, 416	29.8, 22.5
HER4	1.15 ± 0.24	-	-
BIRK	>100,000	>100,000	>100,000
c-Src	>4000	>100,000	1480
Lck	1720, 1990	-	-
Lyn	1527 ± 154	-	-
VEGFR-2	>100,000	>100,000	24,900
HGFR	13,000	20,600	>20,000

n = 1-4 (n = 1 or 2 for each assay; n = 3 or 4, mean ± standard error [SE])

Inhibitory effects of afatinib, gefitinib, and erlotinib on phosphorylation of wild-type and mutant EGFRs were determined by ELISA with recombinant proteins. The IC_{50} values are as shown in the table below.

Inhibitory effect on phosphorylation of EGFR TK (recombinant protein)

EGFR	IC_{50} (nmol/L)		
	Afatinib	Gefitinib	Erlotinib
Wild-type	0.99, 1.1	1.7, 3.3	-
Mutant (L858R)	0.43, 0.17	0.84, 1.4	1.2, 2.7
Mutant (L858R/T790M)	10, 11	1013, 1267	1520, 3562

n = 2 (replications for each assay)

(b) Study in cell lines (Report U[redacted]-1391, U[redacted]-1338)

Inhibitory effects of afatinib, gefitinib, and canertinib on phosphorylation of EGFR and wild-type and mutant HER2 were determined by ELISA in human squamous vulvar cancer cell line, A431, human gastric adenocarcinoma cell line, NCI-N87, human ductal carcinoma cell line, BT-474, and mouse fibroblast cell line, NIH-3T3-HER2, in which mutant HER2 (V659E [active mutant]) was forcedly expressed. The IC_{50} values are as shown in the table below.

Inhibitory effect on phosphorylation of EGFR and HER2 TKs (cell lines)

Cell line	Expressed TK		IC_{50} (nmol/L)		
			Afatinib	Gefitinib	Canertinib
A431	EGFR	Wild-type	13.4, 15.6	34.6, 15.5	22.1, 17.0
NCI-N87	HER2	Wild-type	75.2 ± 20.4	541, 740	288, 211
BT-474		Wild-type	52.1 ± 12.3	3710, 3600	184, 87.6
NIH-3T3-HER2		Mutant (V659E)	70.9, 134	2000 ± 245.3	85.9 ± 9.5

n = 2 or 3 (n = 2 for each assay; n = 3, mean ± SE)

Inhibitory effects of afatinib, gefitinib, erlotinib, and canertinib on phosphorylation of wild-type and mutant EGFRs were determined in NCI-H1666, NCI-H3255, and NCI-H1975 cell lines by ELISA. The IC_{50} values are as shown in the table below.

Inhibitory effect on phosphorylation of EGFR TK (cell line)

Cell line	Expressed EGFR	IC_{50} (nmol/L)			
		Afatinib	Gefitinib	Erlotinib	Canertinib
NCI-H1666	Wild-type	6.9, 12	72, 40	87, 244	127, 132
NCI-H3255	Mutant (L858R)	5.9, 5.7	10.5, 9.2	52, 95	5, 4.5
NCI-H1975	Mutant (L858R/T790M)	93, 61	>4000, >4000	>4000, >4000	79, 88

n = 2 (replications for each assay)

(c) Study on duration of inhibitory effect on phosphorylation (Report U[redacted]-1264, U[redacted]-1086)
Afatinib was molecularly designed to inhibit phosphorylation of these TKs for an extended period by covalently binding to EGFR and HER2. The X-ray crystallography has demonstrated that afatinib covalently binds to cysteine residue 797 in EGFR.

The duration in which afatinib and gefitinib inhibited phosphorylation of EGFR was determined in A431 cell line. At 0, 8, 24, and 48 hours after treatment with each drug, epidermal growth factor (EGF) was added to A431 cell line for stimulation, and the phosphorylation status of EGFR was calculated by ELISA (percentage of EGFR [%] phosphorylated by the investigational drug to that by the control [vehicle] [100%], the table below).

Duration of inhibitory effect on EGFR phosphorylation (percentage of EGFR [%] phosphorylated by the investigational drug to that by the control [vehicle])

Time between the drug treatment and EGF stimulation	0 hour	8 hours	24 hours	48 hours
Afatinib	0.44 ± 0.08	13 ± 8.3	47 ± 7.1	85 ± 12
Gefitinib	3.1 ± 0.30	129 ± 14	99 ± 11	139 ± 6.0

n = 5 or 6 (mean ± SE)

According to above results, gefitinib no longer inhibited EGFR phosphorylation at 8 hours after the drug treatment, while afatinib still inhibited it even after 8 hours. The applicant explained that gefitinib is considered not to bind to EGFR covalently due to the absence of reactive Michael acceptor group, while afatinib has a Michael acceptor group and can covalently bind to EGFR, thus continuously inhibited EGFR phosphorylation for an extended period.

ii) Growth inhibitory effect on various tumor cell lines (Report U[redacted]-1391, U[redacted]-1702, U[redacted]-1534, U[redacted]-1660, U[redacted]-1703, U[redacted]-1614, U[redacted]-2532, U[redacted]-1301, U[redacted]-1454, U[redacted]-1455, U[redacted]-1342, U[redacted]-1940, U[redacted]-1036, U[redacted]-2392, U[redacted]-2665, U[redacted]-2147)

***In vitro*:**

- The growth inhibitory effect of afatinib on NCI-N87 and BT-474 cell lines was investigated. The IC_{50} values were 5.18 ± 0.80 and 17.3 ± 3.38 nmol/L, respectively.
- The growth inhibitory effect of concomitant of afatinib with radiation on human head and neck squamous cell carcinoma cell line, FaDu, was enhanced, compared with that of radiation alone.

***In vivo*:**

- Afatinib inhibited the tumor growth in athymic (nude) mice subcutaneously implanted with A431, NCI-N87, FaDu, and human ovarian cancer cell line, SKOV-3, as well as human breast cancer cell lines, SUM-149, MDA-MB-453, MCF-7, and SUM-190.
- [redacted]

[redacted].

- The combination therapy of afatinib and radiation enhanced the tumor growth inhibitory effect in nude mice subcutaneously implanted with FaDu cell line, compared with afatinib or radiation alone.

3.(i).A.(2) Secondary pharmacodynamics (Report U[redacted]-1083)

Effects of afatinib on binding of radiolabeled ligands to 50 kinds of receptors, transporters and ion channels were investigated. Receptors to which binding of the ligand was inhibited by afatinib at 5 μmol/L by ≥50% included histamine H_2 receptor, muscarinic acetylcholine M_1 receptor, and cholecystokinin receptor, and their inhibition rate was 68%, 78%, and 51%, respectively.

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

3.(i).A.(3).1) Effects on the central nervous system (Report U[redacted]-1858, U[redacted]-1619 [non-GLP studies, Reference data])

Following a single oral dose of afatinib (4, 8.5, 18 mg/kg) to rats (n=4/sex/group), effects of afatinib on the clinical signs, body temperature, and locomotor activity were investigated. As a result, no effects of afatinib were observed.

Following a single oral dose of afatinib (30, 100, 300 mg/kg) to male mice (n=6/group), the effects on the clinical signs and body temperature were investigated. As a result, although decreased rectal temperature was observed in the 30 mg/kg group compared with that in the control (vehicle) group, no effect was observed in either the 100 or 300 mg/kg group. The applicant explained that there were no findings that may raise issues in clinical use. Afatinib had no effects on the clinical signs or behavior.

Following a single oral dose of afatinib (30, 100, 300 mg/kg) to male mice (n=7/group), the effects on nocturnal locomotor activity were investigated. As a result, no effects of afatinib were observed.

3.(i).A.(3).2) Effects on the cardiovascular and respiratory systems

i) Effects on the human ether-a-go-go-related gene (hERG) current (Report U[redacted]-1580 [non-GLP studies, Reference data])

Effects of afatinib (0.1, 1, 3, 10 μmol/L) on hERG potassium current were investigated in human embryonic kidney (HEK) 293 cell line expressing hERG by whole-cell patch clamping. As a result, the IC_{50} value of afatinib was 2.4 μmol/L.

ii) Effects on the cardiovascular and respiratory systems (Report U[redacted]-1580 [non-GLP studies, Reference data], U[redacted]-1311 [non-GLP studies, Reference data], U[redacted]-1774, U[redacted]-1859, U[redacted]-1467 [non-GLP studies, Reference data])

Effects of afatinib (0.1-10 μmol/L) on myocardial action potential (AP) were investigated in ventricular papillary muscles isolated from guinea pigs. The parameters investigated under stimulation at 0.33 Hz included the resting membrane potential, maximum rate of rise, AP overshoot, AP amplitude, as well as AP durations at 10%, 30%, and 90% of repolarization (APD_{10}, APD_{30}, APD_{90}). As a result, no effects of afatinib were observed.

Male pigs (n=4/group) received afatinib by intravenous bolus administration at doses of 0.2, 0.665, and 2 mg/kg in a dose-escalation manner and then by continuous intravenous infusion at a dose of 6.65 or 20 mg/kg to investigate the effects on the left ventricular pressure (LVP), systolic and diastolic arterial pressure (SAP, DAP), cardiac contractility using the maximum change in left ventricular pressure over time as an indicator, heart rate (HR), and electrocardiogram (ECG) parameters (PR interval, QRS duration, QT interval). In the 6.65 and 20 mg/kg groups, although a decreasing trend and remarkable decrease in cardiac contractility, respectively, were observed when compared with the control (vehicle), C_{max} at these doses were 1200 and 7110 nmol/L,

respectively, which were 7.6 and 45 times, higher than C_{max} in the clinical use, respectively. The applicant explained that such findings may not raise issues in the clinical use.

In a repeat-dose toxicity study in minipigs (n=4/sex/group), afatinib (1, 2.45, 6 mg/kg) was orally administered for 4 weeks to investigate the effects on the ECG parameters. As a result, although increased heart rate and shortened QT interval were observed in animals treated with afatinib, these findings were not observed in either 13-week or 52-week oral dose studies in minipigs. The applicant, therefore, explained that these findings may not raise issues in clinical use [see "3.(iii).A.(2).6) Four-week oral dose study in minipigs"].

Following a single oral dose of afatinib (10, 30, 100 mg/kg) to male rats (n=8/group), the effects on the SAP, heart rate, respiratory rate, and tidal volume were investigated. As a result, SAP and heart rate transiently and slightly increased in animals treated with afatinib at a dose of 100 mg/kg. However, the dose was ≥19 times the amount of the clinical dose. The applicant, therefore, explained that these findings may not raise issues in clinical use. No effects of afatinib were observed either on body temperature and locomotor activity additionally investigated.

Following a single oral dose of afatinib (4, 8.5, 18 mg/kg) to rats (n=8/sex/group), the effects on the respiratory rate, tidal volume, and minute ventilation were investigated. As a result, decreased minute ventilation was observed. However, it was observed only at 4 hours after dosing but not at other measurement time points of 1, 2, 6, and 24 hours post-dose and developed with statistically insignificant decrease in RR and VT. The applicant explained that the finding may not raise issues in clinical use.

iii) Effects on the renal and hepatic functions (Report U[redacted]-1490 [non-GLP studies, Reference data])

Following a single oral dose of afatinib (30, 100, 300 mg/kg) to rats (n=5/sex/group), the effects on the renal functions were investigated. As a result, urine glucose excretion increased at all doses of afatinib compared with the control (vehicle), and at a dose of 300 mg/kg, increase in urine volume associated with increased osmolarity as well as increase in urine aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) activities were observed. The applicant explained that these findings may not raise issues in clinical use, because the dose of 300 mg/kg would be 58 times higher than the clinical dose, and the increased urine glucose excretion observed at all doses was not observed in the other toxicity studies.

Following a single oral dose of afatinib (30, 100, 300 mg/kg) to rats (n=5/sex/group), the effects on hepatic functions were investigated. As a result, increased serum glucose and slightly increased serum AST and alanine aminotransferase (ALT) activities were observed at a dose of 300 mg/kg. However, these findings were observed only at doses ≥58 times higher than the clinical dose, and the applicant explained that these findings may not raise issues in clinical use.

iv) Effects on the gastrointestinal system (Report U[redacted]-1487 [non-GLP studies, Reference data], U[redacted]-1489 [non-GLP studies, Reference data], U[redacted]-1488 [non-GLP studies, Reference data])

Following a single oral dose of afatinib (30, 100, 300 mg/kg) to rats (n=5/sex/group), the effects on the gastrointestinal system were investigated. As a result, gastric emptying decreased at doses of 100 and 300 mg/kg in a dose-dependent manner. The applicant explained that the finding may not raise issues in clinical use, because it developed only at the dose ≥19 times higher than the clinical dose.

Following a single intraduodenal dose of afatinib (30, 100, 300 mg/kg) to male rats (n=6-8/group), the effects on the gastric secretion volume were investigated. As a result, the gastric secretion volume decreased in a dose-dependent manner, and a statistically significant difference in this

parameter was observed at a dose of 300 mg/kg compared with the control (vehicle). It developed only at the dose ≥58 times higher than the clinical dose and the applicant explained that the finding may not raise issues in clinical use.

Following a single oral dose of afatinib (30, 100, 300 mg/kg) to rats (5/sex/group), the effects on the gastrointestinal propulsion were investigated. As a result, gastrointestinal propulsion decreased in a dose-dependent manner, and a statistically significant difference in this parameter was observed at a dose of 300 mg/kg compared with the control (vehicle). It developed only at the dose ≥58 times higher than the clinical dose and the applicant explained that the finding may not raise issues in clinical use.

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

Based on the submitted data and the following investigations, PMDA has concluded that the efficacy of afatinib in *EGFR* mutation-positive NSCLC can be expected.

Mechanism of action and features of afatinib

The applicant explained the mechanism of action and features of afatinib as follows:
Compared with the existing EGFR-TKIs (gefitinib, erlotinib) which selectively and reversibly inhibit TK of wild-type and active mutant (L858R, etc.) EGFR, afatinib differs in the following 2 points and therefore may be used as a useful option for NSCLC patients previously treated with the existing EGFR-TKIs.

- Afatinib inhibits TKs of wild-type and active mutant (L858R, etc.) EGFR, mutant EGFR with the second mutation (T790M) resistant to the existing EGFR-TKIs, and HER2 and HER4 which belong to the EGFR family, at a pharmacologically appropriate concentration, consequently interfering with the oncogenic signal transduction mediated by homo and heterodimer formation of the EGFR family [see "3.(i).A.(1).2).i).(a) Study using enzymes (recombinant proteins)"].

- It has been reported that afatinib, which has a Michael acceptor group, covalently and irreversibly binds to cysteine residue in the ATP binding site of the above EGFR, HER2, and HER4 (*J Pharmacol Exp Ther*. 2012;343:342-50), and the inhibitory activity on TK is maintained for an extended time even after the plasma afatinib concentration decreased to below the lower limit of the its inhibitory effect [see "3.(i).A.(1).2).i).(c) Study on duration of inhibitory effect on phosphorylation"].

The proposed indication of afatinib is for "*EGFR* mutation-positive NSCLC" without any limitation to specific gene mutation types, but the submitted non-clinical pharmacology data only covered L858R and T790M mutations. PMDA asked the applicant to explain the efficacy of afatinib in NSCLC with *EGFR* mutations other than L858R and T790M.

The applicant responded as follows:
Of *EGFR* mutations that occurred in NSCLC, approximately 90% were 2 active mutations, "Del 19" and "L858R." The former is a consequence of in-frame deletion of E746 to A750 in Exon 19, and the latter is a point mutation in Exon 21. Although data on Del 19 EGFR were not included in the submitted data, the efficacy of afatinib in this mutant EGFR has been demonstrated by investigation in Del 19 EGFR-transfected Ba/F3 mouse lymphocytes (*Oncogene*. 2008;27:4702-11).

Many of the remaining 10% *EGFR* mutation-positive NSCLC patients have been reported to have mutations within the TK domain encoded by Exons 18 to 21 (*Nat Rev Cancer*. 2007;7:169-81). Afatinib inhibited the TK of various mutant *EGFR*s although they were different in terms of (a)

the extent of involvement in the cancer progression, and (b) the sensitivity to afatinib (in-house data).

As described above, the applicant determined that afatinib inhibited TKs of most EGFR mutations including L858R.

PMDA considers as follows:
PMDA largely accepted the applicant's explanation about the mechanism of action and features of afatinib.

It is, however, unclear to what extent the inhibitory effect of afatinib on TK of T790M EGFR could contribute to the clinical efficacy in consideration that a foreign phase II/III study (Study 1200.23) in NSCLC patients previously treated with EGFR-TKIs did not verify a statistically significant extension of the overall survival, the primary endpoint, in the patients treated with afatinib [see "4.(iii).B.(4).3) Patients previously treated with EGFR-TKIs"]. Therefore, it is inappropriate for the applicant to explain that afatinib could be a useful option even for NSCLC patients previously treated with existing EGFR-TKI, only based on the non-clinical pharmacology data.

In addition, the global phase III study (Study 1200.32), the pivotal clinical study in this regulatory submission, included not only NSCLC patients with L858R and Del 19 *EGFR* mutations but also patients with less common *EGFR* mutations. However, it is difficult to discuss the efficacy of afatinib in NSCLC patients with less common *EGFR* mutations only based on the clinical data because the number of the applicable patients was limited [see "4.(iii).B.(4).5) *EGFR* mutation types"]. Relationships between the *EGFR* mutation types and efficacy of afatinib would be useful information to select the patients for whom afatinib could be recommended. PMDA, therefore, considers that it is necessary to collect the relevant information and appropriately provide the information to healthcare providers in the medical practices when new information becomes available.

3.(ii) Summary of pharmacokinetic studies

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

Pharmacokinetics (PK) of afatinib in animals was evaluated in mice, rats, rabbits, and minipigs. Investigation of afatinib in terms of plasma protein binding, drug-metabolizing enzymes, and transporters was implemented with human or animal biological samples. Afatinib was measured by LC/MS/MS method with the lower limit of quantitation of 1.0 to 2.0 nmol/L.

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

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

Following a single intravenous or oral administration of ^{14}C-labeled afatinib (^{14}C-afatinib) to male rats at doses of 4 or 8 mg/kg, the plasma afatinib concentrations were determined (the table below). The half-life ($t_{1/2}$) calculated from the plasma radioactivities following the intravenous and oral administrations were 24.4 and 22.1 hours, respectively, which were longer than $t_{1/2}$ from the plasma afatinib concentrations (5.22 and 4.54 hours following the intravenous and oral administrations, respectively). For the reason for the concerned result, the applicant explained that afatinib is covalently bound to the plasma protein to form its covalent adduct with plasma protein [see "3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells"] and then released gradually from the plasma protein followed by the efflux, and thus, $t_{1/2}$ calculated from the plasma radioactivities were longer than that from the plasma afatinib concentrations.

Following a single intravenous or oral dose of 2 mg/kg of afatinib to male and female minipigs, the plasma afatinib concentrations were determined (the table below). The applicant claimed that the PK parameters of afatinib were similar between males and females, although the number of

animals investigated was limited.

Following a single oral dose of 1.95 mg/kg of ^{14}C-afatinib to female rabbits, the plasma afatinib concentrations were determined (the table below). The mean residence time of afatinib was 4.31 hours. $t_{1/2}$ (156 hours) calculated from the plasma radioactivity was longer than that (2.6 hours) from the plasma afatinib concentration. The applicant explained that in addition to formation of the covalent adduct of afatinib with plasma protein, formation of slowly eliminated rabbit-specific metabolites (m3, m4) may be involved in longer $t_{1/2}$ from the plasma radioactivity [see "3.(ii).A.(3).2) *In vivo* metabolism"] and this is the reason for the obtained results.

PK parameters of afatinib (various animal species, single intravenous or oral dose)

Animal species	Route of administration	Dose (mg/kg)	Sex	n	C_{max} (nmol/L)	t_{max}*2 (h)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μmol·h/L)	CL (mL/min/kg)	V_{ss} (L/kg)	F (%)
Rat	Intravenous	4*1	Male	4	1620 (25.3)	-	5.22 (6.69)	2.92 (19.7)	55.3 (22.0)	16.2 (19.6)	-
	Oral	8*1	Male	4	397 (31.2)	4 (2, 4)	4.54 (5.1)	2.60 (19.8)	108*3 (19.9)	43.6*4 (25.9)	44.5
Minipig	Intravenous	2	Male	2	1250, 1170	0.083	17.1, 14.7	2.03, 2.60	33.8, 26.5	13.4, 9.7	-
		2	Female	2	1060, 1260	0.083	10.9, 12.5	1.60, 1.78	43.0, 38.5	14.4, 12.3	-
	Oral	2	Male	2	38.9, 34.0	4, 4	15.9, 11.2	0.22, 0.20	306, 342*4	222, 234*5	11.0, 7.7
		2	Female	2	20.1, 23.5	4, 4	8.3, 7.6	0.29, 0.14	238, 479*4	185, 248*5	18.1, 8.0
Rabbit	Oral	1.95*1	Female	3	34.0 (42.4)	1 (0.5, 1)	2.6 (14.6)	0.178 (59.1)	0.467 (52.0)	-	-

Arithmetic mean (coefficient of variation %), *1: ^{14}C-afatinib, *2: Median (range), *3: CL/F, *4: V_{ss}/F

3.(ii).A.(1).2) Repeat-dose

Following repeated oral administrations of afatinib to male and female mice at a dose of 4 to 36 mg/kg/day for 4 or 13 weeks, the plasma afatinib concentrations were determined. The PK parameters following the 13-week repeated doses are as shown in the table below. C_{max} and AUC_{0-24} of afatinib increased more than dose-proportionally in either repeat-dose study. In the 13-week repeat-dose study in females and males, the ratio of C_{max} on Day 89 (Day 64 at a dose of 36 mg/kg/day) to that on Day 1 was 0.700 and 0.912, respectively, and the ratio of AUC_{0-24} was 0.997 and 0.986, respectively; neither sex-related difference nor accumulation due to the repeated doses were observed in any repeat-dose study.

PK parameters of afatinib (male and female mice, repeated oral dose)

Measurement time point	Dose (mg/kg)	C_{max} (nmol/L)		AUC_{0-24} (nmol·h/L)		t_{max}*1(h)	
		Male	Female	Male	Female	Male	Female
Day 1	9	267	333	1660	1920	2	2
	18	670	1070	5360	6100	2	2
	27	1120	1600	8650	9190	2	2
	36	2220	2360	21,600	18,300	2	2
Day 89*2	9	258	243	1560	1670	4	2
	18	632	671	4550	5900	2	4
	27	1030	1050	9500	9270	4	1
	36	1840	1910	23,200	21,300	4	2

Arithmetic mean, n = 3-4/measurement time point (blood samples drawn from different mice at each measurement time point), *1: Median, *2: Day 64 at a dose of 36 mg/kg/day

Following repeated oral administrations of afatinib to male and female rats at a dose of 1.5 to 18 mg/kg/day for 4, 13, or 26 weeks, the plasma afatinib concentrations were determined. PK parameters following 26-week repeated doses are as shown in the table below. C_{max} and AUC_{0-24} of afatinib increased more than dose-proportionally in either repeat-dose study. In the 4-week repeat-dose study, neither sex-related difference nor accumulation due to the repeated doses were observed, while in the 26-week repeat-dose study in females and males, C_{max} increased 2.75 and 7.05 times, respectively, and AUC_{0-24} increased 2.48 and 6.03 times, respectively, from Day 1 to

Day 177; the accumulation was higher in males than in females. The applicant explained that the percentage of the metabolites in the circulating blood was higher in males than in females [see "3.(ii).A.(3).2) *In vivo* metabolism"], and the plasma concentration of afatinib could have reached the saturation in the process of its metabolism [see "3.(ii).A.(3).2) *In vivo* metabolism"] and this is the reason why the accumulation between sexes were different.

PK parameters of afatinib (male and female rats, repeated oral doses)

Measurement time point	Dose (mg/kg)	C_{max} (nmol/L)		AUC_{0-24} (nmol·h/L)		t_{max}*(h)	
		Male	Female	Male	Female	Male	Female
Day 1	1.5	7.36 (41.4)	6.64 (27.1)	62.2 (43.1)	51.6 (23.6)	4 (2, 4)	3 (2, 4)
	3	15.7 (58.4)	20.6 (41.0)	174 (75.7)	143 (67.7)	4 (2, 8)	2 (2, 4)
	6	56.4 (41.0)	60.4 (38.3)	568 (31.8)	473 (26.0)	4 (4, 8)	2 (1, 4)
Day 177	1.5	37.9 (21.4)	17.2 (50.7)	303 (23.0)	97.7 (45.4)	3 (2, 4)	2 (2, 4)
	3	102 (33.5)	49.6 (46.1)	873 (31.7)	355 (68.7)	4 (2, 4)	2 (1, 2)
	6	345 (49.8)	159 (35.4)	3500 (49.9)	1390 (39.1)	2 (1, 4)	2 (1, 4)

Arithmetic mean (coefficient of variation %), n = 6, *: Median (range)

Following repeated oral administrations of afatinib to male and female minipigs at a dose of 0.5 to 10 mg/kg/day for 2, 4, 13, or 52 weeks, the plasma afatinib concentrations were determined. PK parameters following 52-week repeated doses are as shown in the table below. C_{max} and AUC_{0-24} of afatinib increased more than dose-proportionally in 2-, 4- and 13-week repeat-dose studies. In the 52-week repeat-dose study, no remarkable sex-related difference was observed in either C_{max} or AUC_{0-24} of afatinib, and these parameters at a dose of 1.5 mg/kg increased dose-proportionally compared with those at a dose of 0.5 mg/kg, but those at a dose of 5 mg/kg increased more than dose-proportionally. In the 52-week repeat-dose study in females and males, the ratio of C_{max} on Day 361 to that on Day 1 was 0.816 and 0.838, respectively, and the ratio of AUC_{0-24} was 1.15 and 1.20, respectively; neither sex-related difference nor accumulation due to the repeated doses were observed in any repeat-dose study.

PK parameters of afatinib (male and female minipigs, repeated oral doses)

Measurement time point	Dose (mg/kg)	C_{max} (nmol/L)		AUC_{0-24} (nmol·h/L)		t_{max}*1(h)	
		Male	Female	Male	Female	Male	Female
Day 1	0.5	3.37 ± 1.26	5.27 ± 3.36	26.1 ± 6.72	35.6 ± 21.7	4 (2, 4)	4 (4, 4)
	1.5	30.4 ± 19.1	12.6 ± 5.04	194 ± 130	91.0 ± 31.3	4 (4, 4)	4 (4, 4)
	5*2	92.8 ± 11.5	81.3 ± 19.0	792 ± 142	729 ± 178	4 (4, 4)	4 (4, 4)
Day 183	0.5	3.54 ± 2.47	4.96 ± 3.35	31.8 ± 14.6	41.7 ± 23.3	4 (4, 4)	4 (4, 4)
	1.5	19.4 ± 20.7	8.11 ± 3.63	174 ± 134	77.7 ± 27.0	4 (2, 4)	4 (4, 4)
	5	122 ± 33.1	108 ± 56.2	1300 ± 378	1170 ± 487	4 (2, 4)	4 (2, 8)
Day 361	0.5	2.35 ± 0.65	1.34 ± 0.21	26.2 ± 4.43	19.5 ± 3.46	4 (4, 4)	4 (4, 4)
	1.5	17.0 ± 19.2	6.05 ± 2.51	165 ± 159	82.9 ± 32.5	4 (2, 4)	4 (2, 4)
	5*2	98.7 ± 37.4	80.5 ± 51.9	1180 ± 466	966 ± 537	4 (2, 4)	4 (2, 4)

Arithmetic mean ± standard deviation (SD), n = 4, *1: Median (range), *2: n = 8

The applicant explained that the percentage of the metabolites in the circulating blood was higher in rats than in minipigs and mice [see "3.(ii).A.(3).2) *In vivo* metabolism"], and the plasma concentration of afatinib might have reached saturation in the process of its metabolism, and this is the reason why the accumulation was observed only in rats.

3.(ii).A.(1).3) *In vitro* membrane permeability

The human gastrointestinal membrane permeability of afatinib was investigated in human colon cancer cell line Caco-2. The mean ± standard deviation (SD) of the apparent permeability coefficients of afatinib from the apicolateral surface to the basolateral surface ($P_{app\ A\rightarrow B}$) at the concentrations of 3 and 300 μmol/L were 20.8 ± 5.62 and 121 ± 34.3 nm/sec, respectively. The applicant considered the passive permeability of afatinib to be high in comparison with $P_{app\ A\rightarrow B}$ of mannitol, atenolol, and propanol (2.62, 7.95, and 266 nm/sec, respectively). The mean ± SD of the apparent permeability coefficient of afatinib from the basolateral surface to the apicolateral surface ($P_{app\ B\rightarrow A}$) at the concentrations of 3 and 300 μmol/L were 86.9 ± 8.27 and 69.9 ± 7.95 nm/sec, respectively. At afatinib concentration of 3 μmol/L, $P_{app\ B\rightarrow A}$ was higher than $P_{app\ A\rightarrow B}$, while at 300 μmol/L, $P_{app\ B\rightarrow A}$ decreased. The applicant explained that this implicates an active transport involved in the membrane permeability of afatinib, and transporters may be saturated with afatinib when its concentration increased.

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

3.(ii).A.(2).1) Tissue distribution

Following a single intravenous or oral administration of ^{14}C-afatinib at 4 mg/kg and 8 mg/kg, respectively, to 4 male albino rats, and a single intravenous administration of 4 mg/kg ^{14}C-afatinib to 3 male pigmented rats, the radioactivity tissue distribution was investigated by quantitative whole-body autoradiography. In the albino rats, the radioactivity was quickly distributed to various tissues, but the radioactivity concentrations in the brain at 4 hours after the intravenous and oral administration were 64 and 40 nmol/kg tissue, respectively, which were lower than the blood radioactivity concentrations (2306 and 1474 nmol/kg following the intravenous and oral administration, respectively). Based on the above result, the applicant explained that the permeability of afatinib across the blood-brain barrier may not be high. The radioactivity distribution in pigmented rats was similar to that in albino rats after dosing of intravenous administration, but in pigmented rats, the radioactivity concentration was found to be high in the retina in the eyes (77.7 mmol/kg tissue), the melanin-containing tissue, at 24 hours after intravenous administration.

Following a single oral dose of 2.46 mg/kg ^{14}C-afatinib to minipigs (n=1/sex/group), the radioactivity concentrations at 168 hours post-dose were found to be high in the liver (953 and 1180 nmol/g in the female and male, respectively), in the spleen (1020 and 619 nmol/g in the female and male, respectively), and testis (1460 nmol/g in the male). The applicant explained that afatinib may bind to melanin as suggested by the remarkably high radioactivity concentration in the eyes.

Following repeated oral doses of 3 mg/kg ^{14}C-afatinib to 15 male albino rats for 13 days, the total radioactivity recovered from the liver and kidneys accounted for approximately 0.2% and 0.053%, respectively, of the total radioactivity dose. The blood, plasma, and tissue radioactivity concentrations increased with the increasing repeated doses, suggesting that the radioactivity concentration did not reach the steady state on Day 13. The ratio of the concentration at 312 hours post-dose to that at 24 hours post-dose in the skin, blood, heart, muscle, liver, testis, bone marrow, kidneys, lungs, plasma, fat, and brain was 23.8, 16.1, 14.6, 14.5, 14.2, 13.4, 11.9, 11.9, 10.9, 7.9, 7.0, and 6.7, respectively.

3.(ii).A.(2).2) Plasma protein binding and distribution in blood cells

The mean plasma protein binding rates of ^{14}C-afatinib in plasma samples from rabbits, rats, minipigs, NMRI mice, CD-1 mice, and humans (approximately 50-500 nmol/L, except for 126 nmol/L in plasma samples from NMRI mice and approximately 30 to 4500 nmol/L in plasma samples from CD-1 mice) were 91.8%, 92.6%, 92.9%, 94.3%, 94.6%, and 95%, respectively. The

plasma protein binding rates neither differed among animal species nor clearly depended on the concentration.

The plasma samples from rats, minipigs, and humans were incubated with ^{14}C-afatinib at 37°C for 24 hours and then treated with acetonitrile/acetic acid to precipitate the protein. Based on the results, the applicant explained that 28.5%, 48.1%, and 27.1% of the total radioactivity may covalently bind to plasma protein. When human serum albumin (45 g/L) and α1-acid glycoprotein (0.1, 1, 10 g/L) were incubated with afatinib (150 nmol/L), their binding rates were 79.6% and 11.6% to 90.6%, respectively. The binding rate increased with the increasing α1-acid glycoprotein concentration. In consideration of the binding rate at 10 g/L and clinically possible variation range of the α1-acid glycoprotein concentration (0.6-1.2 g/L), the applicant explained that the variation of α1-acid glycoprotein concentration was unlikely to affect the efficacy and safety of afatinib.

When blood samples from rats, minipigs, and humans were incubated with ^{14}C-afatinib (138 nmol/L) for 2 minutes and 3 hours, the ratios of radioactivity in the blood cells to that in the plasma were 4.95 and 6.38 in rat blood samples, 5.07 and 2.98 in minipig blood samples, and 2.21 and 1.02 in human blood samples, respectively. The applicant, therefore, explained that afatinib would be mainly distributed into blood cells.

3.(ii).A.(2).3) Placental transfer and fetal transfer

Following a single oral dose of 12 mg/kg ^{14}C-afatinib to 5 rats each on Gestation days 12 and 19, the placental radioactivity concentration was approximately 2 times higher than the blood radioactivity concentration, but in fetuses, the radioactivity was observed at a low concentration only in the liver. The applicant explained that placental transfer of afatinib may be low because afatinib is suggested to be a substrate of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) [see "3.(ii).A.(5).3) Transporters"].

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

3.(ii).A.(3).1) *In vitro* metabolism

^{14}C-afatinib at 50 μmol/L was incubated with human hepatic microsome at 37°C for 15 to 90 minutes to investigate the metabolites of afatinib. Following the incubation in the presence of nicotinamide adenine dinucleotide phosphate (NADPH) for 90 minutes, m10 (N-demethylated metabolite, 5.9% of the total radioactivity) and m15 (N-oxidized metabolite, 11.1% of the total radioactivity) were detected as major metabolites. The covalent binding to microsome protein (1.0 mg/mL) in the presence and absence of NADPH was 4.4% and 4.7%, respectively. Based on the result, the applicant explained that NADPH may not be involved in formation of a covalent adduct with microsome protein.

Following incubation of ^{14}C-afatinib at 50 μmol/L with human hepatic cytosol at 37°C for 15 to 90 minutes, no metabolites were detected. Based on the result, the applicant explained that cytosolic enzymes may not be involved in the metabolism of afatinib.

Following incubation of afatinib at 5 μmol/L with sandwich-cultured human hepatocytes at 37°C for 24 hours, m15 (47.8% of the detected metabolites), conjugates formed by Michael addition reaction (m2, m3, m4, etc.; 41.6%), and oxidative metabolites (m10, m14, m18, m20; 9.0%) except for m15 were detected as the metabolites.

^{14}C-afatinib was incubated with recombinant human CYP isoforms (CYP1A1, 2D6, 3A4) and recombinant flavin-containing mono-oxygenase (FMO) isoforms (FMO3, 5) to investigate enzymes involved in the metabolism of afatinib. Based on the results, the applicant explained that afatinib may be metabolized to m10 by CYP3A4 and to m15 by FMO3.

In the presence of a CYP inhibitor (furafylline, sulphaphenazole, quinidine, ketoconazole) of CYP

isoform (CYP1A2, 2C9, 2D6, 3A4), ^{14}C-afatinib at 50 μmol/L was incubated with human hepatic microsome at 37°C for 30 minutes. In the presence of the CYP3A4 inhibitor at 5 μmol/L, the metabolism of afatinib to m10 was decreased to 21.3% of that in the absence of the inhibitor. On the other hand, in the presence of the CYP1A2, 2C9 and 2D6 inhibitors, the metabolism of afatinib to m10 remained unchanged. Based on the results, the applicant explained that CYP3A4 may be involved in the metabolism of afatinib to m10.

Based on the above data, the applicant explained that the above results suggested that CYP3A4 is involved in the metabolism of afatinib, but implication of its oxidative metabolism is low compared to the FMO3-mediated oxidative metabolism and conjugate formation by Michael addition reaction.

3.(ii).A.(3).2) *In vivo* metabolism

Following a single oral dose of 8.5 mg/kg ^{14}C-afatinib to male and female mice, the metabolites in the plasma, urine, and feces were investigated. In the plasma at 4 hours post-dose, unchanged afatinib (82.9% and 80.3% of the plasma radioactivity in females and males, respectively) were mainly found, and the metabolites detected in the plasma included m2 (glutathione conjugate), m6 (O-dealkylated metabolite), m10 (N-demethylated metabolite), m14 (deamidated metabolite), and m24 (glucuronate conjugate), which were found in small amounts. Until 24 hours after dosing, the dosed radioactivity excreted in urine in females and males were 1.0% and 1.3%, respectively. Until 48 hours after dosing, 94.7% was excreted in feces in both males and females. In the feces until 48 hours after dosing, unchanged afatinib (60.3% and 60.0% of the dosed radioactivity in females and males, respectively) was mainly found, and the metabolites detected in the feces included m30 (sulfate conjugate; 32.5%, 31.4%) as well as m6 and m31 (structure unknown), which were found in small amounts. Following a single intraduodenal administration of 8.5 mg/kg of ^{14}C-afatinib to female and male mice, the biliary excretion rate until 6 hours after dosing was 8.8% and 9.1%, respectively.

Following a single oral dose of 8 mg/kg ^{14}C-afatinib to male and female rats, the metabolites in the plasma and urine were investigated. In the plasma at 4 hours post-dose, unchanged afatinib (84.6% and 63.4% of the plasma radioactivity in females and males, respectively) were mainly found. As the metabolites, m2, m12 (structure unknown), m13 (N-acetylcysteine conjugate), and m14 were detected in male rats, and m12 was detected in female rats. Although the reason for the sex-related differences in the metabolites remains unknown, the applicant explained that CYP isoforms reported to have sex-related differences in their expression (CYP2C11, 2C12, 3A2, etc.; *Drug Metab Rev*. 1998;30:441-98) may be involved in the metabolism of afatinib. Until 24 hours after dosing, 2.1% of the dosed radioactivity was excreted in urine in male rats. Following a single intraduodenal administration of 8 mg/kg of ^{14}C-afatinib to male and female rats, in the bile until 6 hours, unchanged afatinib (5.9% of the dosed radioactivity) was mainly found, and the metabolites detected included m1 (peptide adduct), m2, m3, m4, m5 (peptide adduct), m6, m8 (structure unknown), m9 (N-methylated metabolite), and m10, which were found in small amounts. The applicant explained that the metabolites in feces were not investigated for the following reasons: the urine excretion rates following the intravenous and oral administrations (4.8% and 2.1% of the dosed radioactivity, respectively) suggested that only approximately 50% of afatinib would be absorbed when orally administered, and the biliary samples were available.

Following a single oral dose of 2.46 mg/kg ^{14}C-afatinib to male and female minipigs, the metabolites in the plasma, urine, feces, and bile were investigated. In the plasma at 6 hours post-dose, unchanged afatinib (72.4% and 68.2% of the plasma radioactivity in females and males, respectively) was mainly found. m8, m10, and m15 were found in male minipigs, and m10 and m18 (oxidized metabolite) were found in female minipigs as metabolites. Although the reason for the sex-related differences in the metabolites remains unknown, the applicant explained that CYP isoforms reported to have sex-related differences in their expression (CYP1A2, 2E1; *Pharmacol*

Toxicol. 1999;85:174-80) may be involved in the metabolism of afatinib. Until 48 hours after dosing, the dosed radioactivity excreted in urine in females and males were 1.0% and 2.5%, respectively. Until 96 hours after dosing, the dosed radioactivity excreted in feces in females and males were 83.5% and 90%, respectively. In feces of females and males until 96 hours after dosing, unchanged afatinib (68.9% and 66.4% of the dosed radioactivity, respectively) and m10 (8.3% and 13.8% of the dosed radioactivity, respectively) were mainly found. Until 6 hours after dosing, the dosed radioactivity excreted in bile of females and males were 1.9% and 1.0%, respectively.

Following a single oral dose of 1.95 mg/kg of ^{14}C-afatinib to female rabbits, the metabolites in the plasma, urine, and feces were investigated. In the plasma at 4 hours post-dose, unchanged afatinib (21.5% of the plasma radioactivity), m2 (26.6%), and m3 (10.3%) were mainly found. Until 96 hours after dosing, 0.79% of the dosed radioactivity was excreted in urine. Until 168 hours after dosing, 95.4% of the dosed radioactivity was excreted in feces. In the feces until 168 hours after dosing, unchanged afatinib (83.9% of the dosed radioactivity) was mainly found, and the metabolites, m4, m10, and m18, were found in small amounts. Following intraduodenal administration of 1.95 mg/kg of ^{14}C-afatinib to female rabbits, 22.2% of the dosed radioactivity was excreted in the bile until 4 hours post-dose.

The applicant explained that the metabolites detected in urine or feces in healthy adult male subjects (m1, m2, m4, m13, m15) [see "4.(ii).A.(1).1) Pharmacokinetics"] were also detected in urine, feces, or bile in animals, and no human-specific metabolites were found.

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

3.(ii).A.(4).1) Urine, biliary, and fecal excretion

Following a single oral dose of 8.5 mg/kg of ^{14}C-afatinib to male and female mice, a total of 96.8% of the dosed radioactivity was recovered in both males and females until 96 hours post-dose. In females and males, the urine excretion rate was 1.0% and 1.3%, respectively, and the fecal excretion rate was 95.5% and 95.2%, respectively. Following a single intraduodenal administration of 8.5 mg/kg of ^{14}C-afatinib to female and male mice, 11.1% and 9.1%, respectively, of the dosed radioactivity was recovered in bile at 6 hours post-dose; the biliary recovery rates were low. In mice, no sex-related differences were observed in excretion of afatinib.

Following a single intravenous or oral administration of ^{14}C-afatinib to male rats at 4 mg/kg and 8 mg/kg, totals of 96.7% and 96.5%, respectively, of the dosed radioactivity were recovered until 96 hours post-dose. The urine and fecal excretion rates following the intravenous administration were 5.9% and 90.8%, and those following the oral administration were 2.9% and 93.6%, respectively. Following a single intravenous administration of ^{14}C-afatinib to male rats at 4 mg/kg, 28.3% of the dosed radioactivity were recovered in bile at 6 hours post-dose, and following a single intraduodenal administration of ^{14}C-afatinib to male rats at 8 mg/kg, 14.6% of the dosed radioactivity were recovered in bile at 7.5 hours post-dose. The applicant explained that non-biliary excretion route may be involved in the fecal excretion.

Following a single oral dose of 8.5 mg/kg ^{14}C-afatinib to male and female minipigs, totals of 95.6% and 99.5% of the dosed radioactivity were recovered in individual males, and 98.2% and 88.9% were recovered in individual females until 192 hours. The urine excretion rate was 1.4% and 4.8% in individual males and 0.6% and 2.1% in individual females, and the fecal excretion rate was 94.2% and 93.9% in individual males and 97.1% and 86.5% in individual females. In minipigs, no sex-related differences were observed in excretion of afatinib.

Following a single oral dose of 1.95 mg/kg of ^{14}C-afatinib to female rabbits, a total of 96.3% of the dosed radioactivity was recovered until 192 hours post-dose, and the urine and fecal excretion rates were 0.8% and 95.4%, respectively. Following duodenal administration of 1.95 mg/kg ^{14}C-

afatinib to female rabbits, 22.8% of the dosed radioactivity was recovered in bile at 4 hours post-dose. The applicant explained that afatinib was mainly excreted in the bile in female rabbits.

Following once-daily repeated oral administrations of ^{14}C-afatinib to male rats at 3 mg/kg for 13 days, the urine and fecal excretions of the dosed radioactivity were investigated. Until Day 13 post-dose, 0.7% and 85.0% were excreted in urine and feces, respectively.

Based on the above, the applicant explained that afatinib is mainly excreted in feces in any animal species.

3.(ii).A.(4).2) Excretion in milk

Following a single oral dose of approximately 4 mg/kg ^{14}C-afatinib, the milk radioactivity concentration up to 48 hours post-dose remained higher compared to the plasma radioactivity concentration. The ratio of $AUC_{0\text{-}24}$ of the milk radioactivity to that of the plasma radioactivity was ≥100. In milk, 2.4% to 5.0% of the dosed radioactivity was excreted. This shows that lactating rats excreted adequate amounts of the afatinib-derived radioactivity in milk. The applicant explained that this finding may be attributable to the properties of afatinib, which is lipophilic, and a substrate of BCRP [see "3.(ii).A.(5).3) Transporters"].

3.(ii).A.(5) Pharmacokinetic interactions

3.(ii).A.(5).1) Enzyme inhibition

Following incubation of substrates of CYP isoforms (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, 4A11) with human hepatic microsome in the presence of afatinib (0.1-100 μmol/L), afatinib weakly inhibited metabolism of that of CYP2C9 with the IC_{50} of 79.3 μmol/L. On the other hand, afatinib did not inhibit metabolisms of substrates of the other CYPs even at the highest concentration (100 μmol/L).

Following incubation of UGT1A1 and 2B7 substrates with human hepatic microsome in the presence of afatinib (0.1-100 μmol/L), afatinib inhibited metabolisms of UGT1A1 and 2B7 substrates, with the estimated IC_{50} of 24.2 and 73.7 μmol/L, respectively. Following repeated oral administrations of afatinib to humans at 40 and 50 mg, the C_{max} at the steady state was 0.078 to 0.158 μmol/L [see "4.(ii).A.(2).6) Studies 1200.1 to 4 and Study 1200.24"], and the IC_{50} of afatinib for UGT1A1 and 2B7 was ≥60 times higher than the clinical maximum blood concentration. The applicant, therefore, explained that the concomitant use of afatinib with UGT1A1 or 2B7 substrate is unlikely to interact pharmacokinetically to raise issues in clinical use.

3.(ii).A.(5).2) Enzyme induction

Hepatic microsome was prepared from male rats orally administered afatinib at 4 or 8.5 mg/kg for 4 days to investigate enzyme activities of CYP isoforms (CYP1A, 2B, 3A, 2E1, 4A). As a result, the enzyme activity of any CYP isoform was not increased due to treatment with afatinib.

The mRNA expression levels and enzyme activities of CYP isoforms (CYP1A2, 2B6, 2C8, 2C9, 2C19, 3A4) in sandwich-cultured human hepatocytes were investigated in the presence of afatinib at 0.002 to 5 μmol/L. As a result, no CYP isoform increased mRNA expression level or enzyme activity.

3.(ii).A.(5).3) Transporters

P-gp-mediated transport of afatinib at approximately 3 to 200 μmol/L was investigated in Caco-2 cells. The apparent efflux ratio ($P_{app\ B\rightarrow A}/P_{app\ A\rightarrow B}$) of afatinib was 0.58 to 4.18. The efflux ratio decreased with the increased afatinib concentration. The apparent efflux ratio of afatinib at

approximately 10 μmol/L was 2.93 and in the presence of cyclosporine A and verapamil, both P-gp inhibitors, decreased to 1.16 and 1.11, respectively.

P-gp-mediated transport of afatinib (1-100 μmol/L) was investigated in porcine kidney LLC-PK1 cell line (LLC-P-gp cell line) expressing human P-gp. The apparent efflux ratio of afatinib at 1 μmol/L in LLC-P-gp cell line was 13.1, which was 1.44 times that in LLC-PK1 cell line.

Human BCRP-mediated transport of afatinib (0.1-30 μmol/L) was investigated in Caco-2 cells. The apparent efflux ratio of afatinib was 6.2, and in the presence of Fumitremorgin C, a BCRP inhibitor, decreased to 4.0.

Using recombinant HEK293 cell lines expressing human organic anion transport polypeptide (OATP) 1B1, 1B3, or 2B1 (HEK-OATP1B1, HEK-OATP1B3, or HEK-OATP2B1 cell line, respectively), OATP-mediated transport of afatinib was investigated. Following incubation of afatinib at 0.5 μmol/L with HEK-OATP1B1, HEK-OATP1B3, HEK-OATP2B1, and HEK293 cell lines for 5 minutes, the cellular intake was 293, 300, 259, and 298 μL/mg, respectively; no clear differences were observed between any recombinant HEK293 cell line expressing OATP and original HEK293 cell line. Following incubation of afatinib with HEK-OATP1B1, HEK-OATP1B3, HEK-OATP2B1, and HEK293 cell lines in the presence of dehydroisoandrosterone 3-sulfate, an inhibitor against OATP1B1, 1B3, and 2B1, the cellular intake was 331, 342, 262, and 292 μL/mg, respectively; the inhibitor did not affect transport of afatinib.

Using recombinant HEK293 cell lines expressing human organic anion transporter (OAT) 1 and OAT3 (HEK-OAT1 and HEK-OAT3 cell line, respectively), OAT-mediated transport of afatinib was investigated. Following incubation of afatinib at 0.5 μmol/L with HEK-OAT1, HEK-OAT3, and HEK293 cell lines for 5 minutes, the cellular intake was 319, 244, and 199 μL/mg, respectively; no clear differences were observed between any recombinant HEK293 cell line expressing OAT and original HEK293 cell line. Following incubation of afatinib with HEK-OAT1, HEK-OAT3, and HEK293 cell lines in the presence of probenecid, an OAT inhibitor, the cellular intake was 370, 296, and 240 μL/mg, respectively; the inhibitor did not affect transport of afatinib.

Using recombinant HEK293 cell lines expressing human organic cation transporter (OCT) 1, OCT2, and OCT3 (HEK-OCT1, HEK-OCT2, and HEK-OCT3 cell line, respectively), OCT-mediated transport of afatinib was investigated. Following incubation of afatinib at 0.5 μmol/L with HEK-OCT1, HEK-OCT2, HEK-OCT3, or HEK293 cell lines for 5 minutes, the cellular intake was 428, 336, 375, and 317 μL/mg, respectively; no clear differences were observed between recombinant HEK293 cell line expressing OCT and original HEK293 cell line. Following incubation of afatinib with HEK-OCT1, HEK-OCT2, HEK-OCT3, and HEK293 cell lines in the presence of corticosterone, an OCT inhibitor, the cellular intake was 298, 278, 269, and 376 μL/mg, respectively; the inhibitor did not affect transport of afatinib.

Based on the above results, the applicant explained that afatinib may be a substrate of P-gp and BCRP but not of OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, or OCT3, and compared with the passive permeability, the transporters except P-gp and BCRP may rarely contribute to transport afatinib.

The inhibitory effect of afatinib (0.3-300 μmol/L) on efflux of digoxin, a substrate of P-gp, was investigated in Caco-2 cells. As a result, afatinib inhibited P-gp-mediated transport of digoxin in a concentration-dependent manner, and the IC_{50} was estimated to be 24 μmol/L.

The inhibitory effect of afatinib (1-100 μmol/L) on P-gp-mediated transport of digoxin was investigated in LLC-PK1 cells expressing P-gp, and the IC_{50} of afatinib for apparent efflux of

digoxin was estimated to be 1.59 μmol/L. The inhibitory effect of afatinib (0.1-30 μmol/L) on efflux of estrone 3-sulfate (E-sul), a substrate of BCRP, was investigated in Caco-2 cells. As a result, afatinib inhibited the efflux of E-sul in a concentration-dependent manner, and the IC_{50} was estimated to be 0.75 μM.

The inhibitory effect of afatinib (0.01-100 μmol/L) on OATP1B1-, OATP1B3-, and OATP2B1-mediated transport of ^{3}H-labeled estradiol 17β-glucuronate conjugate (substrate of OATP1B1 and OATP1B3) and E-sul (substrate of OATP2B1) was investigated in HEK-OATP1B1, HEK-OATP1B3, and HEK-OATP2B1 cell lines. Afatinib inhibited OATP1B1-, 1B3-, and 2B1-mediated transport in a concentration-dependent manner, and the IC_{50} was estimated to be 82.8, 71.2, and 6.05 μmol/L, respectively.

The inhibitory effect of afatinib (0.01-100 μM) on OAT1-, OAT3-, OCT1-, OCT2-, and OCT3-mediated transport of p-aminohippuric acid (substrate of OAT1), E-sul (substrate of OAT3), and N-methyl-4-phenylpyridinium (substrate of OCT1, 2, and 3) was investigated in HEK-OAT1, HEK-OAT3, HEK-OCT1, HEK-OCT2, and HEK-OCT3 cell line. Afatinib inhibited OCT1- and OCT3-mediated transport in a concentration-dependent manner, and the IC_{50} was estimated to be 20.0 and 11.8 μmol/L, respectively. On the other hand, afatinib did not inhibit OAT1, OAT3, or OCT2 even at 100 μmol/L.

Based on the above data, the applicant explained that the above results suggested that afatinib inhibited P-gp, BCRP, OATP1B1, 1B3, and 2B1 as well as OCT1 and 3 *in vitro*, but pharmacokinetic interactions attributable to inhibition of afatinib against P-gp, BCRP, OATP1B1, 1B3, and 2B1 as well as OCT1 and 3 are unlikely to occur in consideration of the C_{max} (approximately 8 nmol/L) of non-binding afatinib concentration at the steady state in humans at a dose of 50 mg and the IC_{50} of afatinib on each transporter.

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

3.(ii).B.(1) Linearity

In the repeat-dose studies in mice, rats, and minipigs, the AUC and C_{max} of afatinib increased in a greater than dose-proportional manner [see "3.(ii).A.(1).2) Repeat-dose"]. PMDA asked the applicant to discuss the reason for this finding.

The applicant responded that since afatinib is suggested to be a substrate of P-gp, saturation of gastrointestinal P-gp-mediated efflux of afatinib into the luminal side with dose increase could result in the greater than dose-proportional increases of the AUC and C_{max} [see "3.(ii).A.(5).3) Transporters"].

PMDA accepted the applicant's explanation.

3.(ii).B.(2) Tissue distribution

PMDA asked the applicant to explain the safety of afatinib in melanin-containing tissues, because the applicant indicated that afatinib had a high affinity with melanin [see "3.(ii).A.(2).1) Tissue distribution"].

The applicant responded as follows:
Afatinib, which is a highly lipophilic basic compound, could reversibly bind to the melanin-containing tissues (*Pharm Res*. 1990;7:935-41). The applicant, however, considered that afatinib could be distributed in the melanin-containing skin and eyes (retina) at high concentrations, possibly affecting the safety in these tissues.

Adverse events in the melanin-containing tissues in the global phase III study (Study 1200.32) were evaluated. As the skin-related events, rash/acne (54 of 54 Japanese patients [100%], 152 of

175 non-Japanese patients [86.9%]) and dry skin (26 of 54 Japanese patients [48.1%], 43 of 175 non-Japanese patients [24.6%]) occurred at high incidences, and Grade 3 rash/acne occurred more frequently in Japanese patients than in non-Japanese patients. However, the concerned events could be tolerated with actions such as symptomatic treatment and dose reduction at the onset [see "4.(iii).B.(3) Safety"]. The major events in the eyes included conjunctivitis and dry eye, and no retina-related adverse events occurred. Based on the above, the applicant considered that afatinib is unlikely to have specific safety issues in the melanin-containing tissues.

PMDA accepted the applicant's explanation.

3.(iii) Summary of toxicology studies

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

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

3.(iii).A.(1).1) Rodent

Male and female NMRI mice orally received afatinib at doses of 191 mg/kg (males and females), 382 mg/kg (males), and 763 mg/kg (females). One of 3 animals at a dose of 763 mg/kg was sacrificed moribund 1 day after dosing. In the sacrificed moribund animal, observed clinical signs included remarkably decreased activity, abdominal respiration, hypothermia, eyelid closure, increased abdominal size, and perioronasal crusts, and macroscopic pathological findings included discoloration and erosion of gastric mucosa, thinning of cecal wall, and dilated gastrointestinal tract filled with gas or body fluid. The approximate lethal dose was determined to be 763 mg/kg.

Male and female Wistar rats orally received afatinib at doses of 191 (males and females), 382 (males), and 763 (females) mg/kg. All of the animals at doses of 382 and 763 mg/kg died or were sacrificed moribund. In the dead or sacrificed moribund animals, observed clinical signs included piloerection, diarrhea, hypothermia, and emaciation, and macroscopic pathological findings included dilated gastrointestinal tract filled with gas or body fluid and redness and necrosis of the gastrointestinal mucosa. The approximate lethal dose was determined to be 191 to 382 mg/kg.

3.(iii).A.(1).2) Non-rodent (Reference data, non-GLP Study)

Male and female Goettingen minipigs orally received afatinib at doses of 0.5, 2, 4, 8, 16, or 32/16 mg/kg/day for 3 or 4 days in a dose-escalation manner to evaluate the acute toxicity of afatinib. No deaths occurred at any dose. In the 8 mg/kg/day group, loose stool (males) occurred on Day 4. In the 16 mg/kg/day group, loose stool occurred from Day 1. In the 32 mg/kg/day group, liquid stool, and decreased food consumption and body weight occurred on Day 1, and thus the dose was reduced to 16 mg/kg/day on Day 2 and thereafter, but no recovery was observed even at the reduced dose. Clinical chemistry findings included increased serum urea nitrogen and creatinine concentrations. Macroscopic pathological findings included hyperemia of the glandular stomach part and duodenal mucosa as well as slight hyperemia (females) and petechia (females) in the urinary bladder mucosa.

Based on the above, the approximate lethal dose was determined to be >32 mg/kg.

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

Minipigs were selected as non-rodent animal species for toxicity evaluation of afatinib, because *in vitro* metabolism studies with human hepatic microsome and *in vivo* metabolism study in minipigs [see "3.(ii).A.(3) Metabolism"] showed that the metabolites in minipigs were similar to those in humans, and gastrointestinal disorder was observed in pharmacology studies in dogs.

3.(iii).A.(2).1) Thirteen-week oral dose studies in mice

Male and female ICR mice orally received afatinib at doses of 0 (vehicle control), 9, 18, 27, or

36 mg/kg/day for 13 weeks. During the treatment period, 2 males at a dose of 27 mg/kg/day as well as 4 males and 1 female at a dose of 36 mg/kg/day were sacrificed moribund due to aggravated general condition. Clinical signs in the sacrificed moribund animals included enlarged lymph nodes in the axilla, lower jaw, etc.; alopecia, and skin hypertrophy.

In the groups of ≥18 mg/kg/day, clinical signs included piloerection, alopecia, swelling of the oronasal part (except for males of the 18 mg/kg/day group) and neck as well as redness of lid margin. Hematological findings included increased neutrophil count, and clinical chemistry findings included decreases in alkaline phosphatase (ALP) activity, cholesterol (except for females of the 18 mg/kg/day group), triglyceride, albumin, and albumin/globulin ratio. Macroscopic pathological findings included enlarged lymph nodes in the axilla, lower jaw, etc., and organ-weight-related findings included increased spleen weight and decreased ovary weight. Histopathological findings included extramedullary hematopoiesis in the spleen, reactive changes and increased apoptosis in the mesenteric and mandibular lymph nodes, thickening and hyperplasia in the small and large intestinal mucosa, erosion (except for males of the 18 mg/kg/day group), inflammation in the submucosa (except for males of the 18 mg/kg/day group and females of the 36 mg/kg/day group), epidermal hyperplasia of the skin (except for males of the 18 and 27 mg/kg/day groups), inflammation and folliculitis of the skin, atrophy of the corneal epithelium, as well as decreased corpora lutea count in the ovary.

In the 27 mg/kg/day group, observed clinical signs included decreased body weight gain associated with decreased food consumption and redness of forelimb palms (females). Hematological findings included decreased hematocrit, hemoglobin, and red blood cell count, and clinical chemistry findings included decreased glucose (females). Histopathological findings included extramedullary hematopoiesis in the liver (females), hyperplasia of lymphoid follicles in the thymus, epithelial hyperplasia in the gallbladder, skin ulcer, and myometrial atrophy.

In the 36 mg/kg/day group, the treatment was discontinued due to aggravated general condition in Week 10, and all surviving animals were subjected to necropsy. Observed clinical signs included decreased body weight gain associated with decreased food consumption, redness of forelimb palms (females), skin peeling (females), swelling of eyelid (males), and incomplete eyelid opening. Histopathological findings at this dose were the same as those at a dose of 27 mg/kg/day.

Based on the above, the no observed adverse effect level (NOAEL) was determined to be 9 mg/kg/day.

3.(iii).A.(2).2) Two-week repeated oral dose exploratory study in rats (Reference data, non-GLP Study)

Male Wistar rats orally received afatinib at a dose of 0 (vehicle control), 10, 30, or 100 mg/kg/day for 2 weeks.

In the 30 mg/kg/day group, observed clinical signs included redness and mild thickening of the upper lip, and macroscopic pathological findings included jelly-like content and wall thinning in the intestinal tract. Organ-weight-related findings included decreased prostate weight. Histopathological findings included erosive and ulcerative cystitis, atrophy of the villi of the duodenal mucosa and the pancreas exocrine portion.

In the 100 mg/kg/day group, observed clinical signs included redness of the facial skin, diarrhea, and remarkable decreases in body weight and food consumption. All of the animals were sacrificed moribund on Day 11. Clinical chemistry findings included increases in plasma urea nitrogen and globulin, as well as decreases in albumin and albumin/globulin ratio. Macroscopic pathological findings at this dose were the same as those at a dose of 30 mg/kg/day. Organ-weight-

related findings included decreases in thymus, spleen, and prostate weights. Histopathological findings included erosive and ulcerative cystitis, erosive gastritis and duodenitis, pustular dermatitis, and decreased cell count in the spleen and bone marrow, as well as atrophy of the thymus, salivary gland, and prostate.

Based on the above, the NOAEL was determined to be 10 mg/kg/day.

3.(iii).A.(2).3) Four-week oral dose studies in rats
Male and female Wistar rats orally received afatinib at a dose of 0 (vehicle control), 4, 8.5, or 18 mg/kg/day for 4 weeks.

In the 18 mg/kg/day group, 12 males and 4 females died or were sacrificed moribund on Day 17 and thereafter. Clinical signs in dead or sacrificed moribund animals included dehydration, debility, crusty eyelids, piloerection, and discolored urine as well as increased deep respiration or tachypnea. Histopathological findings included erosion and ulcer of the gastric mucosa, atrophy of the gastrointestinal mucosa, spleen, and thymus, purulent and granulomatous folliculitis, and pustular dermatitis as well as dilated renal tubule and papillary necrosis in the kidneys.

In the groups of ≥8.5 mg/kg/day, observed clinical signs included labial thickening (except for females of the 8.5 mg/kg/day group). Hematological findings included dose-dependently increased neutrophil count, and clinical chemistry findings included increased globulin as well as decreases in albumin (except for females of the 8.5 mg/kg/day group) and albumin/globulin ratio. Bone marrow smear findings included enhanced myeloid cell hematopoiesis and decreased erythropoiesis. Urinalysis findings included decreased urine volume (except for females of the 8.5 mg/kg/day group). Organ-weight-related findings included decreased prostate weight, macroscopic pathological findings included enlargement of head/neck and axillary lymph nodes, and histopathological findings included changes in the kidneys such as papillary necrosis (except for females of the 8.5 mg/kg/day group) and purulent and granulomatous folliculitis of the facial skin as well as dose-dependent epithelial atrophy of the esophagus, forestomach (except for females of the 8.5 mg/kg/day group), small intestine, large intestine, and uterus.

In the 18 mg/kg/day group, observed clinical signs included decreases in body weight gain and food consumption, loose or liquid stool, swelling of oronasal part, and piloerection, as well as alopecia. These clinical signs were aggravated more remarkably in males than those in females. Clinical chemistry findings included increased plasma urea nitrogen concentration. Urinalysis findings included increases in N-acetyl-β-D-glucosaminidase, creatinine, and microprotein. Organ-weight-related findings included increased axillary lymph node weight and decreased thymus weight (males), and histopathological findings included lymphoid follicles and paracortical hyperplasia in the axillary or mandibular lymph node, atrophy of the thymus, spleen, prostate, and seminal vesicle, epithelial atrophy of the skin, glandular stomach (males), and vagina, enhanced myelopoiesis, and changes in the glandular stomach (males) and forestomach such as erosion, ulcer, and gastrointestinal edema as well as apoptosis in the testis. The increased axillary lymph node weight is determined to be a change subsequent to the skin disorder.

After a 2-week recovery period, all of the findings resolved or were resolving.

Based on the above, the NOAEL was determined to be 4 mg/kg/day.

3.(iii).A.(2).4) Thirteen-week oral dose study in rats
Male and female Wistar rats orally received afatinib at a dose of 0 (vehicle control), 2, 5, or 10 mg/kg/day for 13 weeks. At a dose of 10 mg/kg/day, 2 males and 1 female were sacrificed moribund. In the sacrificed moribund animals, observed clinical signs included skin lesions, and histopathological findings included severe renal papillary necrosis on the unilateral kidney in 2

males, of which 1 male was found to have pyelonephritis potentially causing debility. The pyelonephritis was determined to be an incidental finding unrelated to afatinib, because the affected animal was found to have bacterial flora in the papilla renalis, suggesting infection; none of the other animals was found to have infectious pyelonephritis; and no pyelonephritis was observed in the 4-week study in rats including the dose of 18 mg/kg/day or 26-week study in rats of which the treatment period was longer than that of this study.

In the 5 mg/kg/day group, observed clinical signs included slightly decreased body weight gain (males), wavy fur, and rough fur or lackluster fur (males). Hematological findings included mild to moderate increases in white blood cell count and neutrophil count. Histopathological findings included folliculitis and degenerative hair follicles.

In the 10 mg/kg/day group, observed clinical signs included decreased body weight gain (males), wavy fur, rough fur, lackluster fur, alopecia of the neck, shoulders, and perigenital region, squamous skin of the tail as well as reddish swollen, or crusty oronasal part. Hematological findings included increases in white blood cell count and neutrophil count. Urinalysis findings included decreased urine volume and increased protein associated with presence of white blood cells or red blood cells (blood), which were particularly remarkable in males. Macroscopic pathological findings included swelling of axillary and mandibular lymph nodes, and organ-weight-related findings included increased axillary lymph node weight. Histopathological findings included lymphoid follicles hyperplasia in the mandibular lymph node related to the inflammatory lesion of the skin, papillary necrosis in the kidneys, and ulcer, crust, and slight to mild inflammatory cell infiltration of the skin, as well as slight to severe folliculitis, which was the most remarkable in the facial (oronasal) and tail parts.

In all dosing groups, the serum troponin T (TnT) concentration (determined under non-GLP conditions) serving as a cardiotoxic marker did not increase compared with that in the control group or published background data.

After a 6-week recovery period, all of these findings except for skin lesion and papillary necrosis in the kidney resolved.

Based on the above, the NOAEL was determined to be 2 mg/kg/day.

3.(iii).A.(2).5) Twenty-six-week oral dose study in rats

Male and female Wistar rats orally received afatinib at a dose of 0 (vehicle control), 1.5, 3, or 6 mg/kg/day for 26 weeks. No animals were sacrificed moribund or died in association with afatinib treatment.

In the 3 mg/kg/day group, observed clinical signs included wavy fur, rough fur, and swollen or crusty oronasal parts, and histopathological findings included folliculitis, hyperplasia of the lymphoid follicles in the axillary lymph node, and increases in plasmatocytes (males) and histiocytes, as well as extramedullary hematopoiesis in the spleen.

In the 6 mg/kg/day group, observed clinical signs included decreased body weight gain (males) and squamous skin of the tail in addition to findings observed in the 3 mg/kg/day group. Hematological findings included increases in platelet count (males), white blood cell count, and neutrophil count, and clinical chemistry findings included increased globulin as well as decreases in albumin (males) and albumin/globulin ratio (males). Urinalysis findings included decreased urine volume, increased protein excretion, and presence of white blood cells (males). Histopathological findings included papillary necrosis in the kidneys and inflammatory changes of the nasal cavity.

After an 8-week recovery period, all of the findings resolved or were resolving.

Based on the above, the NOAEL was determined to be 1.5 mg/kg/day.

3.(iii).A.(2).6) Four-week oral dose study in minipigs

Male and female Goettingen minipigs orally received afatinib at a dose of 0 (vehicle control), 1, 2.45, or 6 mg/kg/day for 4 weeks. No animals were sacrificed moribund or died in association with afatinib treatment.

In the 1 mg/kg/day group, histopathological findings included atrophy of forestomach epithelium (males), esophagus epithelium (males), and seminal vesicle.

In the ≥2.45 mg/kg/day group, observed clinical signs included loose stool (except for females of the 2.45 mg/kg/day group). Hematological findings included mildly increased neutrophil count (males), and clinical chemistry findings included slightly increased serum urea nitrogen concentration (except for females of the 2.45 mg/kg/day group). The slightly increased serum urea nitrogen was determined to have no toxicological significance because no morphological changes were observed in the kidneys. In the 2.45 and 6 mg/kg/day groups, findings included a dose-dependent increase in heart rate as well as continuous shortening of the QT interval at 3.5 hours after dosing on Day 1 and before dosing and at 3.5 hours after dosing on Days 10 and 24. Increased heart rate observed in this study was not observed in either the 13- or 52-week oral dose study in minipigs in which the exposure level was comparable to that in this study. This finding was determined to have no toxicological significance. The reduction of the QT interval was determined to be a change attributable to increased heart rate observed in this study (*J Pharmacol Toxicol Methods*. 2008;57:202-11, *Toxicol Sci.* 1998;45:247-58). In the 6 mg/kg/day group, serum TnT (determined under non-GLP conditions) were below the lower limit of detection (0.01 ng/mL).

In the 2.45 mg/kg/day group, histopathological findings included atrophy of the epithelia of the larynx (females), esophagus, forestomach (males), and glandular stomach as well as mucus acini of the seminal vesicle, sublingual gland, etc.

In the 6 mg/kg/day group, histopathological findings included inflammatory cell infiltration in the forestomach, and atrophy of the mucus acini in the laryngeal gland (males) and esophageal gland as well as epithelial atrophy of the small intestine, trachea, and cornea (females) in addition to findings observed at a dose of 2.45 mg/kg/day.

After a 2-week recovery period, all of the findings resolved.

Based on the above, the NOAEL was determined to be <1 mg/kg/day.

3.(iii).A.(2).7) Thirteen-week oral dose study in minipigs

Male and female Goettingen minipigs orally received afatinib at a dose of 0 (vehicle control), 0.5, 2, or 7 mg/kg/day for 13 weeks. Since loose stool continued for 1 month, the dose of 7 mg/kg/day was reduced to 5.5 mg/kg/day on Day 32 and thereafter. On Days 43, 44, and 46 to 77, however, the dose of 7 mg/kg/day was administered by mistake. No animals were sacrificed moribund or died in association with afatinib treatment.

In the groups of ≥2 mg/kg/day, histopathological findings included epithelial atrophy of the gastrointestinal and prostate, atrophy of mucus acini in the laryngeal gland (except for females of the 2 mg/kg/day group) and the sublingual gland (except for males of the 2 mg/kg/day group), as well as increased myelopoiesis.

In the 7 mg/kg/day group, observed clinical signs included loose stool. Hematological findings included increases in white blood cell count and neutrophil count, and clinical chemistry findings included increases in serum urea nitrogen and globulin, as well as decreases in albumin (males) and albumin/globulin ratio. In the 7 mg/kg/day group, serum TnT (determined under non-GLP conditions) was below the lower limit of detection (0.01 ng/mL). Histopathological findings included epithelial atrophy of the trachea (males) and cornea.

After a 6-week recovery period, all of the findings resolved or were resolving.

Based on the above, the NOAEL was determined to be 0.5 mg/kg/day.

3.(iii).A.(2).8) Fifty-two-week oral dose study in minipigs

Male and female Goettingen minipigs orally received afatinib at doses of 0 (vehicle control), 0.5, 1.5, or 5 mg/kg/day for 52 weeks. No animals were sacrificed moribund or died in association with afatinib treatment.

In the 0.5 mg/kg/day group, histopathological findings included epithelial vacuolation and atrophy (males) of the upper gastrointestinal tract. These changes were, however, attributable to pharmacodynamic action of afatinib and the lesions were slight to mild in severity, these findings were determined to have no toxicological significance.

In the groups of ≥1.5 mg/kg/day, histopathological findings included epithelial vacuolation (except for females of the 1.5 mg/kg/day group) and atrophy of the upper gastrointestinal tract as well as epithelial atrophy of mucus acini in the laryngeal gland and cornea.

In the 5 mg/kg/day group, observed clinical signs included intermittent short-term loose stool or liquid stool on Day 4 and thereafter. The concerned finding no longer developed on Day 137 and thereafter. Hematological findings included increased neutrophil count (males), and clinical chemistry findings included increases in serum urea nitrogen (males) and globulin, as well as decreased albumin/globulin ratio.

After a 6-week recovery period, all of the findings resolved or were resolving. In the 5 mg/kg/day group, 1 female for observation of the recovery showed increases in serum TnT (determined under non-GLP conditions) slightly exceeding the lower limit of detection (0.01 ng/mL) (0.041 ng/mL on Day 178, 0.052 ng/mL on Day 359). This finding was, however, determined to have no toxicological significance, considering that histopathological findings did not include morphological changes in the heart, and the serum TnT in normal pigs was reported to be 0.1 ng/mL (*Thromb Res*. 2005;116:431-42).

Based on the above, the NOAEL was determined to be 0.5 mg/kg/day.

3.(iii).A.(3) Genotoxicity

In the bacterial reverse mutation assay, the reverse mutant colony count of TA98 strain mildly increased irrespective of metabolism activation. In the chromosomal aberration assay in human lymphocytes, the incidence of chromosomal aberrations increased. The increased incidence of chromosomal aberrations was observed only at the afatinib concentrations leading to cytotoxicity. Afatinib was, therefore, determined not to induce chromosomal aberrations. All of the gene mutation assay in the liver, duodenal, and skin derived from Muta mice (CD_2-lacZ80/HazfBR) and bone marrow micronucleus assay as well as comet assays with the liver, kidney, and jejunum in rats showed negative results.

3.(iii).A.(4) Carcinogenicity
Afatinib is expected to be an antineoplastic drug indicated for advanced or recurrent NSCLC patients, and carcinogenicity data have not been submitted in this application. A dose-finding study for the carcinogenicity study in transgenic (Tg) mice was conducted.

Male and female wild-type rasH2 mouse (CByB6F1-Tg [HRAS] 2Jic) litters orally received afatinib at a dose of 0 (vehicle control), 9, 18, or 36 mg/kg/day for 8 weeks. No animals were sacrificed moribund or died in association with afatinib treatment.

In the 9 mg/kg/day group, hematological findings included decreases in hemoglobin, hematocrit, and red blood cell count (males) as well as increased neutrophil count (females). Organ-weight-related findings included increased thyroid weight (females), and histopathological findings included inflammatory cell infiltration in the skin (males), epidermal thickening (males), and atrophy of the skin appendages (males) as well as decreased corpora lutea count in the ovary.

In the 18 mg/kg/day group, hematological findings included increases in monocyte (females), platelet (females), and reticulocyte (males) count in addition to findings observed at a dose of 9 mg/kg/day, and clinical chemistry findings included increased AST as well as decreases in total protein and albumin (males). Organ-weight-related findings included increased spleen weight (males) in addition to findings observed at a dose of 9 mg/kg/day, and histopathological findings included decreased corpora lutea count in the ovary, decreased secretory granules in the salivary gland (females), and epithelial atrophy of the cornea.

In the 36 mg/kg/day group, observed clinical signs included decreased body weight gain (females) and alopecia of the torso in Week 4 and thereafter. Hematological findings included decreases in hemoglobin, hematocrit, and red blood cell count (females) as well as increases in neutrophil, monocyte, and platelet count (males) in addition to findings observed at a dose of 18 mg/kg/day, and clinical chemistry findings included decreases in glucose (males), total protein (females), albumin (females), and cholesterol. Organ-weight-related findings included increased adrenal gland weight (females) and decreased thymus weight (females) in addition to findings observed at a dose of 18 mg/kg/day. Histopathological findings included decreased secretory granules in the salivary gland (females), epithelial atrophy of the cornea, decreased corpora lutea count in the ovary, inflammatory cell infiltration in the skin, epidermal thickening (males), and atrophy of the skin appendages (males).

3.(iii).A.(5) Reproductive and developmental toxicity
As reproductive and developmental toxicity studies, studies of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in rats and rabbits, and a rat study for effects on pre- and postnatal development, including maternal function were conducted. The placental transfer and excretion in milk of afatinib in rats were confirmed [see "3.(ii).A.(2).3) Placental transfer and fetal transfer" and "3.(ii).A.(4).2) Excretion in milk"].

3.(iii).A.(5).1) Fertility and early embryonic development to implantation in rats
Wistar rats orally received afatinib at a dose of 0 (vehicle control), 4, 6, or 8 mg/kg/day to evaluate the estrous cycle, mating behavior, and fertility. Males received afatinib for 4 weeks before mating, during mating, and for ≥5 weeks from confirmation of mating to necropsy, while females received afatinib for 2 weeks before mating, during mating, and from Gestation days 0 to 7.

In the ≥6 mg/kg/day groups, aggravated clinical signs including decreased body weight gain (except for females of the 6 mg/kg/day group) were observed in parental animals. Findings related to male reproductive competence included slightly decreased vaginal plug count and slightly increased incidence of decreased sperm count observed in the vaginal smears. These findings were considered to have little toxicological significance because the fertility remained unaffected.

Findings related to female reproductive competence at a dose of 8 mg/kg/day included decreases in corpora lutea count, implantation site count, and number of live fetuses as well as mildly increased postimplantation embryonic losses. The mildly increased postimplantation embryonic losses as well as decreases in corpora lutea count, implantation site count, and number of live fetuses were changes related to decreased maternal body weight (*Fundam Appl Toxicol.* 1993;20:15-22, *Teratology.* 1979;19:245-50). These findings were determined to be consequences of the general toxicity in the dams but not reproductive and developmental toxicity.

Based on the above, the NOAEL was determined to be 8 mg/kg/day for the male and female fertility and early embryonic development.

3.(iii).A.(5).2) Embryo-fetal development in rats

Pregnant Wistar rats orally received afatinib at a dose of 0 (vehicle control), 4, 8, or 16 mg/kg/day from Gestation day 6 to 17. On Gestation day 20, cesarean section was performed to investigate the fetal outer surface, viscera, and skeletons.

Findings related to maternal clinical conditions included decreases in body weight gain and food consumption at doses of ≥8 mg/kg/day, and piloerection and loose or liquid stool, as well as crust mainly in the oronasal and perirhinal parts at a dose of 16 mg/kg/day. In the 16 mg/kg/day group, 1 animal had hunchback position, piloerection, and liquid stool and thus was sacrificed moribund on Gestation day 12.

Findings related to embryo-fetal development at a dose of 16 mg/kg/day included decreased fetal and placental weight, as well as slightly increased incidences of delayed ossification and unossificated bones. The decreased fetal weight was a change subsequent to the decrease in maternal body weight gain and therefore determined to be non-attributable to fetal toxicity of afatinib.

Based on the above, the NOAELs were determined to be 8 mg/kg/day for maternal general toxicity and 16 mg/kg/day for embryo-fetal development.

3.(iii).A.(5).3) Embryo-fetal development in rabbits

Pregnant Himalaya rabbits orally received afatinib at a dose of 0 (vehicle control), 2.5, 5, or 10 mg/kg/day from Gestation day 6 to Gestation day 18. On Gestation day 29, cesarean section was performed to investigate the fetal outer surface, viscera, and skeletons.

Findings related to dams included decreased fecal volume and liquid stool at doses of ≥5 mg/kg/day, and decreases in body weight gain and food consumption, as well as gastric ulcer at a dose of 10 mg/kg/day. Due to such remarkable maternal toxicity, 4 dams died or were sacrificed moribund during the treatment period and after end of the treatment. Findings related to maternal reproductive function included complete abortion attributable to the maternal toxicity in 1 dam at a dose of 5 mg/kg/day and in 3 dams at a dose of 10 mg/kg/day.

Findings related to embryo-fetal development included various variations and malformations such as ventricular septal defect at doses of ≥2.5 mg/kg/day, and decreased fetal body weight, dwarf runts, curvature in extremities, excessive blood vessels in the aortic arch, and right or left carotid artery, as well as variations such as small testis at a dose of 10 mg/kg/day. The variations at a dose of 10 mg/kg/day exceeded the range of background data and were, therefore, considered to be possibly related to afatinib. The incidences of many of the malformations observed in animals receiving afatinib were not dependent on the dose, and those of all of the malformations fell within the range of the background data. The malformations were unrelated to afatinib. Afatinib was therefore determined to have no teratogenicity.

Based on the above, the NOAELs were determined to be 2.5 mg/kg/day for dams and 5 mg/kg/day for embryos and fetuses. The exposure at the dose leading to embryo-fetal toxicity was below the clinical exposure.* Therefore, the following caution statement will be included in the package insert: afatinib should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefit outweighs the possible risks associated with the treatment, and women of childbearing potential should be instructed to use appropriate contraception.

*: In the Japanese phase I/II study (Study 1200.33) in Japanese NSCLC patients, the mean $AUC_{\tau,ss}$ in patients who received multiple oral dose of afatinib once daily at a dose of 50 mg for 28 days (Day 28) was 1010 ng·h/mL.

3.(iii).A.(5).4) Pre- and postnatal development in rats, including maternal function

Pregnant Wistar rats orally received afatinib at a dose of 0 (vehicle control), 4, 6, or 8 mg/kg/day from Gestation day 6 to Lactation day 20. The evaluation covered the gestation period and delivery of F_0 (dams) as well as development, sensory function, reflex, and reproductive competence of F_1 (offsprings).

Findings related to dams at doses of 6 and 8 mg/kg/day included mildly decreased body weight gain from Lactation day 1 to Lactation day 4 and mildly decreased food consumption from Gestation day 6 to Gestation day 9.

Findings related to offsprings at doses of 6 and 8 mg/kg/day included decreases in body weight at birth, pre-weaning body weight gain, and body weight at 5 weeks of age, but there were no effects on the sensory function, reflex, and, reproductive competence. The effects on the body weight were mild and not determined to be toxic.

Based on the above, the NOAEL was determined to be 8 mg/kg/day for dams and offsprings.

3.(iii).A.(6) Local irritation

To ensure the safety of handlers of afatinib, single dose skin and eye mucosa irritation studies in rabbits were conducted. No skin irritation was observed. The eye mucosa irritation study indicated remarkable irritation on the eyes (conjunctival edema, swelling of eyelid, hyperemia of the iris and conjunctiva).

3.(iii).A.(7) Other toxicity

3.(iii).A.(7).1) Four-week oral dose study of maleic acid in minipigs

To evaluate the effects of maleic acid alone, male and female Goettingen minipigs orally received the vehicle or maleic acid at a dose of 3 mg/kg/day (equivalent to the amount of maleic acid anion present in afatinib at the high dose in the 4-week oral dose study in minipigs) for 4 weeks. As a result, there were no clinical, hematological, clinical chemistry, macroscopic, or histopathological findings.

3.(iii).A.(7).2) [redacted]. In the animals at a dose of 10/100 mg/kg/day, the dose was reduced from 10/100 mg/kg/day to 7.5/100 mg/kg/day on Days 11 and 12, but deaths and remarkable toxicity were observed and the animals were sacrificed moribund on Day 12. [redacted].

After a 4-week recovery period, all of the findings resolved or were resolving.

Based on the above, the NOAEL was determined to be 2.5/10 mg/kg/day.

3.(iii).A.(7).3) [redacted]. In the 16/100 mg/kg/day group, 1 each of males and females died. In the groups of ≥8/32 mg/kg/day, toxicity findings related to the pharmacodynamic action of afatinib were observed, and these changes were determined to be similar to ones observed in the 4-week single drug toxicity studies.

After a 4-week recovery period, all of the findings resolved or were resolving.

Based on the above, the NOAEL was determined to be 4/10 mg/kg/day.

3.(iii).A.(7).4) Photosafety

Afatinib is confirmed to have photoabsorption at 344 nm, and the phototoxicity was investigated in an *in vitro* study in mouse 3T3 fibroblasts. The results suggested that afatinib may have phototoxicity.

It has been reported that patients treated with EGFR-TKIs (gefitinib, erlotinib, lapatinib tosilate) experienced adverse events in the skin related to the pharmacodynamic action (*J Oncol*. 2009;2009:Article ID 849051, *J Clin Oncol*. 2005;23:5235-46). Similar adverse events in the skin are also expected to occur in patients to be treated with afatinib. The applicant explained that they would take measures to prevent adverse events from occurring in the skin by including the following instructions for proper use in the package insert: patients should wear clothing and use sunscreen agents to protect their skin from sunlight to avoid direct exposure to sunlight irrespective of the phototoxicity potential of afatinib.

3.(iii).A.(7).5) Immunotoxicity

In the 4-week oral dose study in rats, the immunotoxicity was evaluated by a subset analysis of white blood cells in the blood and spleen and an assay of natural killer cell activity in the spleen. In the 18 mg/kg/day group, mild immunological changes were observed (mild decrease in B lymphocyte percentage in the peripheral blood and spleen, mild decrease in natural killer cell activity). In the 18 mg/kg/day group, many animals were sacrificed moribund due to aggravated clinical signs. The mild immunological changes observed at this dose were considered to be non-specific reactions caused by excessive toxicity.

3.(iii).A.(7).6) Toxicity of impurities

[redacted]. The repeat-dose toxicity studies with batches containing these impurities as well as genotoxicity studies of the Related Substance A, Related Substance B, and Related Substance C were conducted. The following study data were determined to ensure the safety of these impurities within the acceptance range.

(a) General toxicity of impurities

Two 13-week repeat-dose studies in rats were conducted: one study used the formulation containing the Related Substance A, Related Substance C, and Related Substance B at the concentrations not less than the upper specification limit, and the other one used the formulation in which these impurities were not detected. The study data indicated no difference in toxicity findings between these studies, and no intensified toxicity due to the impurities was found. The potential doses of the impurities in humans weighing 60 kg were estimated from their maximum doses in rats in this study and compared with the clinical maximum doses of the impurities in humans contained at the upper specification limit. For all of the impurities evaluated, the safety margin was ≥15.

(b) Genotoxicity of impurities
The genotoxicity of the Related Substance A and Related Substance C was evaluated by bacterial reverse mutation assay and chromosomal aberration assay in human lymphocytes. These impurities were found to have no genotoxicity.

The genotoxicity of the Related Substance B was evaluated by bacterial reverse mutation assay, and bone marrow micronucleus assay as well as comet assays with the liver, stomach, and jejunum in rats. In the reverse mutation assay, mildly increased reverse mutant colony count of TA98 strain without metabolism activation was observed at the high concentration exposure (1000 μg/plate), but both micronucleus and comet assays showed negative results.

Among potential impurities, the maximum daily clinical doses of the impurities with genotoxicity or potential genotoxicity were confirmed to be <1.5 μg, the threshold of toxicological concern.

3.(iii).B. Outline of the review by PMDA
Based on the submitted data and the following review, PMDA has concluded that afatinib has no safety margin, but may be clinically used because afatinib is indicated for a fatal disease.

Genotoxicity of afatinib and the Related Substance B (impurity)
Although how afatinib and Related Substance B would cause mutations remains to be investigated at present, the applicant explained the genotoxicity of afatinib and the Related Substance B as follows:
Although the bacterial reverse mutation assay showed weak positive results in TA98 strain, the micronucleus and comet assays in rats showed negative results. Taking account of the weight of scientific evidence, afatinib and the Related Substance B are considered to have no genotoxic potential.

PMDA considers as follows:
The bacterial reverse mutation assay showed positive results, which were weak, and development of genotoxicity cannot be ruled out. On the other hand, the *in vivo* genotoxicity studies showed negative results, indicating that the genotoxicity of afatinib is fairly unlikely to occur in humans. In consideration of the seriousness of the target disease, clinical use of afatinib is acceptable as long as the genotoxicity data are included in the package insert as reference information.

4. Clinical data
4.(i) Summary of biopharmaceutic studies and associated analytical methods
4.(i).A Summary of the submitted data
The oral preparations of afatinib maleate (hereinafter referred to as afatinib) include the formulation of the ^{14}C-labeled drug substance, powder formulation for oral solution, 5, 20, and 100 mg plain tablets (TF1 formulations), 5, 20, and 100 mg film-coated tablets (TF2 formulations) and 20, 30, 40, and 50 mg formulations to be marketed (FF formulations).

The powder formulation for oral solution, TF2 and FF formulations were used in a relative bioavailability study, TF1 formulations in 3 foreign phase I studies, TF2 formulations in 7 foreign phase I and 7 foreign phase II studies, and FF formulations in 8 foreign phase I, 5 foreign phase II, 1 Japanese phase I/II, 1 foreign phase I/II, and 2 foreign phase III studies. In these studies, the pharmacokinetics (PK) of afatinib were investigated.

4.(i).A.(1) Assay

Assays of afatinib in human plasma and urine were performed by high performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) with the lower limits of quantitation of 0.1 to 0.5 and 0.5 to 5 ng/mL, respectively.

4.(i).A.(2) Food effect on PK of afatinib

Foreign phase I study (5.3.3.2-4, Study 1200.3 [[redacted] to [redacted]])

An open-label crossover study was conducted as a sub-study (13 subjects) of the phase I study in patients with advanced solid cancer (Study 1200.3) to investigate the food effects on the PK of afatinib. In this study, a single oral dose of afatinib at 40 mg was administered in the fasted state* and fed state after a high-fat/high calorie diet (approximately 945 kcal in total, containing fat with approximately 500-600 kcal) (after a meal) shown in the table below. Compared with the PK in the fasted state, absorption was delayed in the PK after a meal. The ratios (90% confidence interval [CI]) (%) of the geometric means of the $AUC_{0-\infty}$ and C_{max} of afatinib in the fed state to those in the fasted state were 61.2 [49.6, 75.4] and 49.5 [36.0, 68.2], respectively. The exposure to afatinib in the fed state was significantly lower than that in the fasted state.

* Afatinib was to be administered 1 hour before a meal.

The applicant explained the mechanism of the food effects on the PK of afatinib as follows: Afatinib was suggested to be a substrate of P-gp [see 3.(ii).A.(5).3) Transporters]. The drug concentration in the gastrointestinal tract following fed administration decreased due to food and digestive juice, and compared with that following fasted administration, the PK thereby increased susceptibility to P-gp-mediated efflux, resulting in the decreased gastrointestinal tract absorption. Consequently, the exposure to afatinib in the fed state was lower than that in the fasted state.

PK parameters of afatinib in the fasted state and after a high fat meal

	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max}*(h)
Fasted state	676 (62.3)	24.9 (50.5)	3.0 (1.0, 6.9)
After a high fat meal	414 (62.8)	12.2 (82.6)	6.9 (3.1, 8.1)

Geometric mean (geometric coefficient of variation, %), n = 13, *: Median (range)

4.(i).A.(3) Relative bioavailability study

Foreign phase I study (5.3.1.1-2, Study 1200.35 [[redacted] to [redacted]])

An open-label crossover study was conducted to investigate the relative bioavailability of FF formulation to the oral solution, prepared by dissolving 20 mg of afatinib (powder formulation for oral solution) in 80 mL of 0.2% hydroxyethyl cellulose solution, and TF2 formulation. In this study, a single oral dose of the oral solution, TF2 formulation or FF formulation was administered to 22 healthy adult subjects. As a result, the geometric mean $AUC_{0-\infty}$ of the FF formulation 20 mg tablets was 103 ng·h/mL, and its ratios (%) [90% CI] to the geometric mean $AUC_{0-\infty}$of the oral solution 20 mg and TF2 formulation 20 mg tablets (114 and 115 ng·h/mL, respectively) were 92.2 [76.3, 111.5] and 86.5 [70.45, 106.31], respectively. The geometric mean C_{max} of the FF formulation 20 mg tablets was 4.14 ng/mL, and its ratios (%) [90% CI] to the geometric mean C_{max} of the oral solution 20 mg and TF2 formulation 20 mg tablets (4.93 and 5.02 ng/mL, respectively) were 85.3 [68.8, 105.9] and 80.3 [64.71, 99.56], respectively. The geometric mean blood concentration over time of the TF2 and FF formulation was similar, and the t_{max} and mean residence time of both formulations were 5 and 35.9 hours, respectively. The applicant therefore explained that there was no difference in mean absorption time between TF2 and FF formulation.

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

Food effect

In consideration that the PK of afatinib was affected by food [see "4.(i).A.(2) Food effect on PK of afatinib"], PMDA asked the applicant to explain the necessity of cautions for the administration timing of afatinib.

The applicant responded as follows:

In Study 1200.3, the exposure to afatinib in the fed state was statistically significantly lower than that in the fasted state. In clinical studies subsequent to Study 1200.3, afatinib was, therefore, to be administered in the fasted state to decrease the variation of the PK and increase the exposure. In the global phase III study (Study 1200.32), the protocol stipulated that "afatinib should be administered 1 hour before a meal or earlier or 3 hours after a meal or later." Although the administration of afatinib in the fed state would not raise considerable safety issues, the efficacy might decrease. The applicant, therefore, considered it necessary to administer afatinib in the fasted state. The fasted administration of afatinib was included in the Dosage and Administration and the following caution statement will be included in the Precautions for Dosage and Administration section in consideration of the administration timing of afatinib in Study 1200.32: afatinib should not be administered between 1 hour before and 3 hours after a meal to avoid food effect [see "4.(iii).B (5) Dosage and administration"].

PMDA accepted the applicant's explanation.

4.(ii) Summary of clinical pharmacology studies

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

The PK of afatinib in healthy adult subjects, subjects with hepatic impairment, and patients with solid cancer including NSCLC were investigated in the following cases: (a) afatinib monotherapy and (b) concomitant use of afatinib with the other antineoplastic drug*, ritonavir, or rifampicin.

*: (a) letrozole, (b) docetaxel hydrate (DTX), (c) temozolomide (TMZ), (d) trastuzumab (genetical recombinant, trastuzumab), (e) concomitant use of cisplatin (CDDP) and fluorouracil (5-FU) (CDDP/5-FU), (f) concomitant use of CDDP and paclitaxel (PTX) (CDDP/PTX)

4.(ii).A.(1) Healthy adult subjects

4.(ii).A.(1).1) Pharmacokinetics (5.3.2.3-5)

A single oral dose of ^{14}C-labeled afatinib at 15 mg was administered to 8 healthy adult subjects to investigate the metabolites in the plasma, urine, and feces. In the plasma at 6 hours post-dose, unchanged afatinib was observed, but no metabolites were detected. The urine and fecal excretion rates until 72 hours post-dose were 2.7% and 70%. In the urine until 72 hours, unchanged afatinib, m1, m2, m4, m13, and m15 were observed in small amounts. In the feces until 72 hours, unchanged afatinib (62.3%) was mainly found, and m2, m4, and m13 were observed in small amounts as the metabolites.

4.(ii).A.(1).2) Foreign phase I study (5.3.3.1-1, Study 1200.25 [[redacted] to [redacted] 20[redacted]])

An open-label study in 8 healthy adult subjects was conducted to investigate the mass balance after a single oral dose of ^{14}C-labeled afatinib at 15 mg (the table below). Compared with AUC of the total plasma radioactivity until 24 hours after dosing of afatinib (AUC_{0-24}), the AUC_{0-24} of plasma unchanged afatinib was 73%. The applicant explained that the $t_{1/2}$ of plasma unchanged afatinib was lower than that of the plasma and whole blood radioactivities, suggesting the presence of the metabolites with longer $t_{1/2}$ than that of unchanged afatinib in the plasma and whole blood.

The whole blood radioactivity concentration changed over time as with the total plasma radioactivity concentration. The concentration reached the peak (C_{max}) at approximately 6 hours post-dose, and the AUC_{0-24} of the total plasma radioactivity was approximately 80% of that of the

whole blood total radioactivity. The applicant explained that the urine excretion rate of the total radioactivity until 216 hours after dosing of afatinib was 4.29% of the dosed radioactivity, while the fecal excretion rate was 85.4% of the dosed radioactivity, and the total recovery of the radioactivity (mean) until 312 hours was 89.5%, suggesting that the total radioactivity would be mainly excreted in feces.

PK parameters of the plasma unchanged afatinib, total plasma radioactivity, and whole blood total radioactivity

	Plasma unchanged afatinib	Total plasma radioactivity	Total whole blood radioactivity
$AUC_{0\text{-}24}$ (ng·h/mL)	80.2 (34.9)	110 (40.1)	138 (47.1)
$AUC_{0\text{-}tz}$ (ng·h/mL)	144 (32.3)	231 (69.9)	446 (59.1)
C_{max} (ng/mL)	6.19 (38.4)	7.58 (36.0)	8.01 (41.2)
t_{max} (h)[*1]	6.0 (1.5, 8.0)	6.0 (0.75, 8.0)	6.0 (0.75, 6.1)
$t_{1/2}$ (h)	33.9 (14.3)	118 (65.1)[*2]	195 (83.9)[*2]
CL/F (mL/min)	1530 (31.2)	325 (51.1)	141 (104)
Vz/F (L)	4500 (37.6)	3330 (37.1)	2390 (34.8)

Geometric mean (geometric coefficient of variation %), n = 8, *1: Median (range), *2: Due to the blood collection time point (96 hours), it might be underestimated.

4.(ii).A.(1).3) Foreign phase I study (5.3.1.1-1, Study 1200.80 [[redacted] to [redacted] 20[redacted]])

An open-label study in 48 healthy adult subjects was conducted to investigate the PK of afatinib after a single oral dose of afatinib at 20, 30, 40, or 50 mg (the table below). The exposure to afatinib ($AUC_{0\text{-}\infty}$, C_{max}) increased more than dose-proportionally, and the CL/F and Vz/F decreased with the increasing dose. The applicant explained that the increase in exposure to afatinib exceeding the dose proportion was considered attributable to saturation of P-gp-mediated efflux in the intestinal tract in the process of absorption.

PK parameters of afatinib

	Dose			
	20 mg	30 mg	40 mg	50 mg
n	12	12	11	12
C_{max} (ng/mL)	7.78 (42.3)	13.7 (44.7)	24.3 (33.1)	37.1 (37.4)
Dose-corrected C_{max} (ng/mL/mg)	0.389 (42.3)	0.457 (44.7)	0.608 (33.1)	0.741 (37.4)
$AUC_{0\text{-}\infty}$ (ng·h/mL)	189 (35.1)	327 (35.5)	549 (32.1)	724 (48.7)
Dose-corrected $AUC_{0\text{-}\infty}$ (ng·h/mL/mg)	9.43 (35.1)	10.9 (35.5)	13.7 (32.1)	14.5 (48.7)
t_{max} (h)[*]	5.0 (2.0, 8.0)	5.0 (1.0, 6.0)	5.0 (5.0, 6.0)	5.0 (4.0, 5.0)
$t_{1/2}$ (h)	30.7 (10.6)	32.9 (24.8)	29.6 (12.6)	28.5 (15.5)
CL/F (mL/min)	1770 (35.1)	1530 (35.5)	1210 (32.1)	1150 (48.7)
Vz/F (L)	4700 (43.9)	4350 (42.7)	3110 (39.1)	2840 (54.8)

Geometric mean (geometric coefficient of variation, %), *: Median (range)

4.(ii).A.(2) Cancer patients

4.(ii).A.(2).1) Foreign phase I study (5.3.3.2-1, Study 1200.1 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study in 38 patients with advanced solid cancer was conducted to investigate the PK of afatinib after oral administration of afatinib at a dose of 10, 20, 30, 45, 70, 85, or 100 mg once daily for 14 days (the table below). The applicant explained that PK parameters of afatinib had large inter-individual variability, and dose-proportionality was not clear.

The ratios of the geometric mean $AUC_{0\text{-}24}$ and C_{max} on Day 14 to those on Day 1 were 2.42 to 3.82 and 1.76 to 2.74, respectively.

PK parameters of afatinib

Dose	Date of measurement	n	AUC_{0-24} (ng·h/mL)	C_{max} (ng/mL)	t_{max}* (h)	$t_{1/2}$ (h)	CL/F (mL/min)	Vz/F (L)
10 mg	1	3	82.0 (103)	8.03 (125)	3.0 (2.1, 4.0)	20.1 (15.1)	1160 (90.2)	2020 (107)
	14	3	199 (56.9)	14.1 (72.1)	3.0 (2.0, 4.0)	35.9 (12.0)	839 (56.9)	2610 (42.8)
20 mg	1	3	67.9 (25.5)	7.29 (51.0)	2.0 (2.0, 5.0)	29.0 (470)	1820 (269)	4570 (32.8)
	14	3	241 (59.4)	16.2 (51.9)	4.0 (4.0, 4.0)	39.7 (13.4)	1390 (59.4)	4760 (49.3)
30 mg	1	3	498 (21.3)	58.6 (42.5)	2.0 (0.6, 2.0)	18.5 (14.6)	634 (24.6)	1020 (19.2)
	14	3	1310 (57.5)	111 (69.7)	1.0 (0.5, 2.1)	37.7 (25.1)	383 (57.5)	1250 (64.0)
45 mg	1	3	343 (22.0)	30.2 (20.0)	3.1 (2.0, 5.0)	18.0 (53.4)	1320 (23.8)	2060 (42.8)
	14	3	840 (35.0)	68.4 (31.7)	3.0 (2.0, 4.1)	43.4 (31.4)	893 (35.0)	3350 (57.3)
70 mg	1	18	744 (91.9)	67.7 (93.8)	2.1 (0.5, 4.1)	15.5 (36.6)	1020 (67.6)	1360 (107)
	14	16	2620 (36.3)	180 (34.5)	2.0 (0.5, 5.0)	39.6 (38.7)	445 (36.3)	1530 (33.5)
85 mg	1	6	1040 (69.4)	87.1 (80.5)	3.0 (2.0, 7.0)	14.3 (13.4)	920 (70.9)	1140 (63.1)
	14	4	2340 (47.6)	163 (53.0)	2.0 (2.0, 2.0)	30.8 (12.9)	604 (47.6)	1610 (36.4)
100 mg	1	2	1290 (43.1)	138 (31.3)	1.2 (0.5, 2.0)	13.8 (0.226)	931 (43.1)	1110 (43.3)
	14	1	2750	243	1.0	28.6	606	1500

Geometric mean (geometric coefficient of variation, %), *: Median (range)

4.(ii).A.(2).2) Foreign phase I study (5.3.3.2-2, Study 1200.2 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 43 patients with advanced solid cancer (43 patients included in PK analysis) to investigate the PK of afatinib after oral administration of afatinib at a dose of 10, 20, 40, 55, or 65 mg once daily for 21 days. At a dose of 40 mg, the geometric means (geometric coefficient of variation, %) of the plasma concentration before dosing on Days 1, 8, 15, and 21 were 11.5 (59.8), 27.5 (79.9), 29.3 (82.2), and 24.2 (75.6) ng/mL, respectively. The applicant explained that the plasma afatinib concentration reached the C_{max} around 2 to 5 hours post-pose, and the AUC and C_{max} were considered to reach the steady state on Day 8, although their inter-individual variability was large.

The ratios of the geometric mean AUC_{0-24} and C_{max} on Day 21 to those on Day 1 were 1.81 to 3.07 and 1.36 to 2.35, respectively.

4.(ii).A.(2).3) Foreign phase I study (5.3.3.2-3, Study 1200.17 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 7 patients with advanced solid cancer who completed the prescribed treatment sessions with afatinib without progression in Study 1200.1 or Study 1200.2 to investigate the safety and PK of long-term treatment with afatinib at their optimal dose in the previous study. The plasma concentrations before dosing remained almost constant irrespective of the number of treatment days although the inter-individual variability was large.

4.(ii).A.(2).4) Foreign phase I study (5.3.3.2-4, Study 1200.3 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 53 patients with advanced solid cancer (52 patients included in PK analysis) to investigate the PK of afatinib after oral administration of afatinib at a dose of 10, 20, 30, 40, or 50 mg once daily.

The ratios of the geometric mean AUC and C_{max} on Day 27 to those on Day 1 were 1.89 to 3.97 and 1.42 to 3.28, respectively. In the dose range in this study, the variability of the peak-trough concentrations on Day 27 was 59.8% to 83.3%.

4.(ii).A.(2).5) Foreign phase I study (5.3.3.2-5, Study 1200.4 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study in 30 patients with advanced solid cancer (30 patients included in PK analysis) was conducted to investigate the PK of afatinib after oral administration of afatinib at a dose of 10, 20, 40, or 60 mg once daily. In the dose range in this study, the variability of the peak-trough concentrations on Day 27 was 46.8% to 67.7%.

4.(ii).A.(2).6) Studies 1200.1 to 4 and Study 1200.24 (5.3.5.3-1)

The PK data obtained from the foreign phase I studies (Studies 1200.1, 1200.2, 1200.3, 1200.4) and foreign phase II study (Study 1200.24) in patients with advanced solid cancer are as shown in the table below.

PK parameters of afatinib

Dose	n	$AUC_{0\text{-}24}$ (ng·h/mL)	$AUC_{\tau,ss}$ (ng·h/mL)	C_{max} (ng/mL)	$C_{max,ss}$ (ng/mL)	t_{max} *1 (h)	$t_{max,ss}$ *1 (h)	$t_{1/2}$ (h)	$t_{1/2,ss}$ (h)
20 mg	15	119 (56.6)*2	380 (77.2)	11.6 (85.1)*3	24.5 (88.5)	3.0 (0.5, 24.0)*3	4.98 (0.5, 9.1)	22.3 (80.3)*4	47.1 (51.6)
30 mg	10	189 (95.9)	660 (92.4)*5	16.3 (139)	46.5 (120)*5	2.0 (0.6, 6.9)	2.01 (0.5, 4.0)*5	21.3 (82.1)	33.4 (56.8)*6
40 mg	30	324 (68.9)	631 (85.9)*7	25.2 (73.3)	38.0 (105)*8	4.0 (0.6, 9.1)	3.0 (0.5, 23.8)*8	26.9 (61.1)	36.3 (57.1)*9
50 mg	73	459 (68.0)*10	1130 (59.6)*11	40.8 (76.6)	77.0 (63.6)*11	3.1 (0.9, 9.1)	3.8 (1.0, 7.1)*11	21.9 (54.8)*3	22.3 (25.4)*6

Geometric mean (geometric coefficient of variation, %), $AUC_{\tau,ss}$: AUC during the interval τ at the steady state, *1: Median (range), *2: n = 12, *3: n = 13, *4: n = 11, *5: n = 8, *6: n = 7, *7: n = 26, *8: n = 27, *9: n = 23, *10: n = 69, *11: n = 51

4.(ii).A.(2).7) Foreign phase II study (5.3.5.2-4, Study 1200.22 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted], 20[redacted])])

An open-label study was conducted to investigate the PK of afatinib after oral administration of afatinib at a dose of 40 or 50 mg once daily in 129 patients with inoperable or recurrent *EGFR* mutation-positive NSCLC (adenocarcinoma) who had not received chemotherapy or had received ≥1 regimen of chemotherapy (except for epidermal growth factor receptor [EGFR] tyrosine kinase inhibitors [EGFR-TKIs]) (129 patients included in the PK analysis). At a dose of 40 mg, the geometric means (geometric coefficient of variation, %) of the plasma concentration before dosing on Days 15, 29, and 57 were 31.7 (45.9), 27.9 (63.1), and 26.3 (62.0) ng/mL, respectively, while at a dose of 50 mg, the corresponding geometric means were 40.6 (60.8), 33.7 (64.1), and 27.8 (75.0) ng/mL, respectively. These means remained almost constant irrespective of treatment days although the inter-individual variability was large.

4.(ii).A.(2).8) Foreign phase III study (5.3.5.1-2, Study 1200.23 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted], 20[redacted])])

A double-blind study was conducted to investigate the efficacy, safety, and PK of afatinib after oral administration of afatinib at a dose of 50 mg once daily for ≥12 weeks in 585 patients with inoperable or recurrent NSCLC (adenocarcinoma) who had received 1 or 2 regimens of chemotherapy including platinum antineoplastic drugs (except for EGFR-TKIs) and EGFR-TKIs (390 patients in the afatinib group [384 patients included in PK analysis], 195 patients in the placebo group). At a dose of 50 mg, the geometric means (geometric coefficient of variation, %) of the plasma concentration before dosing on Days 15, 29, and 57 were 39.1 (64.3), 34.1 (65.2), and 33.0 (52.8) ng/mL, respectively. These means remained almost constant irrespective of treatment days although the inter-individual variability was large.

4.(ii).A.(2).9) Foreign phase III study (5.3.5.1-1, Study 1200.32 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted to investigate the efficacy, safety, and PK of afatinib after oral administration of afatinib once daily at a dose of 40 mg or intravenous administrations of CDDP at 75 mg/m^2 and pemetrexed sodium hydrate (PEM) at 500 mg/m^2 at intervals of 3 weeks in 345 chemotherapy-naive patients with inoperable or recurrent *EGFR* mutation-positive NSCLC (adenocarcinoma) (230 patients in the afatinib group [218 patients included in PK analysis], 115 patients in the placebo group). At a dose of 40 mg, the geometric means (geometric coefficient of variation, %) of the plasma concentration before dosing on Days 22, 29, and 43

were 28.0 (85.0), 25.8 (69.5), and 23.7 (66.5) ng/mL, respectively. These means remained almost constant irrespective of treatment days although the inter-individual variability was large.

4.(ii).A.(2).10) Japanese phase I/II study (5.3.3.2-9, 5.3.5.2-1, Study 1200.33 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted], 20[redacted])])

(a) Phase I part

An open-label study was conducted to investigate the PK of afatinib after oral administration of afatinib at a dose of 20, 40, or 50 mg once daily in 12 NSCLC patients who had not responded to the standard treatment or for whom any other appropriate therapy was available (the table below). The ratios of the geometric mean $AUC_{0\text{-}24}$ and C_{max} on Day 28 with respect to those on Day 1 were 1.96 to 3.97 and 1.63 to 4.41, respectively.

PK parameters of afatinib

Dose	Date of measurement	n	$AUC_{0\text{-}24}$ (ng·h/mL)	$AUC_{\tau,ss}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} *1 (h)	$t_{1/2}$ (h)	CL/F (mL/min)	Vz/F (L)
20 mg	1	3	147 (84.5)	-	12.4 (101)	3.9 (3.0, 5.0)	21.3 (63.1)	1200 (39.5)	2200 (122)
	28	3	-	409 (16.5)	26.9 (24.9)	4.0 (2.9, 5.0)	38.5 (14.4)	814 (16.5)	2710 (30.3)
40 mg	1	3	286, 312*2	-	18.9 (45.8)	4.1 (2.0, 9.0)	45.1, 31.9*2	697, 916*2	2720, 2530*2
	28	3	-	1240 (9.73)	83.3 (30.1)	3.0 (2.0, 4.0)	40.4 (11.9)	538 (9.73)	1880 (3.78)
50 mg	1	6	539 (59.0)	-	44.4 (60.6)	3.0 (2.0, 5.0)	14.8 (20.0)	1030 (55.9)	1320 (62.8)
	28	5	-	1010 (71.5)	66.8 (71.6)	3.0 (1.0, 5.0)	33.5 (22.2)	827 (71.5)	2400 (80.6)

Geometric mean (geometric coefficient of variation %), $AUC_{\tau,ss}$: AUC during the interval τ on Day 28, *1: Median (range), *2: n = 2

(b) Phase II part

An open-label study was conducted to investigate the PK of afatinib after oral administration of afatinib once daily at a dose of 50 mg in 62 patients with inoperable or recurrent NSCLC who had received 1 or 2 regimens of chemotherapy including platinum antineoplastic drugs (except for EGFR-TKIs) and EGFR-TKIs for ≥12 weeks (62 patients included in PK analysis). The geometric means (geometric coefficient of variation, %) of the plasma trough concentrations on Days 1 and 15 in Cycle 2 (plasma concentrations 16-32 hours after the previous administration) were 38.3 (71.2) and 28.6 (138) ng/mL, respectively, of which the inter-individual variability was large. The plasma trough concentration on Day 15 was lower than that on Day 1. The applicant claimed that this low value may have resulted from the dose reduction due to the adverse events in some patients. The applicant explained that the relationship between the plasma trough concentrations of afatinib and adverse events was not clarified due to the limited number of subjects.

4.(ii).A.(3) Drug interaction studies

4.(ii).A.(3).1) Foreign phase II study (5.3.5.4-25, Study 1200.5 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was concluded to investigate the PK of afatinib in 28 patients with estrogen receptor-positive metastatic breast cancer who had received letrozole (28 patients included in PK analysis), and in this study, afatinib was administered once daily at a dose of 30, 40, or 50 mg concomitantly with letrozole at a dose of 2.5 mg for 28 days. The applicant explained that in the patients receiving concomitant use of afatinib at 40 mg with letrozole, the geometric means (geometric coefficient of variation, %) of the $AUC_{\tau,ss}$ and $C_{max,ss}$ were 660 (41.3) ng·h/mL and 43.8 (42.0) ng/mL, respectively, which were not largely different from the $AUC_{\tau,ss}$ (631 ng·h/mL) and $C_{max,ss}$ (38.0 ng/mL) in patients receiving afatinib alone at a dose of 40 mg in the pooled analysis [see "4.(ii).A.(2).6) Studies 1200.1 to 4 and Study 1200.24"], and concomitant use with letrozole did not affect the PK parameters of afatinib.

4.(ii).A.(3).2) Foreign phase I study (5.3.3.2-7, Study 1200.6 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 31 patients with EGFR or HER2 positive advanced solid cancer (24 patients included in PK analysis) to investigate the PK of afatinib after concomitant

use of afatinib with DTX. One treatment cycle consisted of 21 days, and afatinib was to be orally administered at a dose of 10 to 30 mg on Days 2 to 14 or on Days 2 to 21 of DTX treatment and the cycle could be repeated up to 6 times. The applicant explained that in the patients receiving concomitant use of afatinib at 20 mg with DTX, the geometric means (geometric coefficient of variation, %) of the $AUC_{0\text{-}24}$ and C_{max} were 120 (68.2) and 230 (93.1) ng·h/mL and 7.18 (114) and 14.1 (90.3) ng/mL in Cycles 1 and 2, respectively, which were not largely different from the $AUC_{0\text{-}24}$ (119 ng·h/mL) and C_{max} (11.6 ng/mL) in patients receiving afatinib alone at 20 mg in the pooled analysis [see "4.(ii).A.(2).6) Studies 1200.1 to 4 and Study 1200.24"], and concomitant use with DTX did not affect the PK parameters of afatinib.

4.(ii).A.(3).3) Foreign phase I study (5.3.3.2-8, Study 1200.20 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 40 patients with advanced solid cancer (40 patients included in PK analysis) to investigate the PK of afatinib after concomitant use of afatinib with DTX. One treatment cycle consisted of 21 days, and afatinib was to be orally administered at a dose of 10 to 160 mg on Days 2 to 4 of DTX treatment, and the cycle could be repeated up to 8 times. The applicant explained that in the patients receiving concomitant use of afatinib at 90 mg with DTX, the geometric means (geometric coefficient of variation, %) of the $AUC_{0\text{-}24}$ and C_{max} were 879 (62.6) and 995 (48.3) ng·h/mL and 71.4 (69.5) and 81.2 (56.7) ng/mL in Cycles 1 and 2, respectively, which were not largely different from the $AUC_{0\text{-}24}$ (1040 ng·h/mL) and C_{max} (87.1 ng/mL) in patients receiving afatinib alone at 85 mg in the pooled analysis [see "4.(ii).A.(2).6) Studies 1200.1 to 4 and Study 1200.24"].

4.(ii).A.(3).4) Drug interaction study with TMZ (5.3.3.2-10, Study 1200.36 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted] [redacted], 20[redacted])])

An open-label study was conducted to investigate the PK of afatinib after concomitant use of afatinib with TMZ in 112 patients with Grade III/IV malignant glioma in the WHO classification who had received chemoradiotherapy (32 patients included in the phase I part [31 patients included in PK analysis], 119 patients included in the phase II part [50 patients included in PK analysis]). The geometric means (geometric coefficient of variation, %) of the $AUC_{\tau,ss}$ and $C_{max,ss}$ of afatinib monotherapy were 918 (65.3) ng·h/mL and 50.5 (58.0) ng/mL, while those of concomitant use of afatinib with TMZ were 1070 (63.7) ng·h/mL and 63.2 (62.1) ng/mL, respectively. Based on the above data, the applicant explained that concomitant use with TMZ slightly increased the exposure to afatinib, but its clinical significance was considered to be small.

4.(ii).A.(3).5) Foreign phase I study (5.3.5.4-2, Study 1200.37 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 47 patients with advanced solid cancer (47 patients included in PK analysis) to investigate the PK of afatinib after concomitant use of afatinib with CDDP/5-FU or CDDP/PTX. The geometric means (geometric coefficient of variation, %) of the $AUC_{\tau,ss}$ of concomitant use of afatinib with CDDP 75 or 100 mg/m^2/5-FU were 858 (56.3) and 221 (49.2) ng·h/mL, and the geometric means (geometric coefficient of variation, %) of the $C_{max,ss}$ were 57.0 (41.1) and 13.4 (28.9) ng/mL, respectively. The applicant explained that the exposure to afatinib tended to decrease with the increasing CDDP dose, but the effects of concomitant use with CDDP on the PK parameters of afatinib could not be determined, because the number of subjects was limited (3 or 6 subjects).

4.(ii).A.(3).6) Foreign phase I study (5.3.5.4-3, Study 1200.68 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted] 20[redacted])])

An open-label study was conducted in 18 patients with HER2-positive metastatic breast cancer or recurrent breast cancer (18 patients included in PK analysis) to investigate the PK of afatinib after concomitant use of afatinib with trastuzumab. The applicant explained that in the patients receiving concomitant use of afatinib at 20 mg with trastuzumab, the geometric means (geometric coefficient of variation, %) of the $C_{max,ss}$ was 17.9 (80.9) ng/mL, which was not largely different from the $C_{max,ss}$ (24.5 ng/mL) in patients receiving afatinib alone at 20 mg in the pooled

analysis [see "4.(ii).A.(2).6) Studies 1200.1 to 4 and Study 1200.24"], and concomitant use with trastuzumab did not affect the PK parameters of afatinib.

4.(ii).A.(3).7) Drug interaction study with ritonavir (5.3.3.4-1, Study 1200.79 [to 20])

An open-label study was conducted in 22 healthy adult subjects to investigate the effects of ritonavir on the PK of afatinib. Ritonavir was orally administered at a dose of 200 mg twice daily for 3 days, and on Day 2 of the ritonavir treatment (1 hour after administration of ritonavir), a single dose of afatinib was orally administered at 20 mg. The $AUC_{0-\infty}$ and C_{max} of concomitant use of afatinib with ritonavir increased from those of afatinib monotherapy, and the geometric mean ratios [90% CI] of the parameter values of concomitant use of afatinib with ritonavir to those of afatinib monotherapy were 147.6 [133.7, 162.9] and 138.5 [120.6, 158.9], respectively. The applicant explained that administration of afatinib alone and concomitant use of afatinib with ritonavir resulted in almost comparable t_{max} (4.0 hours for both) and $t_{1/2}$ in the terminal phase (35.9 hours, 34.1 hours) suggesting that ritonavir may have an effect on absorption of afatinib. The applicant continued that the increased $AUC_{0-\infty}$ and C_{max} of afatinib may be attributable to the P-gp inhibitory effect of ritonavir, which inhibits P-gp and CYP3A4, because CYP3A4 was suggested to be merely involved in the metabolism of afatinib [see "3.(ii).A.(3) Metabolism"].

PK parameters of afatinib monotherapy or concomitant use of afatinib with ritonavir

	n	AUC_{0-24} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max}^{*} (h)	$t_{1/2}$ (h)
Afatinib alone	22	85.6 (43.7)	165 (37.9)	7.71 (47.4)	4.0 (0.5, 5.0)	35.9 (25.1)
Concomitant use with ritonavir	22	128 (30.3)	243 (26.0)	10.7 (30.0)	4.0 (4.0, 5.0)	34.1 (16.8)

Geometric mean (geometric coefficient of variation, %), *: Median (range)

4.(ii).A.(3).8) Drug interaction study with ritonavir (5.3.3.4-2, Study 1200.151 [to 20])

An open-label study was conducted in 24 healthy adult subjects to investigate the effects of ritonavir on the PK of afatinib. Ritonavir was administered at a dose of 200 mg twice daily for 3 days, and on Day 2 of the ritonavir treatment (at the same time or 6 hour before administration of ritonavir), a single dose of afatinib was orally administered at 40 mg. The geometric mean ratios [90% CI] of the $AUC_{0-\infty}$of afatinib treatment with ritonavir at the same time and 6 hours before administration of ritonavir to that of afatinib monotherapy were 118.56 [111.71, 125.82] and 110.76 [107.94, 116.91], and the geometric mean ratios C_{max} were 104.06 [96.68, 112.00] and 105.09 [96.43, 114.53], respectively. The applicant explained that the PK of concomitant use of afatinib with ritonavir was not affected by the timing of administration.

PK parameters of afatinib monotherapy or concomitant use of afatinib with ritonavir

	n	$AUC_{0-\infty}$ (ng·h/mL)	AUC_{0-tz} (ng·h/mL)	C_{max} (ng/mL)	t_{max}^{*1} (h)	$t_{1/2}$ (h)
Afatinib alone	22	426 (22.8)	392 (26.2)*2	19.5 (33.5)	6.0 (4.0, 8.0)	33.0 (25.8)
Concomitant use with ritonavir (same time)	24	515 (27.5)	478 (27.9)	20.7 (29.4)	6.0 (3.0, 8.0)	32.5 (18.2)
Concomitant use with ritonavir (6-hour difference)	22	475 (19.4)	438 (20.3)	20.7 (24.4)	6.0 (0.5, 8.0)	33.9 (24.5)

Geometric mean (geometric coefficient of variation %), *1: Median (range), *2: n = 21

4.(ii).A.(3).9) Drug interaction study with rifampicin (5.3.3.4-3, Study 1200.152 [[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 22 healthy adult subjects to investigate the effects of rifampicin on the PK of afatinib. Rifampicin was orally administered at a dose of 600 mg once daily for 7 days, and on Day 8 of the rifampicin treatment, a single oral dose of afatinib was administered at 40 mg. The $AUC_{0\text{-}24}$, $AUC_{0\text{-}\infty}$, and C_{max} of concomitant use of afatinib with rifampicin were lower than those of afatinib monotherapy, and the geometric mean ratios [90% CI] of the $AUC_{0\text{-}\infty}$ and C_{max} of concomitant use of afatinib with rifampicin to those of afatinib monotherapy were 66.2 [60.8, 72.1] and 78.4 [72.4, 85.0], respectively. The applicant explained that the decreased $AUC_{0\text{-}\infty}$ and C_{max} of afatinib may be attributable to the P-gp induction by rifampicin, which is an inducer of P-gp and CYP3A4, because CYP3A4 was suggested to be merely involved in the metabolism of afatinib [see "3.(ii).A.(3) Metabolism"].

PK parameters of afatinib monotherapy or concomitant use of afatinib with rifampicin

	n	$AUC_{0\text{-}24}$ (ng·h/mL)	$AUC_{0\text{-}\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max} *1 (h)	$t_{1/2}$ (h)
Afatinib alone	22	491 (41.4)	912 (38.3)	38.3 (38.4)	6.0 (5.0, 7.0)	32.8 (18.4)
Concomitant use with rifampicin	21	353 (35.0)	610 (32.1)	30.0 (34.1)*2	6.0 (3.0, 8.0)*2	36.0 (15.1)

Geometric mean (geometric coefficient of variation %), *1: Median (range), *2: n = 22

4.(ii).A.(4) Foreign phase I study in patients with hepatic impairment (5.3.3.2-11, Study 1200.86 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 8 each of patients with mild (Child-Pugh A) and moderate (Child-Pugh B) hepatic impairment and healthy adult subjects (normal hepatic function) with the background that match those of the above patients with mild and moderate hepatic impairment (32 subjects in total) to investigate the PK of afatinib after a single oral dose of afatinib at 50 mg. The PK parameters following single dose of afatinib at 50 mg are as shown in the table below. There were no marked differences in PK parameters of afatinib between the patients with hepatic impairment and healthy adult subjects (normal hepatic function).

PK parameters in patients with hepatic impairment and healthy adult subjects (normal hepatic function)

	n	$AUC_{0\text{-}tz}$ (ng·h/mL)	$AUC_{0\text{-}\infty}$ (ng·h/mL)	C_{max} (ng/mL)	t_{max}* (h)	$t_{1/2}$ (h)	CL/F (mL/min)
Healthy adults (normal hepatic function) (matching the background of the patients below)	8	930 (22.5)	956 (22.7)	30.7 (33.7)	5.0 (3.0, 7.0)	60.3 (14.9)	872 (22.7)
Patients with mild (Child-Pugh A) hepatic impairment	8	842 (50.8)	886 (53.7)	33.7 (51.7)	5.0 (0.5, 8.0)	74.9 (47.6)	941 (53.7)
Healthy adults (normal hepatic function) (matching the background of the patients below)	8	956 (33.3)	985 (32.3)	31.1 (46.0)	7.5 (5.0, 9.0)	59.9 (28.5)	846 (32.3)
Patients with moderate (Child-Pugh B) hepatic impairment	8	904 (31.4)	934 (31.0)	39.5 (40.1)	4.0 (0.5, 5.0)	64.3 (13.1)	892 (31.0)

Geometric mean (geometric coefficient of variation, %), *: Median (range)

4.(ii).A.(5) Study of relationship between the exposure and changes in QT/QTc interval (5.3.4.2-1, Study 1200.24 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label study in 60 non-Japanese patients with solid cancer was conducted to investigate the effect of afatinib on Fridericia-corrected QT (QTcF) interval following daily oral administration of afatinib at a dose of 50 mg.

On Day 14, the mean change (msec) [90% CI] of QTcF from baseline was -0.3 [-2.8, 2.3]. Analysis using a linear mixed-effects model did not indicate correlation between the mean change in QT or QTcF interval from baseline and plasma afatinib concentration.

Based on the above, the applicant explained that afatinib would not prolong the QTcF interval in a clinically significant manner.

4.(ii).A.(6) Population pharmacokinetic (PPK) analysis

4.(ii).A.(6).1) PPK analysis in patients with advanced solid cancer (5.3.3.5-1, 5.3.3.5-4)

Based on the PK data from 3 foreign phase I studies in patients with advanced solid cancer (Studies 1200.1, 1200.2, 1200.3) (109 subjects, 1850 measurement time points) and 2 foreign phase I studies in patients with advanced solid cancer (Studies 1200.4, 1200.20) (187 subjects, 2595 time points), PPK analysis was performed in a non-linear mixed-effects model (NONMEM, ver V.1.1 and VI) to investigate a model describing the PK of afatinib. As a result, the applicant explained that the PK of afatinib was described in a 2-compartment model involving the primary absorption and clearance process, and in terms of the plasma afatinib concentration, the relative bioavailability increased with the increasing dose to 70 mg according to a power function and then leveled off at a dose of >70 mg.

4.(ii).A.(6).2) PPK analysis in patients with inoperable or recurrent NSCLC and patients with metastatic breast cancer (5.3.3.5-2)

Using the 2-compartment model involving the primary absorption and clearance process, the PPK analysis was performed using a non-linear mixed-effects model (NONMEM, ver VI.2.0) based on the PK data (506 subjects, 2550 time points) from foreign phase II study (Study 1200.22) and foreign phase III study (Study 1200.23) in inoperable or recurrent NSCLC patients, as well as 2 foreign phase II studies (Studies 1200.10, 1200.11) in patients with metastatic breast cancer. The covariates for the PK parameters of afatinib included age, sex, ethnicity, physique, smoking history, drinking habit, renal and hepatic impairment, ECOG performance score (ECOG PS), and presence or absence of hepatic metastasis as well as cancer type. The covariates significantly affecting the PK of afatinib included diet, body weight, ECOG PS, LDH, creatinine clearance (CLcr), and sex. To investigate to what extent the above covariates would affect the PK of afatinib, the effect of P-gp inhibitors on the bioavailability was included in the final model.

The applicant explained that the above PKK analysis data suggested the following: (a) in average patients (body weight 64 kg, ECOG PS 0 or 1, CLcr 78 mL/min, LDH 257 U/L, female) receiving afatinib at a dose of 50 mg, the CL/F and distribution volume at the steady state (V_{ss}/F) were 41.1 L/h and 2317 L, respectively, and the $t_{1/2}$, absorption rate constant, and absorption lag time were 46.4 hours, 0.242 h^{-1}, and 0.215 hours, respectively; (b) none of the single covariates affected the plasma afatinib concentration to an extent exceeding the inter-individual variability; and (c) in patients with all of the above covariates (body weight 45 kg, ECOG PS 2, CLcr 30 mL/min, LDH 784 U/L, concomitant use of potent P-gp inhibitors, female), the exposure to afatinib ($AUC_{\tau,ss}$) was estimated to be 4.15 times higher than that in an average patient.

4.(ii).A.(6).3) PPK analysis in patients with advanced solid cancer (5.3.3.5-3)

In addition to the 4 foreign studies in 4.(ii).A.(6).2), PPK analysis was performed to investigate the covariates using the PK data (927 patients [724 NSCLC patients, 90 patients with breast cancer, 73 patients with head and neck squamous cell carcinoma]) from foreign phase II study (Study 1200.28) in patients with head and neck squamous cell carcinoma, Japanese phase I/II study (Study 1200.33), and foreign phase III study (Study 1200.32) in NSCLC patients. The covariates significantly affecting the PK of afatinib was diet, body weight, CLcr, ECOG PS, LDH, ALP, plasma total protein, sex, and cancer type. The applicant explained that the above PKK analysis data suggested the following items.

- In average patients (body weight 62 kg, ECOG PS 1, CLcr 79 mL/min, LDH 241 U/L, ALP 106 U/L, plasma total protein 72 g/L, female, NSCLC) receiving afatinib once daily at a dose of 40 mg, the CL/F and distribution volume at the steady state (V_{ss}/F) were 44.0 L/h and 2370 L, respectively, and the $t_{1/2}$ and absorption rate constant were 45.0 hours and 0.252/h, respectively.

- None of the single covariates affected the plasma afatinib concentration to an extent exceeding the inter-individual variability.

- The $AUC_{\tau,ss}$ in patients with head and neck squamous cell carcinoma was 35% greater than that in NSCLC patients.

4.(ii).A.(7) Pharmacodynamics

In foreign phase I studies in patients with advanced solid cancer (Studies 1200.1, 1200.2, 1200.3), effects of afatinib on the expression levels of the biomarkers (EGFR, MAPK, AKT, Ki67, $p27^{KIP1}$) indicating EGFR activation were investigated by immunohistochemical staining. Afatinib dose-independently decreased the Ki67 expression level and increased the $p27^{KIP1}$ expression level. There were no effects on the other biomarkers (EGFR, MAPK, AKT) investigated.

4.(ii).A.(8) Relationships of the exposure with efficacy and safety

4.(ii).A.(8).1) Relationship of the exposure with efficacy

In Study 1200.32, the relationship of the exposure to afatinib with efficacy was investigated. As a result, there were no marked relationships of the plasma trough concentration of afatinib on Day 42* with the tumor reducing effect, progression-free survival (PFS), or overall survival (OS) on Week 6.

* In the case where the plasma trough concentration of afatinib on Day 42 was not determined, the concentration on Day 29 was used, and in the case where the concentration on Day 29 or 42 was not determined, the concentration on Day 21 was used.

4.(ii).A.(8).2) Relationship of the exposure with the safety

The relationship of the exposure to afatinib with the safety was investigated in the data from 643 subjects included in Studies 1200.22, 1200.32, 1200.23, and 1200.33. The results showed a correlation of the plasma trough concentration of afatinib with the incidences of diarrhoea, rash, and acne. Based on the above results and ones from "(6) Population pharmacokinetic (PPK) analysis," the applicant explained that it would not be necessary to adjust the dose according to the patient background information, but it would be appropriate to adjust the dose according to the tolerability of afatinib in consideration of diarrhoea, rash, and acne, as done in Study 1200.32.

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

4.(ii).B.(1) Differences in the PK of afatinib between Japanese and non-Japanese subjects

PMDA asked the applicant to explain the differences in the PK of afatinib between Japanese and non-Japanese subjects.

The applicant responded that there was no clear difference between Japanese and non-Japanese subjects based on the following data.

- The CL/F and V_{ss}/F of afatinib were compared between Japanese and non-Japanese subjects (these parameter values were corrected based on the body weight for this comparison, because the body weight was suggested as a covariate that might affect the PK of afatinib). These parameter values were estimated by using the PK data from the Japanese clinical study (Study 1200.33), foreign clinical study (Studies 1200.10, 1200.11, 1200.22, 1200.23, 1200.28), and global study (Study 1200.32), based on the above final model of the PPK analysis [see

"4.(ii).A.(6) Population pharmacokinetic (PPK) analysis"]. As a result, the distribution of the concerned PK parameters in Japanese subjects was almost comparable to that in non-Japanese subjects.

- The PK profiles of afatinib at doses of 20, 40, and 50 mg were compared based on the PK data from the Japanese clinical study (Study 1200.33) and pooled analysis results on PK data from the foreign clinical studies (Studies 1200.1, 1200.2, 1200.3, 1200.4, 1200.24) [see "4.(ii).A.(2).6) Studies 1200.1 to 4 and Study 1200.24"]. The geometric mean $AUC_{\tau,ss}$ and $C_{max,ss}$ at the steady state at a dose of 40 mg in Study 1200.33 (1240 ng·h/mL and 83.3 ng/mL, respectively) were higher than those in the pooled analysis results of the foreign clinical studies (631 ng·h/mL and 38.0 ng/mL, respectively), but the exposure distributions of afatinib at doses of 20 and 50 mg in the Japanese clinical studies fell within the same range of those of the foreign clinical studies.

- The PK parameters of afatinib at a dose of 40 mg in the global study (Study 1200.32) were compared between the Japanese and non-Japanese subjects, but no clear difference was noted in exposure to afatinib.

PMDA accepted the applicant's explanation.

4.(ii).B.(2) Pharmacokinetic interactions

The applicant explained the necessity of cautions for concomitant use of afatinib with P-gp inhibitors or inducers as follows:

Afatinib was suggested to be a substrate of P-gp *in vitro* [see "3.(ii).A.(5).3) Transporters"]. In a clinical study, the $AUC_{0-\infty}$ and C_{max} of afatinib increased due to concomitant use with ritonavir, a P-gp inhibitor, (afatinib was administered 1 hour after administration of ritonavir) [see "4.(ii).A.(3).7) Drug interaction study with ritonavir"]. On the other hand, the $AUC_{0-\infty}$ and C_{max} of afatinib treatment with ritonavir at the same time or 6 hours before administration of ritonavir were not clearly different from those of afatinib monotherapy [see "4.(ii).A.(3).8) Drug interaction study with ritonavir"]. Based on the above results, administration of afatinib with ritonavir at the same time or 6 hours before administration of ritonavir is considered unlikely to cause clinically significant pharmacokinetic interactions, while administration of afatinib 1 hour after administration of ritonavir is considered to cause pharmacokinetic interactions. A caution statement will be, therefore, provided for concomitant use of afatinib with P-gp inhibitors including ritonavir.

The C_{max} and $AUC_{0-\infty}$ of afatinib decreased due to concomitant use with rifampicin, a P-gp inducer [see "4.(ii).A.(3).9) Drug interaction study with rifampicin"]. The AUC and C_{max} of afatinib have large inter-individual variability. Based on the degree of drug interaction of afatinib with rifampicin, it is considered unnecessary to adjust the dose of afatinib for concomitant use with rifampicin. A caution statement will, however, be provided saying that concomitant use of afatinib with rifampicin, a potential P-gp inducer, may reduce the efficacy of afatinib.

PMDA accepted the applicant's explanation.

4.(ii).B.(3) Patients with severe hepatic impairment and renal impairment

Considering that careful administration of afatinib is necessary for patients with severe hepatic impairment (Child-Pugh classification C) and severe renal impairment (CLcr <30 mL/min) due to lack of administration experience in such patients, the applicant explained that the relevant caution statement was included in Careful Administration in the package insert.

PMDA accepted the applicant's explanation.

4.(iii) Summary of clinical efficacy and safety

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

As the evaluation data for the efficacy and safety, the results from the following 17 studies were submitted: 1 Japanese phase I/II study, 12 foreign phase I studies, 2 foreign phase II studies, 1 foreign phase III study, and 1 global phase III study. As the reference data, the results from 19 foreign clinical studies were also submitted as follows.

List of clinical studies for the efficacy and safety

Data category	Region	Study number	Phase	Patient population	No. of enrollment	Dosage regimen	Primary endpoint
Evaluation	Japan	1200.33	I/II	(a) Phase I part, NSCLC patients with no other appropriate therapies available (b) Phase II part, patients with inoperable or recurrent NSCLC (adenocarcinoma) who received 1 or 2 regimens of chemotherapy and EGFR-TKIs	(a) 12 (b) 62	(a) Once daily oral dose of afatinib at 20, 40, or 50 mg (b) Once daily oral dose of afatinib at 50 mg	(a) Safety PK (b) Safety Efficacy
	Global	1200.32	III	Chemotherapy-naive patients with inoperable or recurrent *EGFR* mutation-positive NSCLC (adenocarcinoma)	345 (a) 230 (b) 115	21 days as one treatment cycle (a) Once daily oral dose of afatinib at 40 mg (b) Intravenous infusion of CDDP 75 mg/m^2 and PEM 500 mg/m^2 (both on Day 1) at 3-week intervals (up to 6 cycles)	Efficacy Safety
	Foreign	1200.80	I	Healthy adult subjects	48	Single oral dose of afatinib at 20, 30, 40, or 50 mg	PK Safety
		1200.35	I	Healthy adult subjects	22	Single oral dose of afatinib at 20 mg (to-be-marketed formulation [tablets], formulation for phase II study [tablets] or oral solution)	PK Safety
		1200.25	I	Healthy adult subjects	8	Single oral dose of ^{14}C-labeled afatinib at 15 mg (oral solution)	PK Safety
		1200.79	I	Healthy adult subjects	22	- Multiple oral dose of ritonavir twice daily at 200 mg for 3 days, and on Day 2, single oral dose of afatinib at 20 mg - Single oral dose of afatinib at 20 mg Washout of ≥21 days between the treatment periods	PK Safety
		1200.151	I	Healthy adult subjects	24	- Single oral dose of afatinib at 40 mg - Multiple oral dose of ritonavir twice daily at 200 mg for 3 days, and in the first dose of ritonavir on Day 2, single oral dose of afatinib at 40 mg - Multiple oral dose of ritonavir twice daily at 200 mg for 3 days, and on Day 2, single oral dose of afatinib at 40 mg followed by the first oral dose of ritonavir on Day 2 with 6 hours between the dosing sessions. Washout of ≥21 days between the treatment periods	PK Safety
		1200.152	I	Healthy adult subjects	22	Multiple oral dose of rifampicin once daily at 600 mg for 7 days followed by single oral dose of afatinib at 40 mg	PK Safety

Data category	Region	Study number	Phase	Patient population	No. of enrollment	Dosage regimen	Primary endpoint
		1200.86	I	Patients with mild and moderate hepatic impairment and healthy adult subjects	35	Single oral dose of afatinib at 30 or 50 mg	PK Safety
		1200.1	I	Patients with advanced solid cancer	38	Once daily oral dose of afatinib at 10, 20, 30, 45, 70, 85, or 100 mg for 14 days followed by 14-day washout period, and the cycle can be repeated	PK Safety
		1200.2	I	Patients with advanced solid cancer	43	Once daily oral dose of afatinib at 10, 20, 40, 55, or 65 mg for 21 days followed by 7-day washout period, and the cycle can be repeated	Safety PK
		1200.17	I	Patients with advanced solid cancer	7	Oral administration at the optimal dose of each patient under the same regimen as those in Studies 1200.1 and 1200.2	Safety PK
		1200.3	I	Patients with advanced solid cancer	53	Once daily oral dose of afatinib at 10, 20, 30, 40, or 50 mg	Safety PK
		1200.4	I	Patients with advanced solid cancer	30	Once daily oral dose of afatinib at 10, 20, 40, or 60 mg	Safety PK
		1200.24	II	Patients with advanced solid cancer	60	Once daily oral dose of afatinib at 50 mg	Efficacy Safety PK
		1200.22	II	Patients with inoperable or recurrent *EGFR* mutation-positive NSCLC (adenocarcinoma) who (a) did not received chemotherapy or (b) received 1 regimen of chemotherapy	129 (a) 61 (b) 68	Once daily oral dose of afatinib at 40 or 50 mg	Efficacy Safety
		1200.23	II/III	Patients with inoperable or recurrent NSCLC (adenocarcinoma) who received 1 or 2 regimens of chemotherapy and EGFR-TKIs	585 (a) 390 (b) 195	Once daily oral dose of (a) Afatinib 50 mg or (b) placebo under BSC	Efficacy Safety
Reference	Foreign	1200.6	I	Patients with advanced solid cancer	31	21-day treatment cycle, DTX was intravenously administered at a dose of 60 mg/m^2 on Day 1, and, afatinib was orally administered once daily at a dose of 10 or 30 mg on Days 2 to 21 or on Days 2 to 14; or DTX was intravenously administered at a dose of 75 mg/m^2 on Day 1, and afatinib was orally administered once daily at a dose of 10, 20, or 30 mg on Days 2 to 21 or on Days 2 to 14 (up to 6 cycles).	Safety PK Efficacy
		1200.20	I	Patients with advanced solid cancer	45	Cohort 1: 21-day treatment cycle, DTX was intravenously administered at a dose of 60 mg/m^2 on Day 1, and afatinib was orally administered once daily at a dose of 10 mg on Days 2 to 4. Cohort 2 onward: 21 days as one treatment cycle, DTX was intravenously administered at a dose of 75 mg/m^2 on Day 1, and afatinib was orally administered once daily at a dose of 10, 20, 40, 60, 90, 120, or 160 mg on Days 2 to 4 (up to 8 cycles).	Safety PK

Data category	Region	Study number	Phase	Patient population	No. of enrollment	Dosage regimen	Primary endpoint
		1200.36	I	Patients with malignant glioma at WHO classification Grade III or IV who received chemoradiotherapy	32	Once daily oral dose of afatinib at 20, 40, or 50 mg, and once daily oral dose of TMZ 75 mg/m^2 for 21 days followed by 7-day washout period	Safety PK
			II	Patients with malignant glioma at WHO classification Grade IV who received chemoradiotherapy but experienced the first relapse	119 (a) 41 (b) 39 (c) 39	(a) Once daily oral dose of afatinib at 40 mg (b) Once daily oral dose of afatinib at 40 mg, and once daily oral dose of TMZ 75 mg/m^2 for 21 days followed by 7-day washout period (c) Once daily oral dose of TMZ 75 mg/m^2 for 21 days followed by 7-day washout period	Efficacy Safety
		1200.42	III	Patients with inoperable or recurrent NSCLC who received ≥1 regimen of chemotherapy and EGFR-TKIs	Part A 1154	Part A: Once daily oral dose of afatinib at 50 mg	Efficacy Safety
		1200.37	I	Patients with advanced solid cancer	47 (a) 26 (b) 21	21-day treatment cycle (a) Cohort A1: CDDP 50 mg/m^2 and PTX 175 mg/m^2 were intravenously administered on Day 1 and afatinib was orally administered once daily at a dose of 20 mg on Days 3 to 21. Cohort A2: The dose of CDDP in Cohort A1 increased to 75 mg/m^2. Cohort A3: The dose of afatinib in Cohort A2 increased to 40 mg. Cohort A4: The dose of afatinib in Cohort A3 increased to 50 mg. (b) Cohort B1: CDDP 75 mg/m^2 was intravenously administered on Day 1 and 5-FU 750 mg/m^2 on Days 1 to 4, and afatinib was orally administered once daily at a dose of 20 mg on Days 5 to 21. Cohort B2: The dose of afatinib in Cohort B1 increased to 40 mg. Cohort B3: The dose of afatinib in Cohort B2 increased to 50 mg. Cohort B4: For Cohort B3, the dose of afatinib was set at MTD and the dose of CDDP increased to 100 mg/m^2. Cohort B5: The dose of 5-FU in Cohort B4 increased to 1000 mg/m^2.	Safety PK
		1200.68	I	Patients with HER2-positive metastatic breast cancer or advanced breast cancer	18	Trastuzumab was intravenously administered once weekly over 90 minutes (the first dose, 4 mg/kg; the second and subsequent doses, 2 mg/kg), and afatinib was orally administered once daily at 20 or 30 mg.	Safety PK

Data category	Region	Study number	Phase	Patient population	No. of enrollment	Dosage regimen	Primary endpoint
		1239.1	I	Patients with advanced solid cancer	28	Afatinib and nintedanib concomitantly administered under the following dosage and administration Afatinib: Oral administration was started at 10 mg once daily and the dose increased up to 40 mg in 10-mg increments. Nintedanib: Oral administration was started at 150 mg twice daily and the dose increased up to 250 mg in 50-mg increments.	PK Efficacy Safety
		1239.2	II	Patients with metastatic colorectal cancer	46	28-day treatment cycle, nintedanib was orally administered twice daily at a dose of 250 mg on Days 1 to 7 and on Days 15 to 21, and afatinib was orally administered once daily at a dose of 70 mg on Days 8 to 14 and Days 22 to 28 (the dose of afatinib changed to 50 mg under Change No. 2 of the protocol).	Efficacy Safety
		1239.3	II	Patients with castration-resistant prostate cancer	85	28-day treatment cycle, nintedanib was orally administered twice daily at a dose of 250 mg on Days 1 to 7 and on Days 15 to 21, and afatinib was orally administered once daily at a dose of 40 or 70 mg on Days 8 to 14 and on Days 22 to 28 (up to 12 cycles).	Efficacy Safety
		1200.34	III	Chemotherapy-naive patients with inoperable or recurrent *EGFR* mutation-positive NSCLC (adenocarcinoma)	364 (a) 242 (b) 122	21-day treatment cycle (a) Afatinib was orally administered once daily at a dose of 40 mg. (b) CDDP 75 mg/m^2 was intravenously administered on Day 1 and GEM 1000 mg/m^2 on Days 1 and 8 (up to 6 cycles)	Efficacy Safety
		1200.40	II	Patients with inoperable or recurrent *EGFR*-amplified NSCLC who (a) did not receive chemotherapy or (b) received 1 regimen of chemotherapy	69	Once daily oral dose of afatinib at 50 mg	Efficacy Safety
		1200.72	II	Patients with inoperable or recurrent *EGFR* mutation-negative NSCLC (adenocarcinoma) who received 2 regimens of chemotherapy	43	Once daily oral dose of afatinib at 40 mg	Efficacy Safety
		1200.26	II	Patients with *EGFR* mutation-positive or HER2-amplified advanced solid cancer	22	Afatinib was administered once daily at a dose of 50 mg orally or through gastrostomy tube	Efficacy Safety
		1200.10	II	Patients with HER2-negative metastatic breast cancer who received 3 or fewer types of chemotherapy	50	Once daily oral dose of afatinib at 50 mg	Efficacy Safety PK
		1200.11	II	Patients with HER2-positive metastatic breast cancer who received trastuzumab	41	Once daily oral dose of afatinib at 50 mg	Efficacy Safety

Data category	Region	Study number	Phase	Patient population	No. of enrollment	Dosage regimen	Primary endpoint
		1200.44	II	Chemotherapy-naive patients with HER2-positive locally advanced breast cancer	29	(a) Once daily oral dose of afatinib at 50 mg; (b) intravenous dose of trastuzumab at intervals of 1 week (the first dose, 4 mg/kg; and then 2 mg/kg); (c) once daily oral dose of lapatinib at 1500 mg. Up to 6 weeks	Efficacy Safety
		1200.5	II	Patients with estrogen receptor-positive metastatic breast cancer who received letrozole	28	Afatinib at 50 mg and letrozole at 2.5 mg were concomitantly administered once daily.	Efficacy Safety
		1200.74	II	Patients with metastatic colorectal cancer who received regimens including oxaliplatin and irinotecan	94 (a) 36 (b) 15 (c) 43	In the case of wild-type *KRAS* gene, (a) afatinib was orally administered once daily (dose started at 40 mg/m^2 and then increased to 50 mg/m^2 at Week 4); or (b) cetuximab was intravenously administered at intervals of 1 week (the first dose, 400 mg/m^2; and then 250 mg/m^2). In the case of mutant *KRAS* gene, (c) afatinib was orally administered once daily (dose started at 40 mg/m^2 and then increased to 50 mg/m^2 at Week 4).	Efficacy Safety
		1200.28	II	Patients with metastatic or recurrent head and neck squamous cell carcinoma	124 (a) 62 (b) 62	(a) Stage 1, afatinib was orally administered once daily at a dose of 50 mg or through gastrostomy tube; and Stage 2, to patients who experienced progression or could not tolerate the treatment during Stage 1, cetuximab was intravenously administered at intervals of 1 week (the first dose, 400 mg/m^2; and then 250 mg/m^2) (b) Stage 1, cetuximab was intravenously administered at intervals of 1 week (the first dose, 400 mg/m^2; and then 250 mg/m^2); and Stage 2, to patients who experienced progression or could not tolerate the treatment during Stage 1, afatinib was orally administered once daily at a dose of 50 mg or through gastrostomy tube	Efficacy Safety

NSCLC: Non-small cell lung cancer, EGFR: Epidermal growth factor receptor, HER2: Human epidermal growth factor receptor 2, EGFR-TKI: EGFR tyrosine kinase inhibitor, PK: Pharmacokinetic, BSC: Best supportive care, MTD: Maximum tolerated dose, CDDP: Cisplatin, PEM: Pemetrexed sodium hydrate, DTX: Docetaxel hydrate, TMZ: Temozolomide, PTX: Paclitaxel, 5-FU: Fluorouracil, GEM: Gemcitabine hydrochloride, Trastuzumab: Trastuzumab (genetical recombinant), Lapatinib: Lapatinib tosylate hydrate, Irinotecan: Irinotecan hydrochloride, Cetuximab: Cetuximab (genetical recombinant)

The outline of each clinical study was as described below.

Major adverse events other than deaths reported in each clinical study are described in “4.(iv) Adverse events reported in clinical studies,” and PK data in “4.(i) Summary of biopharmaceutic studies and associated analytical methods” and “4.(ii) Summary of clinical pharmacology studies.”

The safety is described based on data for each study; and for the studies with the data cut-off before [redacted], 20[redacted], the results re-tabulated as of [redacted], 20[redacted] are used.

Evaluation data

(1) Clinical pharmacology studies

Data from the following 7 clinical pharmacology studies in healthy adult subjects and patients with mild or moderate hepatic impairment were submitted [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. In these studies, no deaths occurred during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug).

1) **Foreign phase I study (5.3.1.1-1, Study 1200.80 [redacted])**
2) **Foreign phase I study (5.3.1.1-2, Study 1200.35 [redacted])**
3) **Foreign phase I study (5.3.3.1-1, Study 1200.25 [redacted])**
4) **Foreign phase I study (5.3.3.2-11, Study 1200.86 [redacted])**
5) **Foreign phase I study (5.3.3.4-1, Study 1200.79 [redacted])**
6) **Foreign phase I study (5.3.3.4-2, Study 1200.151 [redacted])**
7) **Foreign phase I study (5.3.3.4-3, Study 1200.152 [redacted])**

(2) Japanese clinical study

Japanese phase I/II study (5.3.3.2-9, 5.3.5.2-1, Study 1200.33 [redacted])

(a) Phase I part:

An open-label, uncontrolled study was conducted to investigate the maximum tolerated dose (MTD), safety, and PK of afatinib in NSCLC patients with no other appropriate therapies available (target sample size, 3-9 subjects per group) at 2 study sites in Japan.

One treatment cycle consisted of 28 days, and afatinib was to be orally administered once daily ≥1 hour before or ≥2 hours after a meal at a dose of 20, 40, or 50 mg. The study treatment was to be continued until progression or onset of excessive toxicity.

All of the 12 subjects enrolled in the study received afatinib and were therefore included in the safety analysis.

In Cycle 1, the dose limiting toxicity (DLT) was evaluated. The DLT occurred in 1 of 6 subjects in the 50 mg group (mucosal inflammation), and the MTD was thus determined to be 50 mg.

For the safety, no death occurred during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug).

(b) Phase II part:

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of afatinib in patients with inoperable or recurrent NSCLC who had received 1 or 2 regimens of chemotherapy including platinum antineoplastic drugs (except for EGFR-TKIs) and EGFR-TKIs for ≥12 weeks (target sample size, 60) at 20 study sites in Japan.

One treatment cycle consisted of 28 days, and afatinib was to be orally administered once daily ≥1 hour before or ≥2 hours after a meal at MTD (50 mg), determined in the Phase I part. The study treatment was to be continued until progression or onset of excessive toxicity.

All of the 62 subjects enrolled in the study received afatinib and were therefore included in the safety analysis. Excluding 1 subject in whom imaging evaluation was not made after end of the study treatment, 61 subjects were included in the efficacy analysis.

For the efficacy, the best response and response rate, the primary endpoint, are as shown in the table below.

Best response and response rate (RECIST, N = 61, data cut-off on [redacted], 20[redacted])

Best response	Assessment by the Independent Review Committee (IRC)	Assessment by the attending physician
Complete response (CR)	0	0
Partial response (PR)	5 (8.2%)	8 (13.1%)
Stable disease (SD)*	35 (57.4%)	36 (59.0%)
Progressive disease (PD)	17 (27.9%)	12 (19.7%)
Not evaluable	4 (6.6%)	5 (8.2%)
Response rate [95% CI] (%)	8.2 [2.7, 18.1]	13.1 [5.8, 24.2]

*, Defined as a patient in whom the stable condition continued for ≥42 days.

For the safety, 1 subject died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The death was caused by hypoxia and a causal relationship with afatinib was ruled out.

(3) Global study

Global phase III study (5.3.5.1-1, Study 1200.32 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted], 20[redacted])])

An open-label, randomized, comparative study was conducted to compare the efficacy and safety between afatinib and concomitant use of CDDP and PEM (CDDP/PEM) in chemotherapy-naive patients with inoperable or recurrent *EGFR* mutation-positive* NSCLC (adenocarcinoma) (target sample size, 330) at 133 study sites in 25 countries including Japan.

*: Using TheraScreen:EGFR29 Mutation Kit, deletion mutation in Exon 19 (Del 19), L858R point mutation in Exon 21 (L858R), etc. were investigated.

One treatment cycle consisted of 21 days and the following regimen was used: in the afatinib group, afatinib was to be orally administered once daily at a dose of 40 mg ≥1 hour before or ≥3 hours after a meal, and for the patients who experienced no adverse events or only slight adverse events during Cycle 1, the dose increased to 50 mg administered once daily in the second and subsequent cycles, or reduced in 10-mg decrements in accordance with the dose reduction criteria; and in the CDDP/PEM group, CDDP and PEM were to be intravenously administered at doses of 75 and 500 mg/m^2, respectively, on Day 1 of each cycle at intervals of 3 weeks. The study treatment was to be continued up to 6 cycles, until the disease progression, onset of intolerable adverse events, or other reasons requiring discontinuation in the afatinib group, or until disease progression, onset of intolerable adverse events, or other reasons requiring discontinuation in the CDDP/PEM group.

All of the 345 subjects enrolled in the study (230 subjects in the afatinib group, 115 subjects in the CDDP/PEM group) were included in the intent-to-treat (ITT) population for efficacy analysis. Of the ITT population, excluding 5 subjects (1 subject in the afatinib group, 4 subjects in the CDDP/PEM group) who did not receive the investigational drug, the remaining 340 subjects were included in the safety analysis.

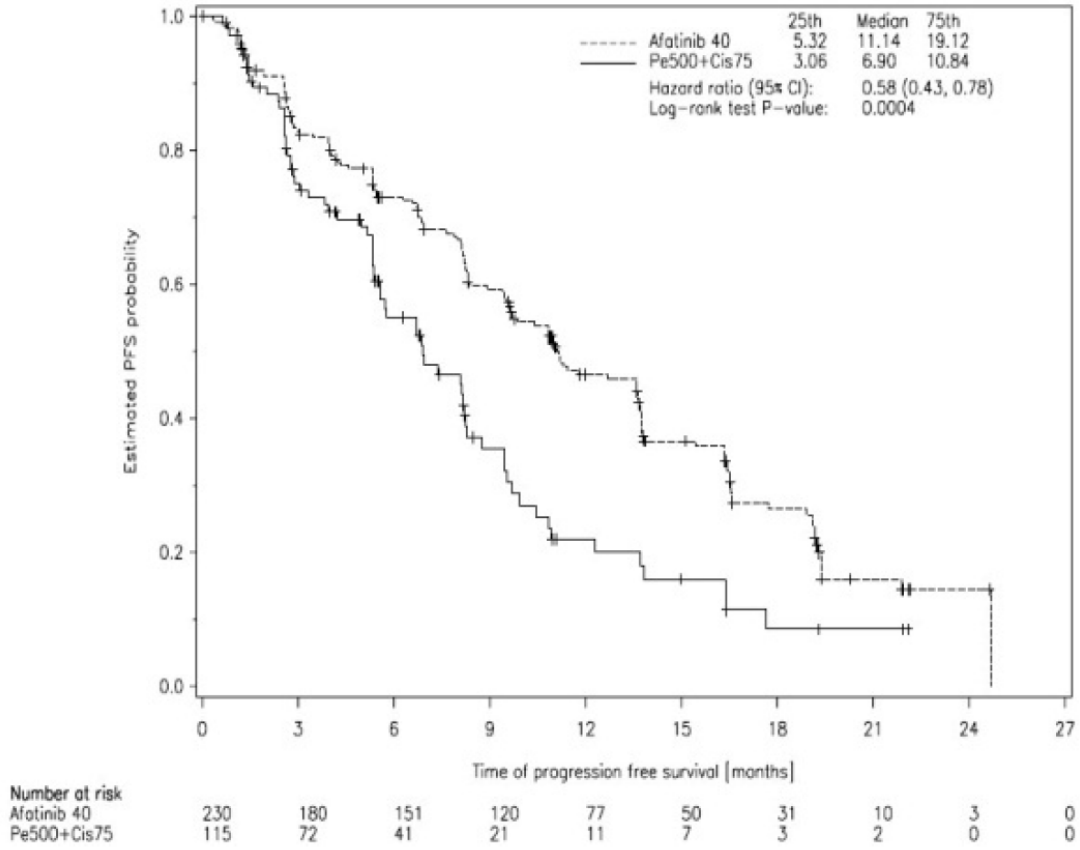
The primary endpoint in this study was the PFS assessed by the Independent Review Committee (IRC), and the pivotal analysis was to be performed when a total of 217 events occurred.

For the efficacy, the analysis results of the PFS data evaluated by the IRC are as shown below.

Analysis results on PFS (ITT population, IRC evaluation, data cut-off on [redacted], 20[redacted])

	Afatinib group	CDDP/PEM group
Number of subjects	230	115
Death or exacerbation (%)	152 (66.1)	69 (60.0)
Median [95% CI] (months)	11.14 [9.63, 13.63]	6.90 [5.39, 8.25]
Hazard ratio [95% CI][*1]	0.577 [0.425, 0.784]	
P value (two-sided)[*2, *3]	0.0004	

[*]1: Cox regression by *EGFR* mutation type (L858R, Del 19, others) and race (Asian, non-Asian) as the stratification factors, [*]2: Stratified log-rank test by *EGFR* mutation type (L858R, Del 19, others) and race (Asian, non-Asian) as the stratification factors, [*]3: Significance level of 0.05 (two-sided)



Kaplan-Meier curve of PFS (ITT population, IRC evaluation, data cut-off on [redacted], 20[redacted])

For the safety, 13 of 229 subjects (5.7%) in the afatinib group and 3 of 111 subjects (2.7%) in the CDDP/PEM group died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 6 subjects, acute respiratory distress syndrome, and death unexplained in 2 subjects each, and dyspnoea, pneumonia, and sepsis in 1 subject each in the afatinib group; and disease progression, death unexplained, and dyspnoea in 1 subject each in the CDDP/PEM group. Of these causes of death, a causal relationship with investigational drug could not be ruled out for acute respiratory distress syndrome, death unexplained, dyspnoea, and sepsis in 1 subject each.

(4) Foreign clinical study

1) Foreign phase I study (5.3.3.2-1, Study 1200.1 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the MTD, safety, and PK of

afatinib in patients with advanced solid cancer (target sample size; up to 60 subjects, 3-6 subjects per cohort, 18 subjects in MTD cohort) at 2 foreign study sites.

One treatment cycle consisted of 28 days, and afatinib was to be orally administered once daily at a dose of 10, 20, 30, 45, 70, 85, or 100 mg for 14 days followed by a 14-day washout period. The study treatment was to be continued until disease progression or until subjects met the discontinuation criteria.

All of the 38 subjects enrolled in the study received afatinib and were therefore included in the safety analysis. In Cycle 1, the DLT occurred in a total of 7 subjects, including 4 of 18 subjects in the 70 mg group (diarrhoea, dehydration, diarrhoea/dehydration, and fatigue/ALT increased/blood creatinine increased/hyponatraemia/hypokalaemia in 1 subject each), in 2 of 6 subjects in the 85 mg group (diarrhoea in 2 subjects), and in 1 of 2 subjects in the 100 mg group (diarrhoea in 1 subject). In Cycle 2 and thereafter, the DLTs occurred in a total of 4 subjects, including 1 of 3 subjects in the 10 mg group (left ventricular hypofunction in 1 subject), 2 of 18 subjects in the 70 mg group (dehydration and diarrhoea/dehydration/left ventricular hypofunction in 1 subject each), and in 1 of 2 subjects in the 100 mg group (rash in 1 subject). The MTD was thus determined to be 70 mg.

For the safety, 1 subject in the 20 mg group, 1 subject in the 30 mg group, and 2 subjects in the 70 mg group died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 1 subject in the 20 mg group, disease progression in 1 subject in the 30 mg group, and disease progression and pulmonary haemorrhage in 1 subject each in the 70 mg group. A causal relationship with afatinib was ruled out for all deaths.

2) Foreign phase I study (5.3.3.2-2, Study 1200.2 [[redacted] 20[redacted] to [redacted] 20[redacted]])
An open-label, uncontrolled study was conducted to investigate the MTD, safety, and PK of afatinib in patients with advanced solid cancer (target sample size, up to 54) at 2 foreign study sites.

One treatment cycle consisted of 28 days, and afatinib was to be orally administered once daily at a dose of 10, 20, 40, 55, or 65 mg for 21 days followed by 7-day washout period. The study treatment was to be continued until disease progression or until subjects met the discontinuation criteria.

All of the 43 subjects enrolled in the study received afatinib and were therefore included in the safety analysis.

In Cycle 1, the DLT was evaluated. The DLTs occurred in 1 of 8 subjects in the 40 mg group (rash in 1 subject), 7 of 20 subjects in the 55 mg group (diarrhoea in 3 subjects, stomatitis, mucosal inflammation, dermatitis acneiform, and inappetence/dehydration/renal failure in 1 subject each), and 3 of 6 subjects in the 65 mg group (diarrhoea, dehydration/fatigue, and dehydration/diarrhoea/nausea/vomiting in 1 subject each). The MTD was thus determined to be 55 mg.

For the safety, 4 subjects in the 55 mg group died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were death unexplained in 2 subjects, and pneumonia/acute respiratory distress syndrome and disease progression in 1 subject each. A causal relationship with afatinib was ruled out for all deaths.

3) Foreign phase I study (5.3.3.2-3, Study 1200.17 [[redacted] 20[redacted] to [redacted] 20[redacted]])
An open-label, uncontrolled study was conducted at 4 foreign study sites to investigate the safety

and PK of afatinib given for an extended period in patients with advanced solid cancer who completed the treatment with afatinib in Study 1200.1 or 1200.2 as specified in the protocol without progression.

The study drug was to be administered to each patient at the optimal dose in the previous study (Study 1200.1 or 1200.2) under the same schedule as that in the previous study. The study treatment was to be continued until disease progression or until subjects met the discontinuation criteria.

All of the 7 subjects enrolled in the study continuously received afatinib and were therefore included in the safety analysis.

For the safety, no deaths occurred during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug).

4) Foreign phase I study (5.3.3.2-4, Study 1200.3 [[redacted] 20[redacted] to [redacted] 20[redacted]])
An open-label, uncontrolled study was conducted to investigate the MTD, safety, and PK of afatinib in patients with advanced solid cancer (target sample size, 60) at 2 foreign study sites.

One treatment cycle consisted of 28 days, and afatinib was to be orally administered once daily at a dose of 10, 20, 30, 40, or 50 mg. The treatment was to be continued until disease progression or until subjects met the discontinuation criteria.

All of the 53 subjects enrolled in the study received afatinib and were therefore included in the safety analysis.

In Cycle 1, the DLT was evaluated. The DLTs occurred in 1 of 7 subjects in the 30 mg group (respiratory disorder in 1 subject), 1 of 26 subjects in the 40 mg group (rash in 1 subject), and 1 of 13 subjects in the 50 mg group (dermatitis acneiform in 1 subject). Many DLTs occurred in the 55 mg group in Study 1200.2 (once daily oral dose of afatinib for 21 days followed by 7-day washout period) and in the 60 mg group in Study 1200.4 (once daily oral dose of afatinib), and the dose did not increase to >50 mg, and the MTD was determined to be 50 mg.

For the safety, 1 subject in the 20 mg group, 3 subjects in the 30 mg group, 2 subjects in the 40 mg group, and 4 subjects in the 50 mg group died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 1 subject in the 20 mg group, pneumonia, dyspnoea/abdominal distension/chest pain, and disease progression in 1 subject each in the 30 mg group, myocardial infarction and disease progression in 1 subject each in the 40 mg group, and lower respiratory tract infection in 2 subjects, and somnolence/intestinal obstruction and disease progression in 1 subject each in the 50 mg group. A causal relationship with afatinib was ruled out for all deaths.

5) Foreign phase I study (5.3.3.2-5, Study 1200.4 [[redacted] 20[redacted] to [redacted] 20[redacted]])
An open-label, uncontrolled study was conducted to investigate the MTD and safety of afatinib in patients with advanced solid cancer (target sample size, up to 42) at 2 foreign study sites.

One treatment cycle consisted of 28 days, and afatinib was to be orally administered once daily at a dose of 10, 20, 40, or 60 mg. The study treatment was to be continued until disease progression or until a subject met the discontinuation criteria.

All of the 30 subjects enrolled in the study received afatinib and were therefore included in the safety analysis.

In Cycle 1, the DLT was evaluated. The DLTs occurred in 1 of 19 subjects in the 40 mg group (diarrhoea in 1 subject) (no DLT occurred in the first 3 subjects, but the DLT occurred after the cohort was expanded in accordance with the protocol) and 2 of 3 subjects in the 60 mg group (diarrhoea in 2 subjects). The MTD was thus determined to be 40 mg.

For the safety, 2 subjects in the 10 mg group and 1 subject in the 20 mg group died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were NSCLC and lung infiltration in 1 subject each in the 10 mg group and disease progression in 1 subject in the 20 mg group. A causal relationship with afatinib was ruled out for all deaths.

6) Foreign phase II study (5.3.4.2-1, Study 1200.24 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the effect on QTcF, efficacy, safety, and PK of afatinib in patients with advanced solid cancer (target sample size, up to 60) at 4 foreign study sites.

Afatinib was to be orally administered once daily ≥1 hour before a meal at a dose of 50 mg. The study treatment was to be continued until disease progression or onset of excessive toxicity.

All of the 60 subjects enrolled in the study received afatinib and were therefore included in the efficacy and safety analyses.

For the efficacy, the response rate [95% CI] (%), the primary endpoint, was 1.7 [0, 8.9] (1 of 60 subjects).

For the safety, 9 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 3 subjects and disease progression/small intestinal obstruction, peritoneal neoplasm/renal disorder/renal failure/urosepsis/ureteric obstruction, lung infection, cardiac arrest, dyspnoea/pneumonia, and rectal cancer metastatic in 1 subject each. A causal relationship with afatinib was ruled out for all deaths.

7) Foreign phase II study (5.3.5.2-2, Study 1200.22 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted] [redacted], 20[redacted])])

An open-label uncontrolled study was conducted to investigate the efficacy and safety of afatinib in patients with inoperable or recurrent *EGFR* mutation-positive NSCLC (adenocarcinoma) who had not received chemotherapy or had received 1 regimen of chemotherapy (excluding EGFR-TKIs) (target sample size, 120) at 30 foreign study sites.

Afatinib was to be orally administered once daily at a dose of 50 mg. The study treatment was to be continued until disease progression or onset of intolerable toxicity. Initially, only patients with inoperable or recurrent *EGFR* mutation-positive NSCLC (adenocarcinoma) who had received 1 regimen of chemotherapy (excluding EGFR-TKIs) were to be included, but the inclusion criteria were changed in association of revision of the protocol (dated [redacted] [redacted], 20[redacted]) so that chemotherapy-naive patients would be enrolled. *EGFR* mutation-positive tumors are known to be highly sensitive to EGFR-TKIs (*Nat Rev Cancer*. 2010;10:760-74). The starting dose of afatinib was therefore reduced to 40 mg by the revision of the protocol (dated [redacted] [redacted], 20[redacted]).

All of the 129 subjects enrolled in the study received afatinib and were therefore included in the efficacy and safety analyses. Of 129 subjects, 99 subjects (38 subjects for the primary treatment, 61 subjects for the secondary treatment) received afatinib at 50 mg and 30 subjects (23 subjects for the primary treatment, 7 subjects for the secondary treatment) received afatinib at 40 mg.

For the efficacy, the best response and response rate, the primary endpoints, are as shown in the table below.

Best response and response rate (RECIST, N = 129, data cut-off on [redacted], 20[redacted])

Best response	IRC Assessment	Asesment by attending physician
Complete response (CR)	2 (1.6%)	0
Partial response (PR)	77 (59.7%)	78 (60.5%)
Stable disease (SD)*1	26 (20.2%)	33 (25.6%)
Progressive disease (PD)	18 (14.0%)	9 (7.0%)
Without target or non-target lesions*2	1 (0.8%)	0
Not evaluable	5 (3.9%)	9 (7.0%)
Response rate [95% CI] (%)	61.2 [52.3, 69.7]	60.5 [51.5, 69.0]

*1: Defined as a patient in whom the stable condition continued for ≥42 days. *2: Defined as a patient in whom no target or non-target lesions were reported at the baseline, and no new lesions developed during the study

The IRC evaluation results on the best response and response rate by the treatment line and starting dose are as shown in the table below.

IRC evaluation results on the best response and response rate (RECIST, data cut-off on [redacted], 20[redacted])

Treatment line	Primary treatment		Secondary treatment	
Starting dose	40 mg	50 mg	40 mg	50 mg
Number of subjects	23	38	7	61
Complete response (CR)	0	2 (5.3)	0	0
Partial response (PR)	14 (60.9%)	24 (63.2%)	4 (57.1%)	35 (57.4%)
Stable disease (SD)*1	4 (17.4%)	8 (21.1%)	1 (14.3%)	13 (21.3%)
Progressive disease (PD)	4 (17.4%)	2 (5.3%)	2 (28.6%)	10 (16.4%)
Without target or non-target lesions*2	0	1 (2.6%)	0	0
Not evaluable	1 (4.3%)	1 (2.6%)	0	3 (4.9%)
Response rate [95% CI] (%)	60.9 [38.5, 80.3]	68.4 [51.3, 82.5]	57.1 [18.4, 90.1]	57.4 [44.1, 70.0]

*1: Defined as a patient in whom the stable condition continued for ≥42 days. *2: Defined as a patient in whom no target or non-target lesions were reported at the baseline, and no new lesions developed during the study

For the safety, 12 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 3 subjects, septic shock, dyspnoea, and respiratory failure in 2 subjects each, and septic shock/multi-organ failure, pneumonia, and hepatic failure in 1 subject each. A causal relationship with afatinib was ruled out for all deaths.

8) Foreign phase II/III study (5.3.5.1-2, Study 1200.23 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted], 20[redacted])])

A double-blind, randomized, comparative study was conducted to compare the efficacy and safety between afatinib and the placebo under the best supportive care (BSC) in patients with inoperable or recurrent NSCLC (adenocarcinoma) who had received 1 or 2 regimens of chemotherapy including platinum antineoplastic drugs (except for EGFR-TKIs) and EGFR-TKIs for ≥12 weeks (target sample size, 560) at 85 study sites in 15 foreign countries.

Afatinib was to be orally administered once daily 1 hour before a meal at a dose of 50 mg in the afatinib group. The study treatment was to be continued until disease progression or until subjects met the discontinuation criteria.

Of 697 subjects enrolled in the screening for the study, 585 subjects meeting the eligibility criteria (390 subjects in the afatinib group, 195 subjects in the placebo group) were randomly assigned in

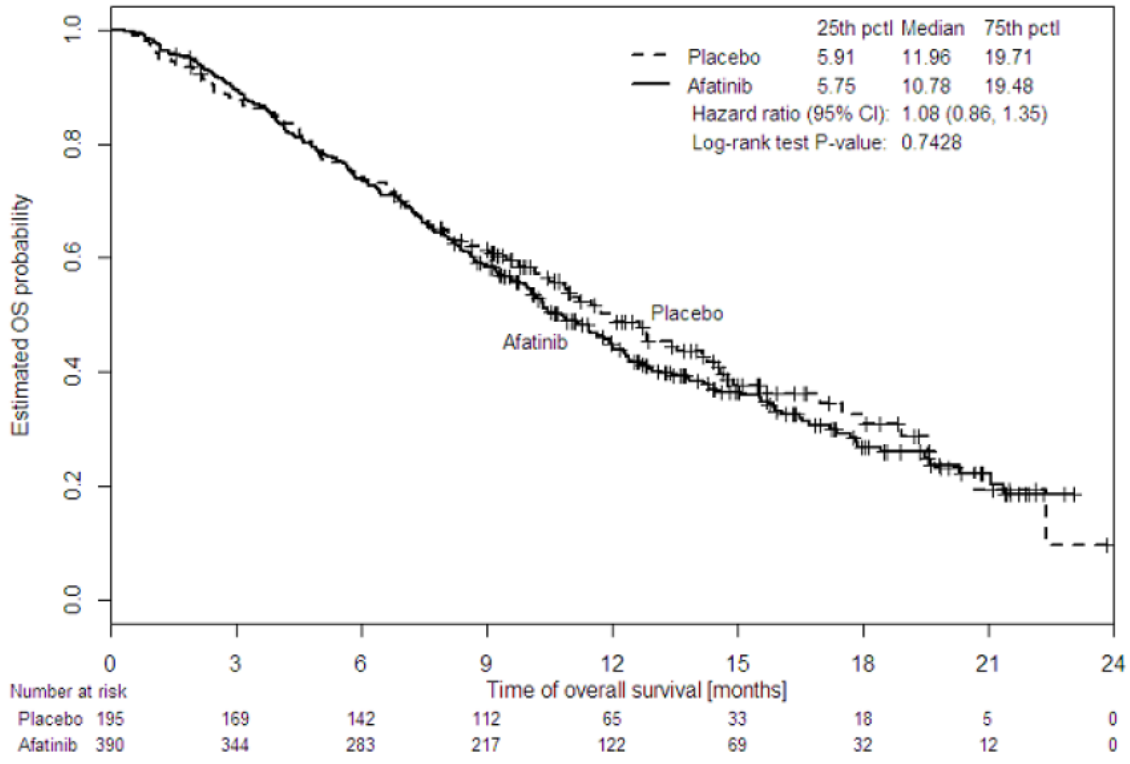
the ITT population for efficacy analysis. All of the randomly assigned subjects received the study drug at least once and were included in the safety analysis.

The primary endpoint of this study was the OS, and the pivotal analysis was to be performed when a total of 359 events occurred. When a total of 40 subjects in the afatinib group underwent ≥1 session of diagnostic imaging during the treatment period, the interim analysis in terms of the objective tumor reduction effect was performed by the Independent Data Monitoring Committee to terminate the ineffective study treatment if applicable. As a result, the study was recommended to be continued. In consideration of this interim analysis, the significance level in the final analysis of the OS was set at 0.0249 (one-sided) based on the Haybittle-Peto method. The analysis results on the OS, the primary endpoint, for efficacy are as shown below.

Analysis results on OS (ITT population, N = 585, data cut-off on [redacted], 20[redacted])

	Afatinib group	Placebo group
Number of subjects	390	195
Number of deaths (%)	244 (62.56)	114 (58.46)
Median [95% CI] (months)	10.78 [9.95, 11.99]	11.96 [10.15, 14.26]
Hazard ratio (95% CI)[*1]	1.077 [0.862, 1.346]	
P value (one-sided)[*2, *3]	0.7428	

[*]1: Cox regression using sex and ECOG PS (0 or 1, 2) at the baseline as stratification factors, [*]2: Stratified log-rank test using sex and ECOG PS (0 or 1, 2) at the baseline as stratification factors, [*]3: Significance level of 0.0249 (one-sided)



Kaplan-Meier curve of OS (ITT population, N = 585, data cut-off on [redacted], 20[redacted])

For the safety, 44 of 390 subjects (11.3%) in the afatinib group and 15 of 195 subjects (7.7%) in the placebo group died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 13 subjects,

respiratory failure in 6 subjects, septic shock and death in 3 subjects each, metastases to the central nervous system in 2 subjects, and lung infection, pneumonia, disease progression/pneumonia/cardiac failure/pulmonary embolism, cerebrovascular accident, acute left ventricular failure, cardiac tamponade, cardio-respiratory arrest, pericardial effusion, sick sinus syndrome/pneumonitis, dyspnoea, haemoptysis, pneumonitis, acute hepatic failure/renal failure acute, reduced general condition, multi-organ failure, sudden cardiac death, and sudden death in 1 subject each in the afatinib group; and disease progression in 6 subjects, respiratory failure in 2 subjects, and disease progression/metastases to the central nervous system, metastases to the central nervous system, death, cardiac failure, dyspnoea, lymphangiosis carcinomatosa, and NSCLC in 1 subject each in the placebo group. Among these events, a causal relationship with the investigational drug could not be ruled out for acute left ventricular failure and acute hepatic failure/acute renal failure in 1 subject each in the afatinib group.

Reference data
Foreign clinical studies
1) Foreign phase I study (5.3.3.2-7, Study 1200.6 [[redacted] to [redacted]])
An open-label, uncontrolled study was conducted to investigate the safety, PK, and efficacy of concomitant use of afatinib with DTX in patients with advanced EGFR or HER2-positive solid cancer (target sample size, up to 71) at 9 foreign study sites.

All of the 31 subjects enrolled in the study received afatinib, and 2 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were pneumonia and hydronephrosis in 1 subject each, and a causal relationship with afatinib was ruled out for all deaths.

2) Foreign phase I study (5.3.3.2-8, Study 1200.20 [[redacted] to [redacted]])
An open-label, uncontrolled study was conducted to investigate the safety and PK of concomitant use of afatinib with DTX in patients with advanced solid cancer (target sample size, up to 42) at 2 foreign study sites.

Of 45 subjects enrolled in the study, 40 subjects received afatinib, and 16 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 3 subjects, reduced general condition in 9 subjects, and reduced general physical condition/pyrexia/cholangitis, disease progression/reduced general condition, septic shock/renal failure, and pleural effusion/dyspnoea in 1 subject each. A causal relationship with afatinib was ruled out for all deaths.

3) Foreign phase I/II study (5.3.3.2-10, Study 1200.36 [[redacted] to ongoing (data cut-off, [redacted])])
(a) Phase I part ([redacted] to ongoing [data cut-off, [redacted]])
An open-label, uncontrolled study was conducted to investigate the safety, PK, and pharmacodynamics of concomitant use of afatinib with TMZ (afatinib/TMZ) in patients with Grade III/IV malignant glioma under WHO classification who had received chemoradiotherapy (target sample size, 12-30) at 9 foreign study sites.

All of the 32 subjects enrolled in the study received afatinib, and 1 subject died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The cause of death was haemorrhage intracranial due to disease progression and its causal relationship with afatinib was ruled out.

(b) Phase II part ([redacted] to ongoing [data cut-off, [redacted]])
An open-label, randomized, comparative study was conducted to investigate the efficacy and safety of afatinib alone, afatinib/TMZ, and TMZ alone in patients with malignant glioma at WHO

classification Grade IV who received chemoradiotherapy but experienced the first relapse (target sample size, 120) at 30 foreign study sites.

Of 119 subjects enrolled in the study, 80 subjects (41 subjects in the afatinib group, 39 subjects in the afatinib/TMZ group) received afatinib, and 3 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression, reduced general condition/disease progression, and respiratory failure in 1 subject each, and a causal relationship with afatinib was ruled out for all deaths.

4) Foreign phase III study (5.3.5.2-3, Study 1200.42 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted] 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of afatinib as Part A in patients with inoperable or recurrent NSCLC who had received ≥1 regimen of chemotherapy including platinum antineoplastic drugs or PEM (except for EGFR-TKIs) and EGFR-TKIs for ≥12 weeks (target sample size, 1100) at 115 foreign study sites. In subjects who had presented the response to afatinib for ≥12 weeks in Part A, an open-label, randomized, comparative study was conducted as Part B to investigate the efficacy and safety of afatinib with PTX added and the other chemotherapy switched from afatinib.

All of the 1154 subjects enrolled in Part A of the study received afatinib, and 202 of 1154 subjects (17.5%) died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). Among these events, a causal relationship with afatinib could not be ruled out in 12 subjects, and the causes of death were interstitial lung disease and pneumonia in 2 subjects each, and endocarditis, lobar pneumonia, dehydration, acute left ventricular failure, atrial fibrillation, dyspnoea, cytolytic hepatitis, and hepatic failure in 1 subject each.

5) Foreign phase I study (5.3.5.4-2, Study 1200.37 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the safety and PK of concomitant use of afatinib with CDDP/5-FU or CDDP/PTX in patients with advanced solid cancer (target sample size, up to 66) at 3 foreign study sites.

All of the 47 subjects enrolled in the study received afatinib, and 6 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were reduced general condition in 3 subjects, and disease progression, atrial fibrillation/acute pulmonary oedema/acute respiratory distress syndrome, and septic shock in 1 subject each. Among these events, a causal relationship with afatinib could not be ruled out for atrial fibrillation/acute pulmonary oedema/acute respiratory distress syndrome, and septic shock in 1 subject each.

6) Foreign phase I study (5.3.5.4-3, Study 1200.68 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted] [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the safety and PK of concomitant use of afatinib with trastuzumab in patients with HER2-positive metastatic or recurrent breast cancer (target sample size, up to 40) at 5 foreign study sites.

All of the 18 subjects enrolled in the study received afatinib, and 1 subject died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The death cause was pulmonary embolism and its causal relationship with afatinib was ruled out.

7) Foreign phase I study (5.3.5.4-11, Study 1239.1 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the safety, PK, and efficacy of concomitant use of afatinib with nintedanib in patients with advanced solid cancer (target sample size, 42) at 4 foreign study sites.

All of the 28 subjects enrolled in the study received afatinib, and 3 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 2 subjects and peritonitis bacterial in 1 subject, and a causal relationship with afatinib was ruled out for all deaths.

8) Foreign phase II study (5.3.5.4-12, Study 1239.2 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of alternative sequential treatments of afatinib and nintedanib in patients with metastatic colorectal cancer (target sample size, 40) at 5 foreign study sites.

All of the 46 subjects enrolled to the study received afatinib, and 11 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were reduced general condition in 3 subjects, disease progression in 2 subjects, and cardio-respiratory arrest, circulatory collapse, pulmonary haemorrhage/dyspnoea, respiratory failure, portal vein thrombosis, and ascites/fatigue in 1 subject each, and a causal relationship with afatinib was ruled out for all deaths.

9) Foreign phase II study (5.3.5.4-13, Study 1239.3 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, randomized, comparative study was conducted to investigate the efficacy and safety of afatinib alone, nintedanib alone, and concomitant use of afatinib at 2 doses with nintedanib in chemotherapy-naive patients with castration-resistant prostate cancer (target sample size, up to 140) at 9 foreign study sites.

Of 85 subjects enrolled in the study, 39 subjects (20 subjects in the afatinib alone group, 19 subjects in the afatinib + nintedanib group) received afatinib, and 2 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression and death unexplained in 1 subject each, and a causal relationship with afatinib was ruled out for all deaths.

10) Foreign phase III study (5.3.5.4-16, Study 1200.34 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted], 20[redacted])])

An open-label, randomized, comparative study was conducted to compare the efficacy and safety between afatinib and concomitant use of CDDP and gemcitabine hydrochloride (GEM) (CDDP/GEM) in chemotherapy-naive patients with inoperable or recurrent *EGFR* mutation-positive NSCLC (adenocarcinoma) (target sample size, 360) at 36 foreign study sites.

Of 910 subjects enrolled in the study, 364 subjects meeting the eligibility criteria (242 subjects in the afatinib group, 122 subjects in the CDDP/GEM group) were randomly assigned, and 352 subjects (239 subjects in the afatinib group, 113 subjects in the CDDP/GEM group) received the study drug at least once. Fourteen of 239 subjects (5.9%) in the afatinib group and 3 of 113 subjects (2.7%) in the CDDP/GEM group died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were respiratory failure in 5 subjects, disease progression in 3 subjects, pneumonia in 2 subjects, and headache, loss of consciousness, multi-organ failure, and sudden death in 1 subject each in the afatinib group; and death unexplained, respiratory failure, and cardiac failure in 1 subject each in the CDDP/GEM group. Among these events, a causal relationship with the investigational drug could not be ruled out for sudden death in 1 subject in the afatinib group and cardiac failure in 1 subject in the CDDP/GEM group.

11) Foreign phase II study (5.3.5.4-17, Study 1200.40 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of afatinib in patients with inoperable or recurrent *EGFR*-amplified NSCLC who had not received chemotherapy or had received 1 regimen of chemotherapy (target sample size, 70) at 10 foreign study sites.

All of the 70 subjects enrolled in the study received afatinib, and 12 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 6 subjects, respiratory failure and death unexplained in 2 subjects each, and respiratory distress and reduced general condition in 1 subject each, and a causal relationship with afatinib was ruled out for all deaths.

12) Foreign phase II study (5.3.5.4-19, Study 1200.72 [[redacted] 20[redacted] to ongoing (data cut-off, [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of afatinib in patients with inoperable or recurrent *EGFR* mutation-negative NSCLC (adenocarcinoma) who had received 2 regimens of chemotherapy including platinum antineoplastic drugs (excluding EGFR-TKIs) (target sample size, 40) at 3 foreign study sites.

Of 43 subjects enrolled in the study, 42 received afatinib, and 9 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were pneumonia in 5 subjects and headache/vomiting, dyspnoea, haemoptysis, and gastrointestinal obstruction in 1 subject each. A causal relationship with afatinib was ruled out for all deaths.

13) Foreign phase II study (5.3.5.4-21, Study 1200.26 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of afatinib in patients with advanced *EGFR* mutation-positive or *EGFR* or *HER2* amplified solid cancer (target sample size, up to 60) at 17 foreign study sites.

Of 22 subjects enrolled in the study, 20 subjects received afatinib, and 3 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 2 subjects and dyspnoea in 1 subject. Among these events, a causal relationship with afatinib could not be ruled out for dyspnoea in 1 subject.

14) Foreign phase II study (5.3.5.4-22, Study 1200.10 [[redacted] 20[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of afatinib in patients with HER2-negative metastatic or recurrent breast cancer who had received 3 or fewer types of chemotherapy (target sample size, 80) at 13 foreign study sites.

All of the 50 subjects enrolled in the study received afatinib, and 5 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 2 subjects, and disease progression/reduced general condition, bronchopneumonia/reduced general condition, and reduced general condition in 1 subject each. Among these events, a causal relationship with afatinib could not be ruled out for reduced general condition in 1 subject who died due to bronchopneumonia/reduced general condition.

15) Foreign phase II study (5.3.5.4-23, Study 1200.11 [[redacted] 20[redacted] to [redacted] 20[redacted]])
An open-label, uncontrolled study was conducted to investigate the efficacy and safety of afatinib in patients with HER2-positive metastatic or recurrent breast cancer who had received trastuzumab (target sample size, up to 40) at 12 foreign study sites.

All of the 41 subjects enrolled in the study received afatinib, and 1 subject died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The death cause was disease progression and its causal relationship with afatinib was ruled out.

16) Foreign phase II study (5.3.5.4-24, Study 1200.44 [[redacted] 20[redacted] to [redacted] 20[redacted]])
An open-label, randomized, comparative study was conducted to compare the efficacy and safety among afatinib, trastuzumab, and lapatinib in chemotherapy-naive patients with locally advanced HER2 positive breast cancer (target sample size, 120) at 16 foreign study sites.

Of 29 subjects enrolled in the study, 10 subjects received afatinib, and no deaths occurred during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug).

17) Foreign phase II study (5.3.5.4-25, Study 1200.5 [[redacted] 20[redacted] to [redacted] 20[redacted]])
An open-label, uncontrolled study was conducted to investigate the efficacy and safety of concomitant use of afatinib with letrozole in patients with estrogen receptor-positive metastatic breast cancer who had received letrozole (target sample size, 30-40) at 5 foreign study sites.

All of the 28 subjects enrolled in the study received afatinib, and 3 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 2 subjects and disseminated intravascular coagulation in 1 subject. A causal relationship with afatinib was ruled out for all deaths.

18) Foreign phase II study (5.3.5.4-33, Study 1200.74 [[redacted] 20[redacted] to [redacted] 20[redacted]])
Of patients with metastatic colorectal cancer who had received regimens of chemotherapy including oxaliplatin and irinotecan hydrochloride (target sample size, 88), (a) patients with wild-type *KRAS* gene were assigned to an open-label, randomized, comparative study to compare the efficacy and safety between afatinib and cetuximab (genetical recombinant) (cetuximab); and (b) patients with *KRAS* mutant gene were assigned to an open-label, uncontrolled study to investigate the efficacy and safety of afatinib. The study was conducted at 13 foreign study sites.

Of 94 subjects enrolled in the study, 77 subjects (36 subjects with wild-type *KRAS* gene, 41 subjects with *KRAS* mutation) received afatinib, and 11 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were disease progression in 8 subjects, and intestinal obstruction, escherichia sepsis/hepatic encephalopathy, and pneumonia in 1 subject each. A causal relationship with afatinib was ruled out for all deaths.

19) Foreign phase II study (5.3.5.4-30, Study 1200.28, [[redacted] 20[redacted] to [redacted] 20[redacted])
An open-label, randomized, crossover study was conducted to compare the efficacy and safety between afatinib and cetuximab in patients with metastatic or recurrent head and neck squamous cell carcinoma (target sample size, 80) at 43 foreign study sites.

Of 124 subjects enrolled in the study, 97 subjects received afatinib, and 27 subjects died during the treatment period or follow-up period (up to 28 days after the last dose of the investigational drug). The causes of death were reduced general condition in 10 subjects, pneumonia in 3 subjects, respiratory failure in 2 subjects, disease progression, tumor haemorrhage, ischaemic stroke/pneumonia aspiration, cardiac arrest, cardio-respiratory arrest, cardiopulmonary failure,

haemorrhage, dyspnoea, pneumonia aspiration, respiratory distress, mouth haemorrhage, and pyrexia in 1 subject each. Among these events, a causal relationship with afatinib could not be ruled out for reduced general condition and pyrexia in 1 subject each.

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

4.(iii).B.(1) Data for review

PMDA concluded that, among the evaluation data submitted for this application, the most important clinical study data for evaluating the efficacy and safety of afatinib was the global phase III study (Study 1200.32) which evaluated the efficacy and safety of afatinib in chemotherapy-naive patients with inoperable or recurrent *EGFR* mutation-positive NSCLC. PMDA thus decided to review the submitted data focused on the Study 1200.32.

4.(iii).B.(2) Efficacy

Based on the following review, PMDA has concluded that afatinib is effective in chemotherapy-naive patients with inoperable or recurrent *EGFR* mutation-positive NSCLC.

4.(iii).B.(2).1) Use of control group

PMDA asked the applicant to explain the appropriateness of CDDP/PEM as the control in Study 1200.32.

The applicant responded as follows:
When the study was planned, EGFR-TKIs were not approved for the treatment of chemotherapy-naive patients with inoperable or recurrent NSCLC in the US, and 2-drug combination chemotherapy (± bevacizumab [genetical recombination]) regimen including platinum antineoplastic drugs was the standard therapy at that time described in Non-Small Cell Lung Cancer of the US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN guideline) (v.2.2008) for chemotherapy-naive patients with inoperable or recurrent NSCLC. Although gefitinib was approved for the treatment of patients with inoperable or recurrent *EGFR* mutation-positive NSCLC in Japan and EU, 2-drug combination chemotherapy including platinum antineoplastic drugs was also widely used in chemotherapy-naive patients.

CDDP/GEM was the standard 2-drug combination chemotherapy including platinum antineoplastic drugs. Foreign studies confirmed (a) non-inferiority of CDDP/PEM to CDDP/GEM in terms of OS with favorable safety; and (b) significant prolonged OS in patients with inoperable or recurrent nonsquamous NSCLC in the CDDP/PEM group compared with those in the CDDP/GEM group (*J Clin Oncol*. 2008;26:3543-51). In Japan, although CDDP/PEM was not approved for the indication of inoperable or recurrent NSCLC in chemotherapy-naive patients, a new drug application of CDDP/PEM was also filed with the same dosage and administration as that in overseas. Based on the above, the applicant considered that the use of CDDP/PEM as the control in Study 1200.32 was justified.

PMDA accepted the applicant's explanation.

4.(iii).B.(2).2) Efficacy endpoint

PMDA asked the applicant to explain the appropriateness of PFS as the primary endpoint for the efficacy in Study 1200.32.

The applicant responded as follows:
The purpose of the drug therapy for inoperable or recurrent NSCLC patients should be to stabilize the condition and suppress the progression but not to cure the disease. Thus, the PFS itself could serve as an efficacy endpoint.

Inoperable or recurrent NSCLC patients who have not received chemotherapy may have relatively long OS, potentially involving multiple treatments after the primary treatment; and in addition, EGFR-TKIs were assumed to be used as the secondary or subsequent treatment for patients with inoperable or recurrent *EGFR* mutation-positive NSCLC in all of the countries participating in Study 1200.32. Therefore, the reason that OS was not set as the primary endpoint for the efficacy was that the OS might be affected by the subsequent treatment.

Based on the above, the applicant considered that the use of the PFS as the primary endpoint for the efficacy in Study 1200.32 was justified.

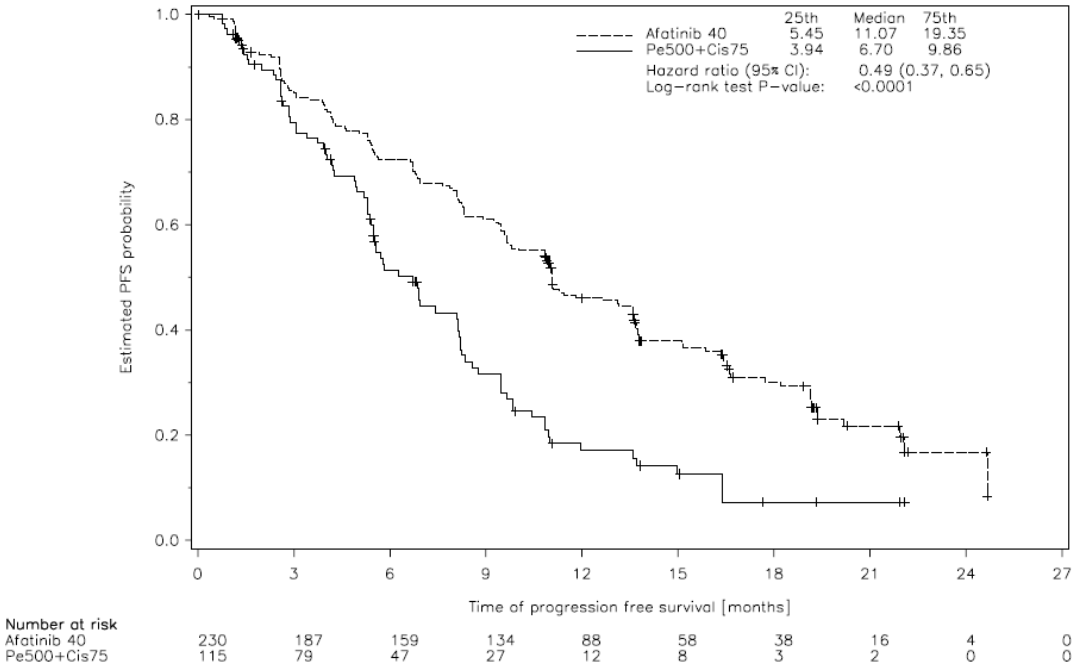
PMDA considers as follows:
It is understandable that there is a concern that multiple subsequent treatments including EGFR-TKIs may be implemented in the control group. The PFS may have a certain clinical significance depending on the effect. However, the OS is the true endpoint in NSCLC patients, and thus the OS should be investigated in addition to the PFS set as the primary endpoint, ensuring comprehensive evaluation.

4.(iii).B.(2).3) Result of efficacy evaluation
Study 1200.32 indicated that afatinib was superior to CDDP/PEM in terms of the IRC-evaluated PFS, the primary endpoint [see "4.(iii).A.(3) Global study"]. The analysis results on the PFS assessed by the attending physician are as shown in the table and figure below.

Analysis results on PFS (ITT population, physician evaluation, data cut-off on [redacted], 20[redacted])

	Afatinib group	CDDP/PEM group
Number of subjects	230	115
Death or exacerbation (%)	155 (67.4)	83 (72.2)
Median [95% CI] (months)	11.07 [9.66, 13.60]	6.70 [5.42, 8.11]
Hazard ratio [95% CI][*1]	0.488 [0.367, 0.649]	
P value (two-sided)[*2, *3]	< 0.0001	

[*]1: Cox regression by using *EGFR* mutation type (L858R, Del 19, others) and race (Asian, non-Asian) as the stratification factors, [*]2: Stratified log-rank test by using *EGFR* mutation type (L858R, Del 19, others) and race (Asian, non-Asian) as the stratification factors, [*]3: Significance level of 0.05 (two-sided)



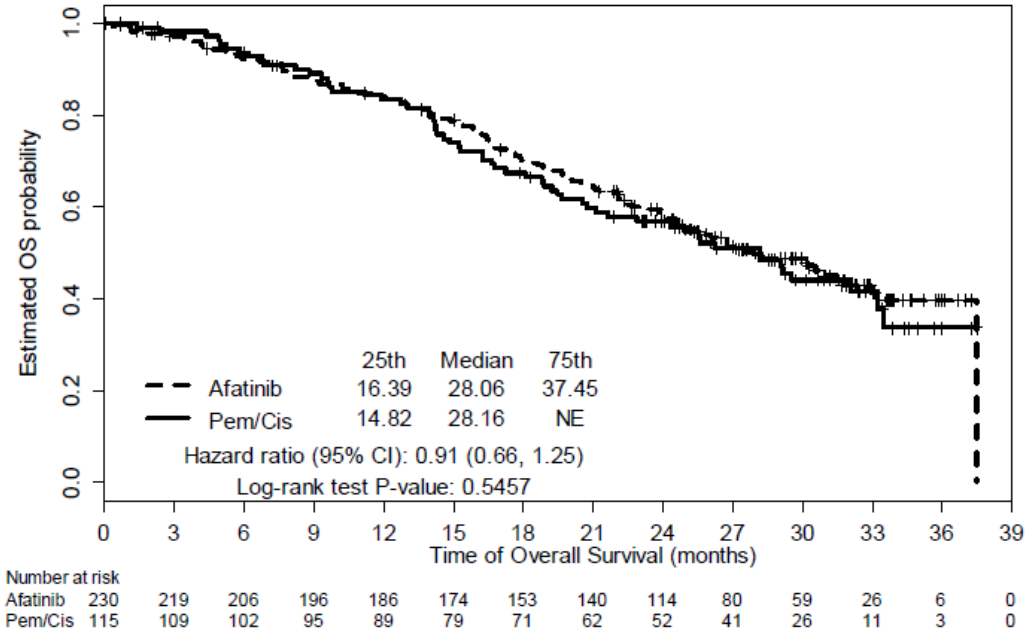
Kaplan-Meier curve of PFS (ITT population, physician evaluation, data cut-off on [redacted], 20[redacted])

In addition, the pivotal analysis of the OS is planned to be performed when a total of approximately 209 patients die. The current analysis results on the OS performed on a request from the US Food and Drug Administration (FDA) (data cut-off on January 21, 2013) are as shown in the table and figure below.

Current analysis results on OS (ITT population, data cut-off on January 21, 2013)

	Afatinib group	CDDP/PEM group
Number of subjects	230	115
Number of deaths (%)	116 (50.4)	59 (51.3)
Median [95% CI] (months)	28.06 [24.64, 32.95]	28.16 [20.73, 33.22]
Hazard ratio [95% CI][*1]	0.907 [0.660, 1.246]	
P value (two-sided)[*2]	0.5457	

[*]1: Cox regression by using *EGFR* mutation type (L858R, Del 19, others) and race (Asian, non-Asian) as the stratification factors, [*]2: Stratified log-rank test by using *EGFR* mutation type (L858R, Del 19, others) and race (Asian, non-Asian) as the stratification factors



Current Kaplan-Meier curve of OS (ITT population, data cut-off on January 21, 2013)

In addition, the applicant explained that Study 1200.34 conducted with the same design as that of Study 1200.32, in which CDDP/GEM was set as the control, demonstrated the efficacy of afatinib as shown by the results on the IRC-evaluated PFS, the primary endpoint (the table below).

Analysis results on PFS (ITT population, IRC evaluation, data cut-off on [redacted], 20[redacted])

	Afatinib group	CDDP/GEM group
Number of subjects	242	122
Death or exacerbation (%)	157 (64.9)	64 (52.5)
Median [95% CI] (months)	11.01 [9.66, 13.73]	5.59 [5.06, 6.70]
Hazard ratio [95% CI][*1]	0.279 [0.201, 0.388]	
P value (two-sided)[*2, *3]	< 0.0001	

[*]1: Cox regression by using *EGFR* mutation type (L858R, Del 19, others) as the stratification factor, [*]2: Stratified log-rank test by using *EGFR* mutation type (L858R, Del 19, others) as the stratification factor, [*]3: Significance level of 0.05 (two-sided)

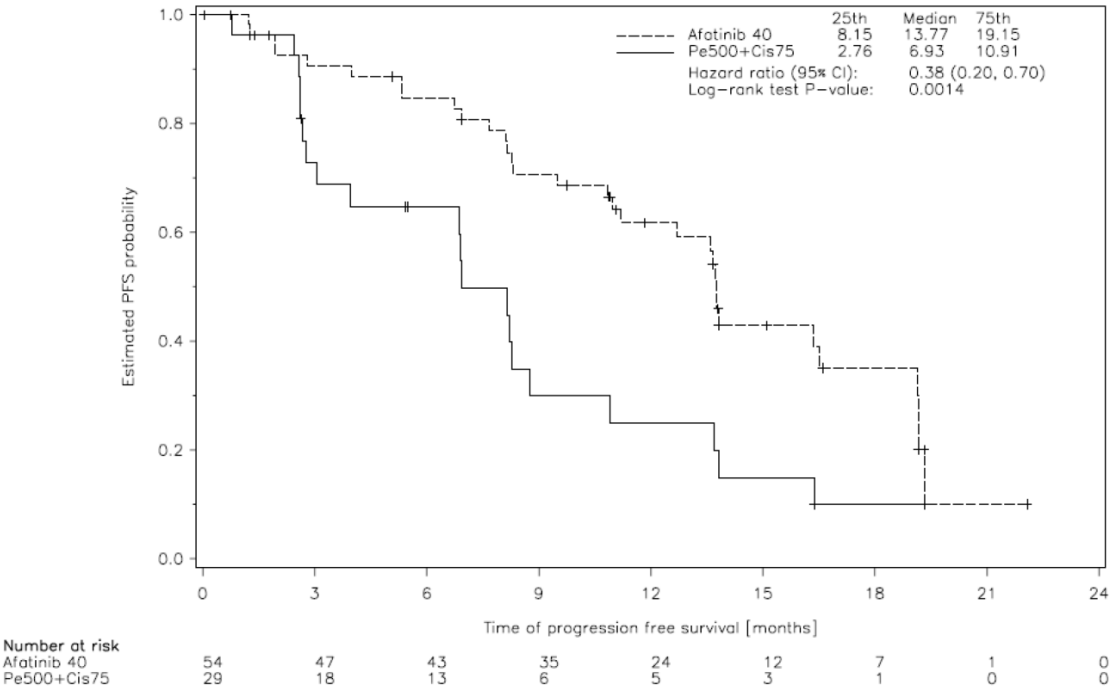
PMDA considers as follows:
Study 1200.32 has presented the results with a certain clinical significance in terms of the effects on the PFS, because the results on the IRC-evaluated PFS, the primary endpoint, showed the superiority of afatinib to CDDP/PEM, the standard chemotherapy; and assessment results by the attending physician supported the above results. In addition, no inferiority of afatinib to the control has been reported in terms of the OS, although this study was neither designed nor conducted to evaluate the OS mainly. Based on the above, the efficacy of afatinib can be expected for patients included in Study 1200.32

4.(iii).B.(2).4) Efficacy in Japanese patients
Results on the IRC-evaluated PFS and OS in 83 Japanese patients (54 patients in the afatinib group, 29 patients in the placebo group) in Study 1200.32 are as shown in the table and figure below.

Analysis results on the PFS in Japanese patients (ITT population, IRC evaluation, data cut-off on [redacted])

	Afatinib group	CDDP/PEM group
Number of subjects	54	29
Death or exacerbation (%)	32 (59.3)	20 (69.0)
Median (95% CI) (months)	13.77 [10.97, 19.17]	6.93 [3.06, 8.77]
Hazard ratio (95% CI)*1	0.377 [0.203, 0.699]	
P value (two-sided)*2	0.0014	

*1: Cox regression by using *EGFR* mutation type (L858R, Del 19, others) as the stratification factor, *2: Stratified log-rank test by using *EGFR* mutation type (L858R, Del 19, others) as the stratification factor



Kaplan-Meier curve of PFS in Japanese patients (ITT population, data cut-off on [redacted])

Current analysis results on OS in Japanese patients (ITT population, data cut-off on January 21, 2013)

	Afatinib group	CDDP/PEM group
Number of subjects	54	29
Number of deaths (%)	16 (29.6)	10 (34.5)
Median (95% CI) (months)	NE [NE, NE]	NE [28.16, NE]
Hazard ratio (95% CI)*1	0.830 [0.377, 1.831]	
P value (two-sided)*2	0.6444	

NE: Not evaluable, *1: Cox regression using only the treatment group as a factor, *2: Log-rank test

PMDA considers as follows:
Although the results on the PFS and OS in Japanese patients were derived from limited sources in terms of the number of patients and observation period, those on the PFS were not inconsistent with those from the overall population in Study 1200.32, and those on the OS did not show the inferiority of afatinib to the control. The efficacy of afatinib therefore can be expected even in Japanese patients included in Study 1200.32.

4.(iii).B.(3) Safety (for adverse events, see "4.(iv) Adverse events reported in clinical studies")

As a result of the review described below, PMDA considers that caution is required when administering afatinib for the following adverse events: interstitial lung disease, liver disorder, diarrhoea, rash/acne (including Stevens-Johnson syndrome [SJS]), stomatitis, nail abnormality (including paronychia), eye disorder (keratitis), cardiac failure, gastrointestinal perforation (including severe gastrointestinal ulcer/gastrointestinal haemorrhage), and pancreatitis acute.

PMDA, however, has concluded that afatinib is tolerable provided that appropriate measures such as monitoring and management of adverse events as well as the treatment interruption or discontinuation, and dose reduction are taken by physicians with sufficient knowledge and experience of cancer chemotherapy.

4.(iii).B.(3).1) Safety profile of afatinib

Based on the safety information in the afatinib and CDDP/PEM groups in Study 1200.32, the applicant explained the safety profile of afatinib in chemotherapy-naive patients with inoperable or recurrent *EGFR* mutation-positive NSCLC as follows:

The safety in the afatinib and CDDP/PEM groups in Study 1200.32 are summarized in the table below.

Safety summary (Study 1200.32)

	Number of patients (%)	
	Afatinib group, N = 229	CDDP/PEM group, N = 111
All adverse events	229 (100)	109 (98.2)
Adverse events of Grade 3 or 4	126 (55.0)	60 (54.1)
Adverse events of Grade 5	13 (5.7)	3 (2.7)
Serious adverse events	66 (28.8)	25 (22.5)
Adverse events leading to treatment discontinuation	32 (14.0)	17 (15.3)
Adverse events leading to dose reduction	131 (57.2)	18 (16.2)

Adverse events of all grades with a ≥10% higher incidence in the afatinib group than in the CDDP/PEM group were diarrhoea, rash/acne, stomatitis, nail abnormality, dry skin, eye disorder, pruritus, epistaxis, and lip disorder. At Grade ≥3, they were diarrhoea, rash/acne, and nail abnormality (the table below). Of adverse events leading to dose reduction, events with a ≥3% higher incidence in the afatinib group than in the CDDP/PEM group were diarrhoea (45 of 229 subjects [19.7%] in the afatinib group, 1 of 111 subjects [0.9%] in the CDDP/PEM group), rash/acne (44 of 229 subjects [19.2%], 0 subjects, respectively), nail abnormality (31 of 229 subjects [13.5%], 0 subjects, respectively), and stomatitis (23 of 229 subjects [10.0%], 1 of 111 subjects [0.9%], respectively). Of adverse events leading to treatment discontinuation, events with a ≥1% higher incidence in the afatinib group than in the CDDP/PEM group were diarrhoea (3 of 229 subjects [1.3%] in the afatinib group, 0 subjects in the CDDP/PEM group).

Adverse events with an incidence of ≥10% in either group (Study 1200.32)

Event	Number of patients (%)			
	Afatinib group (N = 229)		CDDP/PEM group (N = 111)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhoea	220 (96.1)	34 (14.8)	25 (22.5)	2 (1.8)
Rash/acne[*1]	206 (90.0)	37 (16.2)	12 (10.8)	0
Stomatitis[*2]	168 (73.4)	20 (8.7)	19 (17.1)	1 (0.9)
Nail abnormality[*3]	141 (61.6)	27 (11.8)	0	0
Dry skin	69 (30.1)	1 (0.4)	2 (1.8)	0
Decreased appetite	66 (28.8)	10 (4.4)	61 (55.0)	4 (3.6)
Fatigue[*4]	62 (27.1)	7 (3.1)	55 (49.5)	14 (12.6)
Nausea	58 (25.3)	3 (1.3)	75 (67.6)	4 (3.6)
Eye disorder[*5]	52 (22.7)	1 (0.4)	8 (7.2)	0
Vomiting	52 (22.7)	10 (4.4)	52 (46.8)	3 (2.7)
Pruritus	46 (20.1)	1 (0.4)	1 (0.9)	0
Epistaxis	39 (17.0)	0	2 (1.8)	1 (0.9)
Weight decreased	39 (17.0)	2 (0.9)	16 (14.4)	1 (0.9)
Cough	35 (15.3)	0	21 (18.9)	1 (0.9)
Lip disorder[*6]	35 (15.3)	0	2 (1.8)	0
Insomnia	34 (14.8)	0	10 (9.0)	0
Headache	33 (14.4)	1 (0.4)	19 (17.1)	0
Back pain	32 (14.0)	0	13 (11.7)	2 (1.8)
Nasopharyngitis	32 (14.0)	0	9 (8.1)	0
Constipation	30 (13.1)	0	39 (35.1)	0
Alopecia	29 (12.7)	0	20 (18.0)	0
Pyrexia	28 (12.2)	0	7 (6.3)	0
ALT increased	25 (10.9)	4 (1.7)	4 (3.6)	0
Dizziness	25 (10.9)	1 (0.4)	12 (10.8)	0
Upper respiratory tract infection	25 (10.9)	1 (0.4)	4 (3.6)	0
Dyspnoea	17 (7.4)	3 (1.3)	13 (11.7)	1 (0.9)
Anaemia	14 (6.1)	4 (1.7)	31 (27.9)	7 (6.3)
Chest pain	13 (5.7)	0	14 (12.6)	1 (0.9)
Hypertension	11 (4.8)	2 (0.9)	14 (12.6)	1 (0.9)
Oedema	8 (3.5)	1 (0.4)	13 (11.7)	0
Leukopenia	6 (2.6)	1 (0.4)	21 (18.9)	9 (8.1)
Haemoglobin decreased	3 (1.3)	0	13 (11.7)	3 (2.7)
Neutropenia	3 (1.3)	2 (0.9)	35 (31.5)	21 (18.9)

ALT: Alanine aminotransferase

Group terms used to identify adverse events related to inhibitory effect of EGFR:

[*]1: Acne, acne conglobata, acne cystic, acne fulminans, acne pustular, blister, dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, dermatosis, drug eruption, eczema, epidermal necrosis, erythema, exfoliative rash, folliculitis, generalised erythema, mucocutaneous rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash pustular, rash rubelliform, rash scarlatiniform, rash vesicular, skin disorder, skin erosion, skin exfoliation, skin fissures, skin induration, skin irritation, skin lesion, skin necrosis, skin reaction, skin swelling, skin toxicity, skin ulcer, severe skin adverse drug reactions (narrow Standardised MedDRA Queries [SMQs])

[*]2: Aphthous stomatitis, dry mouth, glossitis, glossodynia, mouth ulceration, mucosal erosion, mucosal excoriation, mucosal exfoliation, mucosal hyperaemia, mucosal induration, mucosal inflammation, mucosal necrosis, mucosal ulceration, oedema mucosal, oral mucosa erosion, oral mucosal eruption, oral mucosal erythema, oral mucosal exfoliation, oral toxicity, oropharyngeal blistering, pharyngeal erosion, pharyngeal ulceration, stomatitis, stomatitis haemorrhagic, stomatitis necrotising, throat irritation, tongue blistering, tongue eruption, tongue exfoliation, tongue ulceration

[*]3: Nail atrophy, nail avulsion, nail bed infection, nail bed inflammation, nail bed tenderness, nail discomfort, nail disorder, nail dystrophy, nail growth abnormal, nail infection, nail pitting, nail toxicity, onychalgia, onychoclasis, onychogryphosis, onycholysis, onychomalacia, paronychia

[*]5: Blepharitis, conjunctival hyperaemia, conjunctival irritation, conjunctival oedema, conjunctivitis, corneal erosion, dry eye, eczema eyelids, erythema of eyelid, eye discharge, eye inflammation, eye irritation, eye pain, eye pruritus, eyelid disorder, eyelid erosion, eyelid exfoliation, eyelid folliculitis, eyelid irritation, eyelid margin crusting, eyelid oedema, eyelid pain, eyelid skin dryness, eyelids pruritus, keratitis, lid margin discharge, ocular discomfort, ocular hyperaemia, corneal disorder (narrow SMQs)

[*]6: Chapped lips, cheilitis, cheilosis, lip blister, lip disorder, lip dry, lip erosion, lip exfoliation, lip pain, lip ulceration

Group terms used to identify fatigue highly related to cancer and chemotherapy:

[*]4: Asthenia, autonomic nervous system imbalance, chronic fatigue syndrome, decreased activity, fatigue, lethargy, listless, malaise, sluggishness

PMDA considers as follows:
In Study 1200.32, the incidence of adverse events leading to dose reduction of the investigational drug was higher in the afatinib group than in the CDDP/PEM group, but the incidence of adverse events leading to discontinuation of the investigational drug and serious adverse events in the afatinib group was not largely different from that in the CDDP/PEM group. Afatinib is tolerable with appropriate measures such as treatment interruption or discontinuation, and dose reduction.

However, attention should be paid to events with a higher incidence in the afatinib group than in the CDDP/PEM group, especially to Grade ≥3 events with a ≥10% higher incidence in the afatinib group, i.e., diarrhoea, rash/acne, and nail abnormality. The use of afatinib in Japanese patients were limited, and safety information on afatinib in Japanese patients has not adequately accumulated. Therefore, it is necessary to collect post-marketing safety information on afatinib in Japanese patients [see "4.(iii).B.(6) Post-marketing investigations"].

4.(iii).B.(3).2) Differences in safety between Japanese and non-Japanese patients
The applicant explained the differences in the safety of afatinib between Japanese and non-Japanese patients as follows:
The safety in Japanese and non-Japanese patients in Study 1200.32 is summarized as shown in the table below. The incidence of serious adverse events did not tend to be higher in Japanese patients than in non-Japanese patients, and no fatal adverse events were reported in Japanese patients.

Summary of the safety in Japanese and non-Japanese patients (Study 1200.32)

	Number of patients (%)			
	Japanese patients		Foreign patients	
	Afatinib group N = 54	CDDP/PEM group N = 28	Afatinib group N = 175	CDDP/PEM group N = 83
All adverse events	54 (100)	28 (100)	175 (100)	81 (97.6)
Adverse events of Grade 3 or 4	37 (68.5)	20 (71.4)	89 (50.9)	40 (48.2)
Adverse events of Grade 5	0	0	13 (7.4)	3 (3.6)
Serious adverse events	9 (16.7)	4 (14.3)	57 (32.6)	21 (25.3)
Adverse events leading to treatment discontinuation	10 (18.5)	7 (25.0)	22 (12.6)	10 (12.0)
Adverse events leading to dose reduction	41 (75.9)	5 (17.9)	90 (51.4)	13 (15.7)

Adverse events with an incidence of ≥10% in either Japanese or non-Japanese patients in Study 1200.32 are as shown in the table below.

Of adverse events in the afatinib group in Study 1200.32, events with a ≥20% higher incidence in Japanese patients than in non-Japanese patients were nail abnormality, stomatitis, decreased appetite, dry skin, eye disorder, lip disorder, and nasopharyngitis. The Grade ≥3 adverse events that occurred with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were diarrhoea, rash/acne, and nail abnormality.

Adverse events with an incidence of ≥10% in either Japanese or non-Japanese patients in the afatinib group (Study 1200.32)

Event	Number of patients (%)					
	Japanese patients N = 54			Foreign patients N = 175		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Number of patients with adverse events	54 (100)	36 (66.7)	1 (1.9)	175 (100)	81 (46.3)	8 (4.6)
Diarrhoea	54 (100)	11 (20.4)	0	166 (94.9)	23 (13.1)	0
Rash/acne*	54 (100)	11 (20.4)	0	152 (86.9)	26 (14.9)	0
Nail abnormality*	48 (88.9)	13 (24.1)	0	93 (53.1)	14 (8.0)	0
Stomatitis*	48 (88.9)	4 (7.4)	0	120 (68.6)	15 (8.6)	1 (0.6)
Decreased appetite	26 (48.1)	4 (7.4)	0	40 (22.9)	6 (3.4)	0
Dry skin	26 (48.1)	0	0	43 (24.6)	1 (0.6)	0
Eye disorder*	24 (44.4)	1 (1.9)	0	28 (16.0)	0	0
Lip disorder*	20 (37.0)	0	0	15 (8.6)	0	0
Nasopharyngitis	19 (35.2)	0	0	13 (7.4)	0	0
Nausea	18 (33.3)	1 (1.9)	0	40 (22.9)	2 (1.1)	0
Fatigue*	17 (31.5)	2 (3.7)	0	45 (25.7)	5 (2.9)	0
Weight decreased	16 (29.6)	1 (1.9)	0	23 (13.1)	1 (0.6)	0
Vomiting	14 (25.9)	0	0	38 (21.7)	10 (5.7)	0
Dysgeusia	12 (22.2)	0	0	6 (3.4)	0	0
Epistaxis	12 (22.2)	0	0	27 (15.4)	0	0
Nasal inflammation	10 (18.5)	0	0	3 (1.7)	0	0
Pruritus	10 (18.5)	0	0	36 (20.6)	1 (0.6)	0
Constipation	9 (16.7)	0	0	21 (12.0)	0	0
Insomnia	9 (16.7)	0	0	25 (14.3)	0	0
ALT increased	8 (14.8)	1 (1.9)	0	17 (9.7)	3 (1.7)	0
Back pain	8 (14.8)	0	0	24 (13.7)	0	0
Cystitis	8 (14.8)	0	0	5 (2.9)	0	0
Pyrexia	8 (14.8)	0	0	20 (11.4)	0	0
Alopecia	7 (13.0)	0	0	22 (12.6)	0	0
Headache	7 (13.0)	0	0	26 (14.9)	1 (0.6)	0
Hypertension	6 (11.1)	1 (1.9)	0	5 (2.9)	1 (0.6)	0
Cough	4 (7.4)	0	0	31 (17.7)	0	0
Dizziness	3 (5.6)	1 (1.9)	0	22 (12.6)	0	0
Hypokalaemia	2 (3.7)	1 (1.9)	0	21 (12.0)	4 (2.3)	5 (2.9)
Upper respiratory tract infection	2 (3.7)	1 (1.9)	0	23 (13.1)	0	0

ALT: Alanine aminotransferase, *: Group terms used to identify adverse events related to inhibitory action of EGFR, as described above

Of adverse events leading to dose reduction, events with a ≥5% incidence that occurred more frequently in Japanese patients than in non-Japanese patients were nail abnormality (16 of 54 Japanese patients [29.6%], 15 of 175 non-Japanese patients [8.6%]), rash/acne (15 of 54 Japanese patients [27.8%], 29 of 175 non-Japanese patients [16.6%]), diarrhoea (12 of 54 Japanese patients [22.2%], 33 of 175 non-Japanese patients [18.9%]), and decreased appetite (3 of 54 Japanese patients [5.6%], 4 of 175 non-Japanese patients [2.3%]). Of adverse events leading to treatment discontinuation, the event with a ≥3% incidence that occurred more frequently in Japanese patients than in non-Japanese patients was interstitial lung disease (2 of 54 Japanese patients [3.7%], none in non-Japanese patients).

PMDA considers as follows:
As described above, in Study 1200.32, the following adverse events occurred more frequently in Japanese patients than in non-Japanese patients: all Grades (nail abnormality, stomatitis, decreased appetite, dry skin, eye disorder, lip disorder, nasopharyngitis); Grade ≥3 (diarrhoea, rash/acne, nail abnormality). It is necessary to provide appropriate cautions for these adverse events. However, afatinib is tolerable in Japanese patients as well for the following grounds: the

number of patients who discontinued afatinib due to these events was limited (nail abnormality [1 of 54 Japanese patients (1.9%), 1 of 175 non-Japanese patients (0.6%)], decreased appetite [1 of 54 patients (1.9%), 0 patients, respectively], eye disorder [1 of 54 patients (1.9%), 0 patients, respectively], diarrhoea [0 patients, 3 of 175 patients (1.7%), respectively], stomatitis, dry skin, lip disorder, nasopharyngitis, and rash/acne [0 Japanese and non-Japanese patients]); these events were mostly manageable with appropriate measures such as treatment interruption or discontinuation, and dose reduction; and there were few serious adverse events and no fatal adverse events. Interstitial lung disease leading to treatment discontinuation occurred only in Japanese patients, and thus attention should be paid to the concerned event.

4.(iii).B.(3).3) Interstitial lung disease-like events

Interstitial lung disease due to afatinib and its potentially related events were evaluated as interstitial lung disease-like events.

The applicant explained the interstitial lung disease-like events due to afatinib as follows:
The interstitial lung disease-like events were tabulated using the relevant broad Standardised MedDRA Queries (SMQs).

In Study 1200.32, interstitial lung disease-like events were reported in 7 of 229 subjects (3.1%) only in the afatinib group but not in the CDDP/PEM group. Grade ≥3 events were reported in 3 subjects (acute respiratory distress syndrome in 2 subjects, interstitial lung disease in 1 subject), of whom 2 subjects had fatal events (0.9%, both due to acute respiratory distress syndrome). In addition, 5 of 229 subjects (2.2%; interstitial lung disease in 2 subjects, acute respiratory distress syndrome, lung infiltration, and radiation pneumonitis in 1 subject each) discontinued the treatment.

In all of the unblinded clinical studies in cancer patients (3865 patients treated with afatinib in 46 studies) (data as of data cut-off on [redacted], 20[redacted] in Study 1200.32 tabulated), interstitial lung disease-like events were reported in 59 of 3865 patients (1.5%); Grade ≥3 events were reported in 38 of 3865 patients (1.0%); and 15 of 3865 patients (0.4%) had fatal events. The events for which a causal relationship with afatinib could not be ruled out were reported in 28 of 3865 patients (0.7%) in the table below, and all of the affected patients discontinued afatinib. Many of the patients received combination therapy with steroids and antibiotics.

Severity, treatment, and outcome of interstitial lung disease-like events for which a causal relationship with afatinib could not be ruled out

Study	MedDRA Preferred term	Grade	Number of days to onset	ECOG PS	Comorbid respiratory symptoms and disease	Details of the treatment	Outcome
1200.32	Interstitial lung disease	3	43	1	NSCLC, pleural effusion, cough, hypertension	Steroids, antibiotics, mechanical ventilation	Recovered
1200.32	Interstitial lung disease	1	126	0	NSCLC (metastases to pleura), atrioventricular block, hypertension	No treatment	Recovered
1200.32	Acute respiratory distress syndrome	5	11	1	NSCLC (contralateral metastases to lung), chest pain, cough, dyspepsia, dyspnoea exertional	Steroids	Death
1200.3	Pneumonitis	3	22	1	Chest discomfort (breast cancer)	Steroids, antibiotics	Recovered
1200.22	Interstitial lung disease Lung infiltration	3 1	258 254	0	NSCLC, asthma, hypertension	Steroids, antibiotics	Recovered Recovered
1200.22	Interstitial lung disease	1	57	0	NSCLC, cough, wheezing, hypertension	Steroids, antibiotics	Recovered
1200.22	Interstitial lung disease	2	101	0	NSCLC (metastases to lung), arrhythmia, hypertension	Steroids, antibiotics	Not recovered
1200.22	Interstitial lung disease	1	31	1	NSCLC (metastases to lung), hypertension	No treatment	Not recovered
1200.28	Interstitial lung disease	3	47	1	Not reported	Steroids, antibiotics	Recovered
1200.33	Interstitial lung disease	3	31	1	NSCLC (ipsilateral and contralateral metastases to lung), elevated serum Krebs von den Lungen 6 (KL-6) levels	Steroids, antibiotics, mechanical ventilation	Recovered
1200.33	Interstitial lung disease	1	197	1	NSCLC (ipsilateral and contralateral metastases to lung), seasonal allergy	No treatment	Recovered
1200.34	Interstitial lung disease	4	51	1	NSCLC, chest pain, cough, dyspnoea, obstructive pneumonia	Antibiotics	Recovered
1200.37	Acute respiratory distress syndrome	5	47	0	Cervical cancer with metastases to lung, hypertension	Antiarrhythmic drugs (amiodarone), diuretic drugs, morphine, oxygenation	Death
1200.42	Interstitial lung disease	4	29	1	NSCLC, cough	Steroids	Recovered
1200.42	Interstitial lung disease	3	56	1	NSCLC, dyspnoea, hypertension	Steroids, antibiotics	Recovered
1200.42	Interstitial lung disease	5	65	1	NSCLC	Steroids, antibiotics	Death
1200.42	Interstitial lung disease	5	11	0	NSCLC, lymphangiosis carcinomatosa	Steroids, antibiotics	Death
1200.42	Pneumonitis	3	155	2	NSCLC, shortness of breath, productive cough	Steroids, antibiotics	Recovered
1200.42	Interstitial lung disease	4	11	2	NSCLC, dyspnoea, ischaemic heart disease	Steroids, antibiotics	Not recovered
1200.42	Interstitial lung disease	2	43	1	NSCLC, dyspnoea exertional, hypertension	No treatment	Recovered
1200.42	Pneumonitis	2	23	1	NSCLC, chest pain, dyspnoea	Steroids, antibiotics	Not recovered
1200.42	Interstitial lung disease	2	245	1	NSCLC, dyspnoea	Steroids	Recovered
1200.42	Interstitial lung disease	3	12	2	NSCLC, asthma, dyspnoea, haemoptysis	Steroids, antibiotics	Not recovered
1200.42	Pneumonitis	2	120	1	NSCLC	Steroids, expectorants	Not recovered
1200.42	Interstitial lung disease	1	174	0	NSCLC, cough	No treatment	Recovered
1200.42	Interstitial lung disease	4	7	1	NSCLC, chronic obstructive asthma (with obstructive lung disease), ischaemic heart disease, myocardial infarction (previous), hypertension	Steroids	Not recovered
1200.70	Pneumonitis	3	93	1	NSCLC, cough, dyspnoea, hypertension	Steroids, antibiotics	Recovered
1200.75	Pulmonary fibrosis	5	41	1	Scleroderma	Steroids, antibiotics	Death

In clinical studies in Japanese cancer patients (128 patients treated with afatinib in 2 studies) (data as of data cut-off on [redacted], 20[redacted] in Study 1200.32 tabulated), interstitial lung disease-like events were reported in 7 of 128 patients (5.5%); and Grade ≥3 events were reported in 2 of 128 patients (1.6%) in the table below. No deaths occurred. The events for which a causal relationship with afatinib could not be ruled out were reported in 4 of 128 patients (3.1%), and all of these events resolved.

Severity, treatment, and outcome of interstitial lung disease-like events in Japanese patients

Study	MedDRA Preferred term	Grade	Number of days to onset	ECOG PS	Comorbid respiratory symptoms and disease	Details of the treatment	Outcome	Causal relationship with afatinib
1200.32	Radiation pneumonitis	1	83	1	NSCLC	No treatment	Recovered	None
1200.32	Interstitial lung disease	3	43	1	NSCLC, pleural effusion, cough, hypertension	Steroids, antibiotics, mechanical ventilation	Recovered	Present
1200.32	Interstitial lung disease	1	126	0	NSCLC (metastases to pleura), atrioventricular block, hypertension	No treatment	Recovered	Present
1200.32	Lung infiltration	2	107	1	NSCLC (metastases to lung, pleural effusion)	Antibiotics	Not recovered	None
1200.33	Alveolitis allergic	1	80	1	NSCLC, asthma bronchial, rhinitis allergic	Steroids	Recovered	None
1200.33	Interstitial lung disease	3	31	1	NSCLC (ipsilateral and contralateral metastases to lung), elevated serum KL-6 levels	Steroids, antibiotics, mechanical ventilation	Recovered	Present
1200.33	Interstitial lung disease	1	197	1	NSCLC (ipsilateral and contralateral metastases to lung), seasonal allergy	No treatment	Recovered	Present

No consistent trend was found in terms of clinical symptoms or signs, or time of onset in either overall or Japanese population, and no definitive predictive factors of interstitial lung disease-like events associated with afatinib were identified.

Based on the above, the applicant considered it necessary to observe the patients carefully by monitoring initial symptoms (dyspnoea, cough, pyrexia, etc.) and implementing regular chest imaging during the treatment, and if any abnormality was observed, administration should be discontinued and appropriate measures should be taken.

PMDA considers as follows:
There was no particularly high trend in the incidence of interstitial lung disease-like events due to afatinib in Japanese patients (4 of 54 untreated patients [7.4%], 3 of 62 treated patients [4.8%]) compared with the incidence* in clinical studies of the approved EGFR-TKIs. Japanese and foreign clinical studies, however, suggested that the incidence in Japanese patients was higher than that in non-Japanese patients (Study 1200.32; 4 of 54 Japanese patients [7.4%], 3 of 175 non-Japanese patients [1.7%]). In consideration that no predictive factors of interstitial lung disease-like events associated with afatinib have been identified, and no consistent trend has been found in terms of time of onset, it is necessary to confirm complication or history of interstitial lung disease-like events before the afatinib treatment, indicate the drug only for carefully selected patients, pay attention to the onset of interstitial lung disease-like events continuously during the treatment with afatinib, and if any relevant event occurred, appropriate measures should be taken.

*: Interstitial lung disease-like events due to Iressa tablets occurred in 2 of 114 untreated patients (1.8%) and 14 of 244 treated patients (5.7%) (tabulated as interstitial lung disease) (see "Review Report, Iressa Tablets 250, dated

November 16, 2011"); and such events due to Tarceva Tablets occurred in 6 of 103 untreated patient (5.8%)s and 6 of 123 treated patients (4.9%) (see "Review Report, Tarceva Tablets 25 mg, 100 mg, 150 mg, dated May 7, 2013").

4.(iii).B.(3).4) Hepatic function disorder

The applicant explained hepatic function disorder due to afatinib as follows:

Adverse events indicative of hepatic function disorder were tabulated. To avoid underestimation of these events, adverse events related to "hepatic function disorder"* were defined with 4 sets of broad SMQs. Adverse events indicative of hepatic function disorder were classified into ones related to hepatic enzyme increased and the remaining.

*: SMQs used to retrieve events related to "hepatic function disorder," liver related investigations, signs and symptoms except for MedDRA preferred terms of ascites, haemorrhagic ascites, and bacterascites (broad SMQs); hepatic failure, fibrosis and cirrhosis and other liver damaged-related conditions (broad SMQs); hepatitis, non-infectious (broad SMQs); and cholestasis and jaundice of hepatic origin (broad SMQs)

The incidence of hepatic function disorder in Study 1200.32 is as shown in the table below. Grade 4 events were reported in 2 of 229 subjects (0.9%) only in the afatinib group (liver function test abnormal and jaundice in 1 subject each). The incidences of ALT increased and aspartate aminotransferase (AST) increased were higher in the afatinib group than those in the CDDP/PEM group, but there were no differences in incidences of the other events between the 2 groups. Discontinuation due to hepatic function disorder was reported in 2 of 229 subjects (0.9%) in the afatinib group and 1 of 111 subjects (0.9%) in the CDDP/PEM group. Of those who discontinued the study treatment in the afatinib group, 1 subject with jaundice was subjected to magnetic resonance cholangiopancreatography. As a result, hepatic metastases were observed in a wide region, damaging the right hepatic duct. In the remaining 1 subject, Grade 2 blood bilirubin increased occurred. In this patient, the bilirubin value was found to be abnormal both at the baseline and throughout the treatment period, but no clinically significant increases were found in transaminase values. Due to hepatic function disorder, the dose was reduced in 4 of 229 subjects (1.7%) in the afatinib group and 1 of 111 subjects (0.9%) in the CDDP/PEM group.

Incidence of hepatic function disorder (Study 1200.32)

Event	Number of patients (%)				
	Afatinib group N = 229			CDDP/PEM group N = 111	
	All Grades	Grade 3	Grade 4	All Grades	Grade 3
Hepatic enzyme increased	38 (16.6)	6 (2.6)	1 (0.4)	12 (10.8)	2 (1.8)
ALT increased	25 (10.9)	4 (1.7)	0	4 (3.6)	0
AST increased	19 (8.3)	4 (1.7)	0	2 (1.8)	1 (0.9)
Blood ALP increased	8 (3.5)	0	0	2 (1.8)	0
Hepatic function abnormal	5 (2.2)	0	0	1 (0.9)	0
Liver function test abnormal	3 (1.3)	0	1 (0.4)	2 (1.8)	0
Blood bilirubin increased	1 (0.4)	0	0	0	0
Gamma-glutamyltransferase increased	1 (0.4)	0	0	4 (3.6)	1 (0.9)
Hyperbilirubinaemia	1 (0.4)	0	0	0	0
Transaminases increased	1 (0.4)	0	0	0	0
Adverse events other than those related to hepatic enzyme increased	3 (1.3)	0	1 (0.4)	1 (0.9)	0
Hepatitis	1 (0.4)	0	0	0	0
Hypoalbuminaemia	1 (0.4)	0	0	1 (0.9)	0
Jaundice	1 (0.4)	0	1 (0.4)	0	0

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase

In all of the unblinded clinical studies in cancer patients (3865 patients treated with afatinib) (data as of data cut-off on [redacted], 20[redacted] in Study 1200.32 tabulated), fatal hepatic function disorder occurred in 7 of 3865 patients (0.2%), and a causal relationship with afatinib could not be ruled out in 3 of 7 subjects with the fatal event. Of these 3 subjects, 1 subject who had hepatitis B

experienced renal failure acute and acute hepatic failure approximately 10 days after the start of the treatment with afatinib and finally died. In this patient, activation of hepatitis B viruses was serologically documented. The other 1 subject had cytolytic hepatitis as well as acute respiratory failure potentially attributable to the disease progression. The remaining 1 subject experienced cardiac failure congestive and hepatic failure.

In all of the unblinded clinical studies in cancer patients (3865 patients treated with afatinib) (data as of data cut-off on [redacted], 20[redacted] in Study 1200.32 tabulated), 7 of 3865 patients (0.2%) experienced ALT or AST increased (>3 times the upper limit of normal range) associated with ALP increased <2 times the upper limit of normal range and total bilirubin increased (≥2 times the upper limit of normal range within 30 days after ALT or AST increased). These patients were deemed as Potential Hy's law cases. Of these 7 patients, 3 patients received afatinib alone, and 4 patients received the concomitant use of afatinib with the other antineoplastic drugs. In all of the 4 patients receiving concomitant use of afatinib with the other antineoplastic drugs, both bilirubin and ALP values increased. Of 3 patients receiving afatinib alone, 1 patient had biliary obstruction with tumor, the other 1 patient had hepatitis infectious, and the remaining 1 patient with a history of cholecystitis presented a transient increase and then rapid recovery and thus continued afatinib without relapse. As a result, none of the 7 subjects were deemed as Hy's law cases.

PMDA considers as follows:
In Study 1200.32, the incidence of hepatic function disorder was higher in the afatinib group (hepatic enzyme increased in 38 of 229 subjects [16.6%], adverse events other than those related to hepatic enzyme increased in 3 of 229 subjects [1.3%]) than in the CDDP/PEM group (hepatic enzyme increased in 12 of 111 subjects [10.8%], adverse events other than those related to hepatic enzyme increased in 1 of 111 subjects [0.9%]). Attention, therefore, should be paid to hepatic function disorder. In addition, some patients died from hepatic function disorder in foreign studies. Therefore, it is necessary to caution that patients should be monitored through periodic liver function test, and if any abnormalities are observed, appropriate measures such as treatment interruption or discontinuation, and dose reduction should be taken.

4.(iii).B.(3).5) Diarrhoea
The applicant explained diarrhoea due to afatinib as follows:
In Study 1200.32, diarrhoea occurred in 220 of 229 patients (96.1%) in the afatinib group and 25 of 111 patients (22.5%) in the CDDP/PEM group, and Grade 3 events occurred in 34 of 229 patients (14.8%) in the afatinib group and 2 of 111 patients (1.8%) in the CDDP/PEM group. No Grade 4/5 events occurred. The protocol of this study stipulated that afatinib should be interrupted and resumed at a reduced dose in patients with persistent Grade 2/3 diarrhoea despite the use of appropriate antidiarrheal agents and water intake, and afatinib should be discontinued in patients with diarrhoea which was not alleviated to Grade 1 or baseline level within 14 days. Under the above protocol, discontinuation due to diarrhoea was reported only in the afatinib group (3 of 229 patients [1.3%]); dose reduction for the investigational drug was reported in 45 of 229 patients (19.7%) in the afatinib group and 1 of 111 patients (0.9%) in the CDDP/PEM group; and treatment for diarrhoea was required in 204 of 229 patients (89.1%) in the afatinib group and 10 of 111 patients (9.0%) in the CDDP/PEM group. The above data indicated that proactive management of diarrhoea as well as treatment interruption or dose reduction of afatinib suppressed the development of events leading to discontinuation of afatinib due to diarrhoea.

In the afatinib group, 191 of 229 patients (estimated cumulative incidence by Kaplan-Meier method, 83.5%) experienced the first onset of diarrhoea within 14 days after the first dose. It is therefore considered important to manage diarrhoea proactively from the initial stage and throughout the treatment period of afatinib.

In Study 1200.32, diarrhoea occurred in 54 of 54 Japanese patients (100%) in the afatinib group and 9 of 28 Japanese patients (32.1%) in the CDDP/PEM group; and Grade 3 diarrhoea occurred in 11 of 54 Japanese patients (20.4%) only in the afatinib group. Discontinuation due to diarrhoea was not reported in Japanese patients; dose reduction for the investigational drug was reported in 12 of 54 Japanese patients (22.2%) in the afatinib group only; and treatment for diarrhoea was required in 51 of 54 Japanese patients (94.4%) in the afatinib group and 2 of 28 Japanese patients (7.1%) in the CDDP/PEM group. The incidences in Japanese patients were similar to those in the overall population.

Adverse events (electrolyte imbalance, dehydration, or renal function disorder) related to diarrhoea were investigated. The relationship between diarrhoea and electrolyte imbalance in Study 1200.32 was investigated. Of 34 patients who experienced Grade 3 diarrhoea in the afatinib group, 5 patients (14.7%) presented changes in serum potassium of Grade 3/4, but there was no hypokalaemia leading to treatment discontinuation. In Study 1200.32, dehydration occurred in 7 patients (3.1%) in the afatinib group and 2 patients (1.8%) in the CDDP/PEM group without a difference in the incidence between the groups. In the afatinib group, none of the patients discontinued due to dehydration, and all of the affected patients, except for 1 with an unknown outcome of the adverse event, recovered from dehydration. To identify renal function disorder subsequent to diarrhoea, adverse events related to "renal function disorder"[*] were defined with corrected broad SMQs for acute renal failure. Under this definition, events related to renal function disorder were tabulated. In Study 1200.32, renal function disorder occurred in 14 of 229 patients (6.1%) in the afatinib group and 18 of 111 patients (16.2%) in the CDDP/PEM group; and a Grade 3 event occurred in 3 of 229 patients (1.3%) in the afatinib group and 2 of 111 patients (1.8%) in the CDDP/PEM group, but Grade 4/5 events did not occur. Discontinuation due to renal function disorder occurred in 1 of 229 patients (0.4%) in the afatinib group and 2 of 111 patients (1.8%) in the CDDP/PEM group. One patient who discontinued afatinib due to renal function disorder recovered with fluid replacement (water intake).

[*]: SMQs used to retrieve events related to "renal function disorder," broad SMQs related to acute renal failure except for albuminuria, anuria, neonatal anuria, oliguria, proteinuria, protein urine present, and urine output decreased under MedDRA preferred terms.

In the clinical studies, no patients died from diarrhoea, but in the named patient-use programme (in which only patients named by physicians were allowed to use the drug), 2 patients were reported to have died following diarrhoea. It was considered that both patients could not receive appropriate treatment for diarrhoea, potentially leading to this outcome.

As described above, the incidence of diarrhoea caused by afatinib treatment was high, but the number of patients who discontinued afatinib due to diarrhoea was kept low by management with fluid replacement (water intake) and antidiarrheal agents, treatment interruption or dose reduction of afatinib. It is recommended that patients should be carefully monitored and under appropriate management during treatment with afatinib, and treatment interruption and dose reduction of afatinib should be performed where necessary.

PMDA considers as follows:
In Study 1200.32, the incidence of diarrhoea caused by afatinib treatment was high; a large percentage of the patients reduced the dose; and patients died from lack of strict management for diarrhoea. Attention, therefore, should be paid to diarrhoea. Thus, it is necessary to alert that appropriate symptomatic treatment and measures including treatment interruption or discontinuation, and dose reduction should be taken at the time of onset.

4.(iii).B.(3).6) Rash/acne
The applicant explained rash/acne due to afatinib as follows:
To identify events related to skin reaction, "rash/acne"[*] was defined as a group term. The

definition was used to tabulate events related to rash/acne.

*: MedDRA preferred terms included in the group terms of "rash/acne"; acne, acne conglobata, acne cystic, acne fulminans, acne pustular, blister, dermatitis, dermatitis acneiform, dermatitis bullous, dermatitis exfoliative, dermatitis exfoliative generalised, dermatosis, drug eruption, eczema, epidermal necrosis, erythema, exfoliative rash, folliculitis, generalised erythema, mucocutaneous rash, rash erythematous, rash follicular, rash generalised, rash macular, rash maculo-papular, rash maculovesicular, rash morbilliform, rash papular, rash papulosquamous, rash pruritic, rash pustular, rash rubelliform, rash scarlatiniform, rash vesicular, skin disorder, skin erosion, skin exfoliation, skin fissures, skin induration, skin irritation, skin lesion, skin necrosis, skin reaction, skin swelling, skin toxicity, and skin ulcer; and narrow MedDRA SMQs included in the group terms of "rash/acne"; severe skin adverse drug reactions

In Study 1200.32, rash/acne occurred in 206 of 229 patients (90.0%) in the afatinib group and 12 of 111 patients (10.8%) in the CDDP/PEM group; and a Grade 3 event occurred in 37 of 229 patients (16.2%) in the afatinib group only, but no Grade 4/5 event occurred. Discontinuation of the investigational drug due to rash/acne was not reported; dose reduction of afatinib was reported in 44 of 229 patients (19.2%); and treatment for rash/acne was performed in 188 of 229 patients (82.1%) in the afatinib group and 10 of 111 patients (9.0%) in the CDDP/PEM group. In terms of the outcome, rash/acne resolved in 111 of 229 patients (48.5%) in the afatinib group and 10 of 111 patients (9.0%) in the CDDP/PEM group, but did not resolve in 89 of 229 patients (38.9%) in the afatinib group and 2 of 111 patients (1.8%) in the CDDP/PEM group. In the afatinib group, 182 of 229 patients (estimated cumulative incidence by Kaplan-Meier method, 79.7%) experienced the first onset of rash/acne within 28 days after the first dose. In Study 1200.32, rash/acne occurred in 54 of 54 Japanese patients (100%) in the afatinib group and 6 of 28 Japanese patients (21.4%) in the CDDP/PEM group; and a Grade 3 event occurred in 11 of 54 Japanese patients (20.4%) in the afatinib group only. The incidence was higher in the Japanese patients than in non-Japanese patients [see "4.(iii).B.(3).2) Differences in safety between Japanese and non-Japanese patients]. Regarding the time of onset, 49 of 54 patients (estimated cumulative incidence by Kaplan-Meier method, 79.0%) in the afatinib group experienced rash/acne within 28 days after the first dose. The time of onset in Japanese patients was similar to that in the overall population.

Patients in whom severe skin adverse reactions possibly occurred were tabulated using terms related to severe skin adverse drug reactions (narrow SMQs). In all of the unblinded clinical studies in cancer patients (3865 patients treated with afatinib) (data as of data cut-off on [redacted], 20[redacted] in Study 1200.32 tabulated), severe skin adverse reactions occurred in 6 patients (Grade 3 exfoliative rash, SJS, and toxic skin eruption in 2 patients each). SJS in 1 patient developed 10 days after discontinuation of afatinib due to diarrhoea. The event was determined to be non-serious and a causal relationship with afatinib was ruled out for the event, but the outcome was unknown. The other patient with SJS experienced non-serious mucositis on Day 2 of treatment with afatinib and non-serious rash on Day 5. These adverse events were aggravated until Day 30, resulting in diagnosis of serious SJS. The causal relationship with afatinib could not be ruled out. Afatinib was discontinued around Day 35, and the event resolved approximately 40 days later with hospitalization and treatment. Toxic skin eruption that occurred in 2 patients was non-serious in both. Of these subjects, 1 patient discontinued afatinib but was found to have disease progression at the same time, while the other 1 patient continued afatinib at the reduced dose. Exfoliative rash that occurred in 2 patients was non-serious in both. The symptom developed at the reduced dose and then disappeared.

SJS in 1 patient was reported after [redacted], 20[redacted]. The patient was diagnosed with SJS approximately 4 days after discontinuation of afatinib due to diarrhoea. The causal relationship of SJS with afatinib could not be ruled out. The event resolved approximately 30 days later with treatment (antibiotics, steroids).

As described above, the incidence of rash/acne following treatment with afatinib was high, and

dose reduction of afatinib was required for approximately 20% of patients in Study 1200.32. With combination of proactive management and dose reduction, however, none of them discontinued afatinib due to rash/acne. To improve the tolerability of afatinib, the following measures were recommended: patients should be carefully monitored, proactive management of rash/acne (strict prevention from sunburn started before onset, local treatment, systemic treatment of antibiotics, short-term treatment of antihistamines and oral prednisolone after onset) should be performed, and furthermore, treatment interruption and dose reduction of afatinib should be performed where necessary.

PMDA considers as follows:
In Study 1200.32, rash/acne due to afatinib occurred in 206 of 229 patients (90.0%), the incidence was higher in Japanese patients than in non-Japanese patients, and dose reduction of afatinib was observed in 44 of 229 patients (19.2%). Attention, therefore, should be paid to rash/acne.

In clinical studies of afatinib, SJS occurred as a serious event for which a causal relationship with afatinib could not be ruled out. Cautions for this event should be provided.

4.(iii).B.(3).7) Stomatitis
The applicant explained stomatitis due to afatinib as follows:
To evaluate events related to stomatitis, "stomatitis"* was defined as a group term. The definition was used to tabulate events related to stomatitis.

*: MedDRA preferred terms included in the group terms of "stomatitis"; aphthous stomatitis, dry mouth, glossitis, glossodynia, mouth ulceration, mucosal erosion, mucosal excoriation, mucosal exfoliation, mucosal hyperaemia, mucosal induration, mucosal inflammation, mucosal necrosis, mucosal ulceration, oedema mucosal, oral mucosa erosion, oral mucosal eruption, oral mucosal erythema, oral mucosal exfoliation, oral toxicity, oropharyngeal blistering, pharyngeal erosion, pharyngeal ulceration, stomatitis, stomatitis haemorrhagic, stomatitis necrotising, throat irritation, tongue blistering, tongue eruption, tongue exfoliation, tongue ulceration

In Study 1200.32, stomatitis occurred in 168 of 229 patients (73.4%) in the afatinib group and 19 of 111 patients (17.1%) in the CDDP/PEM group. Grade 3 stomatitis occurred in 19 of 229 patients (8.3%) in the afatinib group and 1 of 111 patients (0.9%) in the CDDP/PEM group, a Grade 4 event occurred in 1 of 229 patients (0.4%) in the afatinib group only, but no Grade 5 event occurred. No discontinuation due to stomatitis was reported, and dose reduction of the investigational drug was reported in 23 of 229 patients (10.0%) in the afatinib group and 1 of 111 patients (0.9%) in the CDDP/PEM group. Treatment for stomatitis was performed in 143 of 229 patients (62.4%) in the afatinib group and 11 of 111 patients (9.9%) in the CDDP/PEM group. In terms of the outcome, stomatitis resolved in 126 of 229 patients (55.0%) in the afatinib group and 17 of 111 patients (15.3%) in the CDDP/PEM group, but did not resolve in 32 of 229 patients (14.0%) in the afatinib group and 2 of 111 patients (1.8%) in the CDDP/PEM group. In the afatinib group, 131 of 229 patients (estimated cumulative incidence by Kaplan-Meier method, 57.2%) experienced the first onset of stomatitis within 14 days after the first dose. In Study 1200.32, stomatitis occurred in 48 of 54 Japanese patients (88.9%) in the afatinib group and 7 of 28 Japanese patients (25.0%) in the CDDP/PEM group, and a Grade 3 event occurred in 4 of 54 Japanese patients (7.4%) in the afatinib group only, but no Grade 4 event occurred. The incidence of stomatitis was higher in Japanese patients than in non-Japanese patients [see "4.(iii).B.3.2) Differences in safety between Japanese and non-Japanese patients"]. In the afatinib group, 41 of 54 patients (estimated cumulative incidence by Kaplan-Meier method, 75.9%) experienced stomatitis within 14 days after the first dose. The time of onset in Japanese patients was similar to that in the overall population.

As described above, the incidence of stomatitis following treatment with afatinib was high, and the dose reduction of afatinib was required for approximately 10.0% of patients in Study 1200.32. With combination of proactive management of stomatitis and treatment interruption and dose reduction of afatinib, however, none of the patients discontinued afatinib due to stomatitis. To

improve the tolerability of afatinib, the following measures are recommended: patients should be carefully monitored, proactive management of stomatitis (prevention of the onset with oral hygiene control and appropriate symptomatic treatment at the time of onset) should be performed, and furthermore, treatment interruption and dose reduction of afatinib should be performed where necessary.

PMDA considers as follows:
In Study 1200.32, none of the patients discontinued afatinib due to stomatitis. Therefore, as long as prevention of stomatitis and appropriate symptomatic treatment at the time of onset are secured, afatinib is tolerable. On the other hand, 168 of 229 patients (73.4%) experienced stomatitis, including a Grade 3 event. In light of this finding, it is necessary to provide precautions so that appropriate measures for the relevant symptoms will be taken.

4.(iii).B.(3).8) Nail abnormality (paronychia)
The applicant explained nail abnormality due to afatinib as follows:
To evaluate events related to nail abnormality, "nail abnormality"* was defined as a group term. The definition was used to tabulate events related to nail abnormality.

*: MedDRA preferred terms included in the group terms of "nail abnormality"; Nail atrophy, nail avulsion, nail bed infection, nail bed inflammation, nail bed tenderness, nail discomfort, nail disorder, nail dystrophy, nail growth abnormal, nail infection, nail pitting, nail toxicity, onychalgia, onychoclasis, onychogryphosis, onycholysis, onychomalacia, paronychia

In Study 1200.32, nail abnormality occurred in 141 of 229 patients (61.6%) in the afatinib group only; and a Grade 3 event occurred in 27 of 229 patients (11.8%) in the afatinib group only, but no Grade 4/5 event occurred. In the afatinib group, discontinuation of afatinib due to nail abnormality was reported in 2 of 229 patients (0.9%), and dose reduction of afatinib was reported in 31 of 229 patients (13.5%). Of adverse events reported as nail abnormality in the afatinib group, adverse events reported in ≥5 subjects were paronychia in 130 of 229 patients (56.8%) and nail disorder in 12 of 229 patients (5.2%), and Grade 3 events reported in ≥5 subjects were paronychia in 26 of 229 patients (11.4%).

In Study 1200.32, nail abnormality occurred in 48 of 54 Japanese patients (88.9%) in the afatinib group and a Grade 3 event occurred in 13 of 54 Japanese patients (24.1%) in the afatinib group. The incidence was higher in the Japanese patients than in non-Japanese patients [see "4.(iii).B.3.2) Differences in safety between Japanese and non-Japanese patients"].

As described above, the incidence of nail abnormality due to afatinib was high, but few patients discontinued afatinib due to the relevant event. The applicant considered that nail abnormality could be managed with treatment interruption, dose reduction, and appropriate proactive supportive therapy, so that afatinib could be continued as long as clinical usefulness is obtained.

PMDA considers as follows:
In Study 1200.32, only 2 of 229 patients (0.9%) discontinued afatinib due to nail abnormality. Therefore, afatinib is tolerable with appropriate symptomatic treatment for nail abnormality at the time of onset. On the other hand, 141 of 229 patients (61.6%) experienced nail abnormality including a Grade 3 event. In light of this finding, it is necessary to provide cautions so that appropriate measures for the relevant symptoms should be taken.

4.(iii).B.(3).9) Eye disorder (keratitis)
The applicant explained eye disorder due to afatinib as follows:
To evaluate events related to eye disorder, "eye disorder"* was defined as a group term consisting of MedDRA preferred terms indicative of symptoms of eye disorder. The definition was used to tabulate events related to eye disorder.

*: MedDRA preferred terms included in the group terms of "eye disorder"; Blepharitis, conjunctival hyperaemia, conjunctival irritation, conjunctival oedema, conjunctivitis, corneal erosion, dry eye, eczema eyelids, erythema of eyelid, eye discharge, eye inflammation, eye irritation, eye pain, eye pruritus, eyelid disorder, eyelid erosion, eyelid exfoliation, eyelid folliculitis, eyelid irritation, eyelid margin crusting, eyelid oedema, eyelid pain, eyelid skin dryness, eyelids pruritus, keratitis, lid margin discharge, ocular discomfort, ocular hyperaemia; MedDRA SMQs (narrow) included in the group terms of "eye disorder" (narrow SMQs), corneal disorder

In Study 1200.32, eye disorder occurred in 52 of 229 patients (22.7%) in the afatinib group and 8 of 111 patients (7.2%) in the CDDP/PEM group, and a Grade 3 event occurred in 1 of 229 patients (0.4%, keratitis) in the afatinib group only, but no Grade 4/5 event occurred. Discontinuation of the investigational drug due to eye disorder was reported in 1 of 229 patients (0.4%) in the afatinib group only, and dose reduction of the investigational drug was reported in 2 of 229 patients (0.9%) in the afatinib group only. Treatment for eye disorder was performed in 40 of 229 patients (17.5%) in the afatinib group and 5 of 111 patients (4.5%) in the CDDP/PEM group. In terms of the outcome, eye disorder resolved in 38 of 229 patients (16.6%) in the afatinib group and 7 of 111 patients (6.3%) in the CDDP/PEM group, but did not resolve in 13 of 229 (5.7%) patients in the afatinib group and 1 of 111 patients (0.9%) in the CDDP/PEM group. Of adverse events in the afatinib group reported as eye disorder, adverse events reported in ≥5 subjects were conjunctivitis in 24 of 229 patients (10.5%), dry eye in 13 of 229 patients (5.7%), and blepharitis and keratitis each in 5 of 229 patients (2.2%).

In Study 1200.32, eye disorder occurred in 24 of 54 Japanese patients (44.4%) in the afatinib group and 4 of 28 Japanese patients (14.3%) in the CDDP/PEM group, and a Grade 3 event occurred in 1 of 54 Japanese patients (1.9%) in the afatinib group only. The incidence was higher in the Japanese patients than in non-Japanese patients [see "4.(iii).B.3.2) Differences in safety between Japanese and non-Japanese patients"].

The incidence of keratitis, a clinically significant adverse event, was tabulated using corneal disorder (narrow SMQs). In all of the unblinded clinical studies in cancer patients (3865 patients treated with afatinib) (data as of data cut-off on [redacted], 20[redacted] in Study 1200.32 tabulated), keratitis occurred in 29 of 3865 patients (0.8%). A Grade 3 event occurred in 2 patients (keratitis in both). The causal relationship of the event in 1 subject to afatinib could not be ruled out and the event resolved following treatment discontinuation. No Grade 4/5 adverse event occurred. The most frequently reported adverse event was keratitis in 17 patients followed by corneal erosion in 4 patients, corneal abrasion and ulcerative keratitis in 3 patients each, punctate keratitis in 2 patients, and keratopathy in 1 patient (including multiple events in a single patient). The serious adverse event corneal perforation was not reported.

PMDA considers as follows:
In Study 1200.32, of 52 patients who developed eye disorder due to treatment with afatinib, 51 patients had Grade ≤2 events, corneal perforation did not occur, and discontinuation and dose reduction of afatinib took place in 1 of 229 patients (0.4%) and 2 of 229 patients (0.9%), respectively. Based on the above, afatinib is tolerable in terms of the safety related to eye disorder. However, it is necessary to appropriately inform healthcare providers in the medical practice of the fact that eye disorder occurred in 52 of 229 patients (22.7%) in Study 1200.32.

4.(iii).B.(3).10) Cardiac failure
The applicant explained cardiac failure due to afatinib as follows:
To evaluate adverse events related to cardiac failure, adverse events related to "cardiac failure"* were defined with corrected broad SMQs for cardiac failure. Under this definition, events related to cardiac failure were tabulated.
*: SMQs used to retrieve events related to "cardiac failure"; broad SMQs related to cardiac failure except for oedema, oedema peripheral, peripheral oedema neonatal, and oedema neonatal under MedDRA preferred terms

In Study 1200.32, cardiac failure occurred in 5 of 229 patients (2.2%) in the afatinib group and 1 of 111 patients (0.9%) in the CDDP/PEM group, but all of the relevant events were Grade ≤2. The causal relationship with afatinib could not be ruled out for the events in 3 (diastolic dysfunction in 2 patients, left ventricular dysfunction in 1 patient) of 5 patients who experienced cardiac failure in the afatinib group. LVEF decreased was transient in 4 of 5 patients with cardiac failure and returned to the baseline during the continuous treatment with afatinib. In the remaining 1 patient, Grade 2 left ventricular dysfunction (LVEF of 47%) occurred 567 days after the first dose of afatinib, but the fraction was improved to 56% 1 month after discontinuation of afatinib. Four of 5 patients had multiple risk factors in the heart such as coronary artery disease, hypertension, hypercholesterolaemia, tricuspid regurgitation, mitral regurgitation, pericardial effusion, aortic valve sclerosis, and systolic dysfunction.

Periodic evaluation on the LVEF in Study 1200.32 did not show a marked decrease from the baseline. Under the definition of the clinically significant change of the LVEF as being decreased from the baseline by ≥20% and falling to below the institutional lower limit of normal (for the unknown lower limit, fell to <50%), the relevant change was reported in 3 of 229 patients (1.3%) in the afatinib group and 1 of 111 patients (0.9%) in the CDDP/PEM group. All of the changes in 3 patients in the afatinib group were transient and resolved during the continuous treatment of afatinib.

In all of the unblinded clinical studies in cancer patients (3865 patients treated with afatinib) (data as of data cut-off on [redacted], 20[redacted] in Study 1200.32 tabulated), cardiac failure occurred in 53 of 3865 patients (1.4%), Grade ≥3 events occurred in 20 of 3865 patients (0.5%), and 6 patients had fatal cases (acute left ventricular failure and cardiopulmonary failure in 2 patients each, cardiac failure and acute pulmonary oedema in 1 patient each). A causal relationship with afatinib could not be ruled out for acute left ventricular failure in 2 patients (1 patient had lung infection, the other one had concurrent atrial fibrillation) and acute pulmonary oedema in 1 patient (had atrial fibrillation together).

As described above, the incidences of cardiac adverse events and LVEF decreased were low, and there were a limited number of patients with Grade ≥3 LVEF change, for which a causal relationship with afatinib could not be ruled out. These results did not suggest that afatinib would cause adverse events related to cardiac contractility. The safety of afatinib, however, has not been investigated in patients with abnormal LVEF or a history of significant cardiac diseases. The patients with a cardiovascular risk factor or in a condition predisposed to abnormal LVEF should be examined at the baseline as well as monitored during the treatment with afatinib for the cardiac parameters including the LVEF. In addition, the patients who experienced clinically relevant cardiac signs/symptoms during treatment with afatinib should be monitored for the cardiac parameters including the LVEF.

PMDA considers as follows:
In Study 1200.32, there were no patients who experienced Grade ≥3 serious adverse events or those who discontinued afatinib. However, the following exclusion criteria were set, and the safety of afatinib in patients excluded by the criteria remains unknown. In studies involving cancer patients other than Study 1200.32, Grade ≥3 cardiac failure occurred, and fatal cardiac adverse events occurred in 6 patients. Thus, it is necessary to evaluate the cardiac functions such as the LVEF at the baseline or during the treatment with afatinib and make a careful decision for the use of afatinib in patients with cardiac risk factors. In addition, it is necessary to provide the information on the following exclusion criteria in Study 1200.32 to healthcare providers in the medical practice.

Exclusion criteria

- Patients with history or comorbidity of clinically significant cardiovascular abnormality including inadequately controlled hypertension, congestive cardiac failure at Class III under the New York Heart Association Functional Classification, unstable angina, and inadequately controlled arrhythmia. Patients who experienced myocardial infarction within 6 months before random assignment.
- Patients with the LVEF at rest <50%

4.(iii).B.(3).11) Gastrointestinal perforation and severe gastrointestinal ulcer and haemorrhage

The applicant explained gastrointestinal perforation and gastrointestinal ulcer and haemorrhage of Grade ≥3 due to afatinib as follows:

Adverse events related to gastrointestinal perforation were defined as gastrointestinal perforation with narrow SMQs. Under this definition, events related to gastrointestinal perforation were tabulated. In all of the unblinded clinical studies in cancer patients (3865 patients treated with afatinib) (data as of data cut-off on [redacted], 20[redacted] in Study 1200.32 tabulated), events related to gastrointestinal perforation occurred in 5 patients. The events included peritonitis bacterial in 2 patients (Grade 3, Grade 5), and chemical peritonitis (Grade 2), anal abscess (Grade 2), and intestinal perforation (Grade 3) in 1 subject each. A causal relationship with afatinib was ruled out for all of these events.

Adverse events related to Grade ≥3 gastrointestinal ulcer were defined as gastrointestinal ulcer with narrow SMQs. Under this definition, events related to gastrointestinal ulcer were tabulated. In all of the unblinded clinical studies in cancer patients (3865 patients treated with afatinib) (data as of data cut-off on [redacted], 20[redacted] in Study 1200.32 tabulated), Grade ≥3 gastrointestinal ulcer occurred in 6 patients. Among these events, a causal relationship with afatinib could not be ruled out for the events in 3 subjects (skin ulcer in 2 subjects, mouth ulceration in 1 subject)

Adverse events related to Grade ≥3 gastrointestinal haemorrhage were defined as gastrointestinal haemorrhage with narrow SMQs. Under this definition, events related to gastrointestinal haemorrhage were tabulated. In all of the unblinded clinical studies in cancer patients (3865 patients treated with afatinib) (data as of data cut-off on [redacted], 20[redacted] in Study 1200.32 tabulated), Grade ≥3 gastrointestinal haemorrhage occurred in 17 patients. Among these events, a causal relationship with afatinib could not be ruled out for the events in 6 patients (gastrointestinal haemorrhage in 2 subjects, diarrhoea haemorrhagic, gastric ulcer haemorrhage, haemorrhoidal haemorrhage, and rectal hemorrhage in 1 subject each).

As described above, the events related to gastrointestinal perforation as well as gastrointestinal ulcer and hemorrhage of Grade ≥3 are known as the characteristics of adverse drug reactions in EGFR-TKIs, although their incidences were low. Cautions for these events will be provided in the package insert.

PMDA considers as follows:

Adverse events related to gastrointestinal perforation as well as severe gastrointestinal ulcer and haemorrhage are known as the characteristics of adverse drug reactions in EGFR-TKIs, and Grade ≥3 events including gastrointestinal perforation were reported following afatinib treatment. In consideration of the above, it is necessary to provide appropriate information to healthcare professionals.

4.(iii).B.(3).12) Acute pancreatitis

The applicant explained acute pancreatitis due to afatinib as follows:

Adverse events related to acute pancreatitis were defined as acute pancreatitis with narrow SMQs. Under this definition, events related to acute pancreatitis were tabulated. In all of the unblinded clinical studies in cancer patients (3865 patients treated with afatinib) (data as of data cut-off on

[redacted], 20[redacted] in Study 1200.32 tabulated), events related to acute pancreatitis occurred in 13 patients including Grade 3 events in 5 patients and Grade 4 events in 3 patients. A causal relationship with afatinib could not be ruled out for all of these events. In clinical studies of afatinib, however, there were some patients who experienced acute pancreatitis but recovered without discontinuation of afatinib as well as who experienced acute pancreatitis, discontinued and then resumed afatinib but did not experience the relapse. At present, the applicant considers that the causal relationship of acute pancreatitis with afatinib was not definite.

PMDA considers as follows:
Of adverse events related to acute pancreatitis due to afatinib that occurred in 13 patients, those in 8 patients (61.5%) were Grade ≥3, and such events occur in patients receiving gefitinib, which is also an EGFR-TKI as afatinib. Attention to the concerned events, therefore, should be paid.

4.(iii).B.(4) Clinical positioning and indication
The proposed indication of afatinib was "*EGFR* mutation-positive inoperable or recurrent non-small cell lung cancer." At the time of regulatory submission, the applicant explained that the following caution statements would be included in the "Precautions for Indications" section: (a) an *EGFR* mutation test should be performed before receiving afatinib, and afatinib should be administered referring to the latest information such as the "Lung Cancer Clinical Practice Guidelines" issued by the Japan Lung Cancer Society, including how to handle patients with unknown *EGFR* mutation; (b) the efficacy and safety of afatinib used in adjuvant chemotherapy have not been established; and (c) the eligibility of a patient should be determined by physicians who are familiar with the data presented in the "Clinical Studies" section and thoroughly understand the efficacy and safety of afatinib.

Based on the results of reviews in "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety" and the following review in this section, PMDA has concluded that the indication of afatinib may be set as "*EGFR* mutation-positive inoperable or recurrent non-small cell lung cancer" as proposed. PMDA, however, has considered that the tissue and *EGFR* mutation types of the patients in Study 1200.32 and their treatment history of chemotherapy should be included in the "Clinical Studies" section and the following description should be in the "Precautions for Indications" section of the package insert.

- The eligibility of a patient should be determined by physicians who are familiar with the applicable history of cancer chemotherapy presented in the "Clinical Studies" section and thoroughly understand the efficacy and safety of afatinib.
- An *EGFR* mutation test should be performed. Afatinib should be administered referring to the latest information such as the "Lung Cancer Clinical Practice Guidelines" issued by the Japan Lung Cancer Society, including how to handle patients with unknown *EGFR* mutation.
- The efficacy and safety of afatinib in adjuvant chemotherapy have not been established.

4.(iii).B.(4).1) Clinical positioning of afatinib
PMDA reviewed the therapeutic strategies for *EGFR* mutation-positive inoperable or recurrent NSCLC in the major clinical practice guidelines and textbooks of clinical oncology in Japan and foreign countries. As a result, no descriptions about afatinib were found.

PMDA considers as follows:
Based on the review results in the "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety," PMDA has concluded that afatinib may be positioned as a treatment option for patients with *EGFR* mutation-positive inoperable or recurrent NSCLC who have not received chemotherapy.

4.(iii).B.(4).2) Tissue type

The *EGFR* mutation-positive rate in non-adenocarcinoma was reported to be markedly lower than that in adenocarcinoma (adenocarcinoma, approximately 30%-40%; non-adenocarcinoma, approximately 2%-3%) (*J Clin Oncol*. 2005;23:2556-68, *Clin Cancer Res*. 2006;12:4416s-20s). In light of this finding, only patients with adenocarcinoma, likely to have *EGFR* mutation, were included in Study 1200.32. PMDA asked the applicant to explain the clinical usefulness of afatinib in patients with non-adenocarcinoma *EGFR* mutation-positive inoperable or recurrent NSCLC who have not received chemotherapy.

The applicant responded as follows:

At present, there are no clinical data on the efficacy and safety of afatinib in the relevant patients, including published articles. *EGFR* mutation, however, is an important factor in proliferation and survival of tumor cells. In consideration of this, the clinical usefulness of afatinib is expected in treatment for *EGFR* mutation-positive inoperable or recurrent NSCLC irrespective of tissue types.

PMDA considers as follows:

The above explanation of the applicant is understandable to some extent, and at present it is not necessary to limit the tissue type to adenocarcinoma in the indication. A clinical study demonstrating clinical usefulness of afatinib (Study 1200.32) targeted only adenocarcinoma in terms of the tissue type (including tumors with adenocarcinoma-dominant mixed tissue images). Understanding this fact sufficiently, patients considered eligible to receive afatinib should be selected by physicians, and therefore it is necessary to provide the relevant information in the "Clinical Studies" section in the package insert.

4.(iii).B.(4).3) Patients previously treated with EGFR-TKIs

The applicant explained the clinical usefulness of afatinib in patients with *EGFR* mutation-positive NSCLC who had received EGFR-TKIs as follows:

A foreign phase II/III study (Study 1200.23) in patients with inoperable or recurrent NSCLC who received 1 or 2 regimens of chemotherapy including platinum antineoplastic drugs (excluding EGFR-TKIs) and received EGFR-TKIs did not show the superiority of afatinib to placebo in terms of the OS, the primary endpoint [see "4.(iii).A. Evaluation data (4).8) Foreign phase II/III study"].

The median PFS (IRC evaluation), the secondary endpoint, on the other hand, was 2.2 months longer in the afatinib group (3.3 months) than in the placebo group (1.1 months) (hazard ratio [95%CI], 0.381 [0.306, 0.475]; P <0.0001; log-rank test). In consideration of the following non-clinical and clinical data, the clinical usefulness of afatinib is expected especially in patients with *EGFR* mutation-positive NSCLC who had received EGFR-TKIs.

- In a non-clinical pharmacology study, afatinib inhibited the tumor growth in human NSCLC-derived NCI-H1975 cell line with *EGFR* mutation (T790M), which would render the cells resistant to approved gefitinib and erlotinib, known reversible EGFR-TKIs [see "3.(i).A.(1).1) Growth inhibitory effect on epidermal growth factor receptor (EGFR) mutation-positive NSCLC cells"].
- In Study 1200.23, stored tissue specimens from some patients were tested for *EGFR* mutation. The median PFS (IRC evaluation) in the patients without *EGFR* mutation (negative) was 2.79 months in the afatinib group (31 patients) compared with 1.84 months in the placebo group (14 patients) (hazard ratio, 0.606; P = 0.216), while the median PFS in the patients with *EGFR* mutation (positive) was 3.29 months in the afatinib group (62 patients) compared with 0.99 months in the placebo group (34 patients) (hazard ratio, 0.514; P = 0.009).

PMDA considers as follows:

The above clinical data in patients with *EGFR* mutation-positive NSCLC who received EGFR-TKIs in Study 1200.23 were exploratory analysis results. At present, it is difficult to draw conclusions about the clinical usefulness of afatinib in these patients. Understanding that the clinical study demonstrating the clinical usefulness of afatinib (Study 1200.32) only included the patients who did not receive chemotherapy in the past, patients considered appropriate to receive afatinib should be selected by physicians. PMDA therefore has concluded that the relevant caution statements should be included in the sections of "Precautions for Indications" and "Clinical Studies" in the package insert.

4.(iii).B.(4).4) Use of afatinib in patients with unknown *EGFR* mutation

At the time of regulatory submission of afatinib, the package insert of gefitinib indicated for *EGFR* mutation-positive NSCLC provided the following caution statements in the "Precautions for Indications" section because some patients in whom the test for *EGFR* mutation is not performed due to medical reasons, etc., may possibly be *EGFR* mutation-positive, and thus the use of gefitinib in patients with unknown *EGFR* mutation should be appropriately determined based on the latest knowledge (see "Review Report, Iressa Tablets 250, dated November 16, 2011").

- An *EGFR* mutation test should be performed. Afatinib should be administered referring to the latest information such as the "Lung Cancer Clinical Practice Guidelines" issued by the Japan Lung Cancer Society, including how to handle patients with unknown *EGFR* mutation.

The applicant explained that the above caution statement would be included in the "Precautions for Indications" section in the package insert of afatinib based on the package insert of gefitinib.

PMDA accepted the applicant's explanation.

4.(iii).B.(4).5) EGFR mutation types

In Study 1200.32, tumor biopsy specimens were tested for *EGFR* mutation with TheraScreen: EGFR29 Mutation Kit at the central laboratory. The detected *EGFR* mutation types are as shown below.

- Del 19, 170 of 345 patients (49.3%) (113 of 230 patients [49.1%] in the afatinib group, 57 of 115 patients [49.6%] in the CDDP/PEM group)
- L858R, 138 of 345 patients (40.0%) (91 of 230 patients [39.6%] in the afatinib group, 47 of 115 patients [40.9%] in the CDDP/PEM group)
- Other mutations, 37 of 345 patients (10.7%) (26 of 230 patients (11.3%) in the afatinib group, 11 of 115 patients [9.6%] in the CDDP/PEM group)

The applicant explained the clinical usefulness of afatinib by *EGFR* mutation type as follows:
Clinical usefulness of afatinib in patients with frequently observed Del 19 and L858R *EGFR* mutations was evaluated. The PFS in patients with Del 19 *EGFR* mutation was longer in the afatinib group than in the CDDP/PEM group (hazard ratio [95%CI], 0.278 [0.176, 0.441] [$P <$ 0.0001, log-rank test], median PFS, 13.7 months in the afatinib group, 5.6 months in the CDDP/PEM group). The PFS in patients with L858R *EGFR* mutation was longer in the afatinib group than in the CDDP/PEM group (hazard ratio [95%CI], 0.733 [0.461, 1.165] [$P = 0.1871$, log-rank test]; median PFS, 10.8 months in the afatinib group, 8.1 months in the CDDP/PEM group).

In addition to Del 19 and L858R *EGFR* mutations, 10 types of *EGFR* mutations were detected. All of these mutations occurred infrequently affecting limited number of patients, and it is, therefore, difficult to draw the conclusion about the efficacy of afatinib in patients with these

mutations, but a certain fraction of the patients in the afatinib group were responders (the table below).

Analysis results on the efficacy (best overall response [RECIST] and PFS) in patients with infrequently observed *EGFR* mutations
(Study 1200.32, ITT population, IRC evaluation, data cut-off on [redacted], 20[redacted])

EGFR mutation type		Afatinib group N = 230		CDDP/PEM group N = 115	
		Number of patients (%)	Best overall response (number of patients)	Number of patients (%)	Best overall response (number of patients)
T790M	(1) T790M only	2 (0.9)	SD (1), PD (1)	0	—
	(2) Del 19 + T790M	3 (1.3)	SD (1), PD (2)	0	—
	(3) L858R + T790M	5 (2.2)	PR (1), SD (4)	2 (1.7)	PR (1)、SD (1)
	(4) G719S, G719A, and G719C + T790M	1 (0.4)	SD (1)	0	—
Exon 20 insertions	(5) Exon 20 insertions only	6 (2.6)	SD (5), NE (1)	3 (2.6)	SD(3)
S768I	(6) S768I only	1 (0.4)	PR (1)	0	—
	(7) L858R + S768I	2 (0.9)	PR (2)	0	—
G719X[*1]	(8) G719S, G719A, and G719C only	3 (1.3)	PR (1), PD (1), NE (1)	1 (0.9)	SD (1)
	(9) G719S, G719A, and G719C + S768I	0	—	2 (1.7)	PR (2)
L861Q	(10) L861Q only	3 (1.3)	SD (1), PD (1), NE (1)	3 (2.6)	SD (1), Non-CR/Non-PD[*2](2)

Infrequently observed overall *EGFR* mutation Number of patients (%)		Afatinib group 26 (11.3)	CDDP/PEM group 11 (9.6)
PFS	Death or exacerbation (%)	22 (84.6)	8 (72.7)
	Median [95%CI] (months)	2.76 [2.56, 6.70]	9.92 [3.84, 13.83]
	Hazard ratio [95%CI]	1.892 [0.836, 4.279]	
	P value (two-sided)[*3, *4]	0.1198	

PR: Partial response, SD: Stable disease, PD: Progressive disease, NE: Not evaluable, *1: G719S, G719A, or G719C, *2: Patients without target lesion present at the baseline but with non-target lesion in SD, *3: Log-rank test, *4: Significance level of 0.05 (two-sided)

As described above, afatinib prolonged the PFS in patients with frequently observed *EGFR* mutations (Del 19, L858R) as well as a certain fraction of the patients with infrequently observed *EGFR* mutations. Afatinib thus may serve as a treatment option for not only patients with Del 19 and L858R *EGFR* mutations but also patients with inoperable or recurrent NSCLC with *EGFR* mutations other than Del 19 or L858R mutation.

PMDA considers as follows:
Based on the subgroup analysis results of the PFS in patients with inoperable or recurrent NSCLC with Del 19 and L858R *EGFR* mutations in Study 1200.32, the efficacy of afatinib may be expected in these patients although the number of the applicable patients was limited. On the other hand, it is difficult to evaluate the efficacy of afatinib in patients with inoperable or recurrent non-Del 19 or L858R *EGFR* mutation-positive NSCLC because the number of applicable patients was highly limited.

The types of *EGFR* mutations for which afatinib may be indicated have not been determined at present due to recent findings including resistant mutations (T790M). The applicable mutations will be updated as new findings become available. When considering whether to administer afatinib or not based on the *EGFR* mutation type, therefore, physicians should make the decision based on the latest knowledge. PMDA has concluded that the following caution statement should be included in the "Precautions for Indications" section in the package insert: afatinib should be administered referring to the latest information such as the "Lung Cancer Clinical Practice Guidelines" issued by the Japan Lung Cancer Society.

4.(iii).B.(4).6) Efficacy and safety of afatinib used in adjuvant chemotherapy
Clinical data on the efficacy and safety of afatinib used in adjuvant chemotherapy have not been available. The applicant, thus, explained that the relevant caution statement will be included in the "Precautions for Indications" section in the package insert.

PMDA accepted the applicant's explanation.

4.(iii).B.(5) Dosage and administration
The proposed dosage and administration of afatinib is "The usual adult dosage is 40 mg of afatinib orally administered once daily in the fasted state. The dose may be adjusted according to the conditions of the patient as appropriate, but should not exceed 50 mg once daily." The proposed "Precautions for Dosage and Administration" included the following contents.

- The initial dose for patients with NSCLC exacerbated after treatment of EGFR-TKIs is afatinib 50 mg once daily.
- Criteria for dose reduction, interruption, and discontinuation
- The dose may be increased to 50 mg in patients who have continued the once-daily treatment at a dose of 40 mg for ≥3 weeks without safety problems (diarrhoea, skin eruption, stomatitis, and other Grade ≥2 adverse drug reactions). Once the dose of afatinib is reduced, the dose should not be increased.
- It is reported that C_{max} and AUC decrease following administration of afatinib after a high-fat meal. Afatinib should not be administered between 1 hour before and 3 hours after a meal to avoid food effect.

Based on the results of reviews in "4.(i).B Food effect" and the following reviews in this section, PMDA has concluded that the dosage and administration section of afatinib should state that "The usual adult dosage is 40 mg of afatinib orally administered once daily in the fasted state. The dose may be adjusted according to the conditions of the patient as appropriate. The dose may be increased up to 50 mg once daily." In addition, the following information should be included in the Precautions for Dosage and Administration section to raise cautions.

- Criteria for dose reduction, interruption, and discontinuation
- The dose may be increased to 50 mg in patients who have continued the once-daily treatment at a dose of 40 mg for ≥3 weeks without diarrhoea, skin disorder, stomatitis, or other Grade ≥2 adverse drug reactions.
- It is reported that C_{max} and AUC decrease after administration of afatinib in the fed state. Afatinib should not be administered between 1 hour before and 3 hours after a meal to avoid food effect.
- The efficacy and safety of the combination therapy of afatinib with other antineoplastic drugs have not been established.

4.(iii).B.(5).1) Starting dose of afatinib
The applicant explained the rationale for setting the starting dose as follows:
The MTDs in Studies 1200.3 and 1200.4of the foreign phase I studies for afatinib administered once daily were 50 and 40 mg, respectively [see "4.(iii).A. (4).4) Foreign phase I study and 4.(iii).A.(4).5) Foreign phase I study"]. In Study 1200.22, the efficacy and safety at doses of 50 and 40 mg were investigated. As a result, these 2 starting doses provided almost the same efficacy, and the tolerability at a dose of 40 mg was higher than that at a dose of 50 mg. The applicant thus determined it appropriate to select the starting dose at a more tolerable 40 mg. Therefore, the starting dose was set at 40 mg in Study 1200.32, involving patients with inoperable or recurrent *EGFR* mutation-positive NSCLC who have not received chemotherapy. This study verified the superiority of afatinib to CDDP/PEM and confirmed the acceptable tolerability of afatinib,

demonstrating its clinical usefulness. The applicant thus determined it appropriate to set the starting dose in the relevant patients at "40 mg" in the proposed dosage and administration.

The applicant also considered that the higher starting dose may have more chances to overcome the resistance to EGFR-TKIs in patients with inoperable or recurrent EGFR mutation-positive NSCLC who have previously received EGFR-TKIs, and thus determined it appropriate to set the starting dose at 50 mg for such patients. The starting dose was, therefore, set at 50 mg in Study 1200.23 involving patients with inoperable or recurrent NSCLC who had received 1 or 2 regimens of chemotherapy including platinum antineoplastic drugs (except for EGFR-TKIs) and EGFR-TKIs. Although Study 1200.23 did not show the superiority of afatinib to placebo, the study showed clinical usefulness of afatinib [see "4.(iii).B.(4).3) Patients previously treated with EGFR-TKIs"]. The applicant thus determined it appropriate to set the starting dose at "50 mg" for patients with inoperable or recurrent *EGFR* mutation-positive NSCLC who have previously received EGFR-TKIs in the Precautions for Dosage and Administration section.

PMDA considers as follows:
Study 1200.32 showed clinical usefulness of afatinib in chemotherapy-naive patients with inoperable or recurrent *EGFR* mutation-positive NSCLC. It is appropriate to set the starting dose at 40 mg for these patients in the proposed dosage and administration.

On the other hand, Study 1200.23 does not demonstrate clinical usefulness of afatinib in patients with inoperable or recurrent NSCLC who have previously received EGFR-TKIs [see "4.(iii).B.(4).3) Patients previously treated with EGFR-TKIs"]. Therefore, PMDA has concluded that it is appropriate not to set the starting dose (50 mg) for these patients, which the applicant intended to include in the Precautions for Dosage and Administration section at the time of regulatory submission.

4.(iii).B.(5).2) Dose adjustment of afatinib
In Study 1200.32, the dose in patients who tolerated the investigational drug in Cycle 1 (21 days) well was to be increased to 50 mg in the subsequent cycles.

The applicant explained the above dose increase of afatinib as follows:
In Study 1200.32, the dose was increased to 50 mg in 16 of 229 patients (7.0%) (Japanese patients not included). Patients at the increased dose of 50 mg experienced characteristic adverse events (rash/acne, stomatitis, diarrhoea, nail abnormality) of EGFR-TKIs. Of 16 patients at the increased dose, 9 patients (56.3%) experienced adverse events leading to dose reduction but not to discontinuation. The dose of 50 mg was considered tolerable. In the Japanese phase I/II study (Study 1200.33), adverse events in Japanese patients who received afatinib once daily at the starting dose of 50 mg were comparable to those in Study 1200.32 in which patients received afatinib once daily at the starting dose of 40 mg and were allowed to increase the dose to 50 mg once daily. The dose of 50 mg was therefore considered tolerable in Japanese patients also.

Based on the above, the applicant considered that the dose may be increased to 50 mg in patients who continued the once-daily treatment at a dose of 40 mg for ≥3 weeks without safety problems, and thus this information will be included in the Precautions for Dosage and Administration section.

The applicant explained the criteria for dose reduction, interruption, and discontinuation as follows:
In Study 1200.32, the criteria for dose reduction, interruption, and discontinuation were set as shown in the table below, and the dose of afatinib was not to be increased once it was reduced. The protocol stipulated the following measure for rash: when Grade 2 rash continued for ≥7 days

despite the treatment of it or when rash was intolerable, afatinib can be reduced after interrupting for up to 14 days and then start at the reduced dose.

In consideration of the settings as well as adverse events leading to dose reduction at especially high incidences (diarrhoea, rash) in Study 1200.32, the criteria for dose reduction, interruption, and discontinuation would be included in the Precautions for Dosage and Administration section. To ensure the safety in patients, the duration of Grade ≥2 diarrhoea, which would be used as an indicator for the dose reduction, was set as ≥2 days as stipulated for non-Japanese patients in Study 1200.32.

Criteria for dose reduction, interruption, and discontinuation in Study 1200.32

Type of adverse events and Grade	Measures taken
Any of the following adverse events assessed as causally related to afatinib, • Grade ≥3 CTCAE • Grade ≥2 diarrhoea persistent for consecutive ≥2 days (48 hours) (≥7 days in Japan*) despite treatments with appropriate antidiarrheal agents/fluid replacement (water intake) • Grade ≥2 nausea or vomiting persistent for consecutive ≥7 days despite treatments with antiemetic agents/fluid replacement (water intake) • Grade ≥2 aggravated renal function (abnormal serum creatinine value, new development of proteinuria or new development of decreased GFR from the baseline by >50%)	Interrupt afatinib until the event improves to Grade ≤1 or baseline. Resume afatinib at the dose reduced by 10 mg after the event improves to Grade ≤1 or baseline (discontinue afatinib if the previous dose is 20 mg). Discontinue afatinib if the event does not improve to Grade ≤1 or baseline within 14 days.

*: In Japan, "Grade ≥2 diarrhoea at CTCAE persistent for ≥7 days" was selected because loperamide (20 mg/day), to be used as an antidiarrheal agent, was not allowed in Japan at this dose, and therefore it would take extra time to control diarrhoea.

PMDA accepted the applicant's explanation.

4.(iii).B.(5).3) Concomitant use with other antineoplastic drugs

Although clinical data showing clinical usefulness of concomitant use of afatinib with other antineoplastic drugs have not been submitted, the concerned caution statement was not included in the Precautions for Dosage and Administration section. PMDA asked the applicant to explain the efficacy and safety of concomitant use of afatinib with other antineoplastic drugs.

The applicant responded as follows:

Multiple clinical studies of concomitant use of afatinib with other antineoplastic drugs are currently ongoing. The relevant study data have not been available so far, and the efficacy and safety of concomitant use of afatinib with other antineoplastic drugs have not been established. This information will be included in the Precautions for Dosage and Administration section to raise cautions.

PMDA accepted the applicant's explanation.

4.(iii).B.(6) Post-marketing investigations

The applicant explained the post-marketing investigations as follows:

To investigate adverse drug reactions of afatinib under the routine use of afatinib after the market launch, a post-marketing surveillance (PMS) including consecutive patients will be conducted in patients with inoperable or recurrent *EGFR* mutation-positive NSCLC.

The priority investigation items for PMS include diarrhoea, rash/acne, and nail abnormality, which are events frequently leading to treatment interruption or dose reduction in Japanese patients in Study 1200.32 and are characteristic events of EGFR-TKIs. Interstitial lung disease,

which occurred in 7 of 128 Japanese patients (5.4%) and was rated at Grade 3 in 2 of 128 patients (1.6%), is also included in consideration of the seriousness of the event and the incidence in Japanese patients receiving EGFR-TKIs.

The incidences of diarrhoea, rash/acne, and nail abnormality of Grade ≥3, which led to dose reduction of afatinib in Japanese patients, were 21.9% (28 of 128 patients), 17.2% (22 of 128 patients), and 13.3% (17 of 128 patients). Assuming that the incidences of these events are unchanged, the margin of 95% CI of each event may be estimated with the probability of approximately 5% if data are accumulated from 800 patients. In addition, assuming that the incidence of interstitial lung disease is unchanged from that in Japanese patients (5.5%, 7 of 128 patients), the margin of 95% CI may be estimated with the probability of 4.0% to 7.3% if data are accumulated from 800 patients. Based on the above, the target sample size in PMS was set at 800 patients.

The enrollment period of PMS is planned to be set as 1 year. The observation period in PMS was set at 1 year because the following findings were noted in Study 1200.32: (a) diarrhoea, rash/acne, and nail abnormality occurred even after 1 year of afatinib treatment, but their incidences gradually decreased; (b) Grade ≥4 adverse events that occurred after treatment for 1 year were limited to Grade 5 metastases to the central nervous system in 1 subject, for which a causal relationship with afatinib was ruled out; (c) the events that did not occur within the first 1 year of the treatment but occurred at least twice after treatment for 1 year were limited to Grade 1/2 left ventricular dysfunction, and new adverse events did not occur with increasing treatment period.

PMDA considers as follows:
The adverse events following treatment of afatinib were similar to the characteristic events of EGFR-TKIs, but the incidences of some events were higher in Japanese patients than those in non-Japanese patients in Study 1200.32, although the number of Japanese patients who received afatinib was limited. In consideration of the above, it is necessary to conduct a post-marketing surveillance to collect safety information on afatinib under the routine use in Japan and provide the surveillance results to the healthcare providers of the medical practices.

In addition, the target sample size to be included in PMS should be reconsidered so that the risk of interstitial lung disease can be estimated at a certain precision as well, because the incidence of this event following treatment of afatinib and approved EGFR-TKIs was higher in Japanese patients than in non-Japanese patients.

4.(iv) Adverse events reported in clinical studies
Deaths reported in clinical studies submitted as the safety evaluation data are described in the "4.(iii) Summary of clinical efficacy and safety." Major adverse events other than deaths are shown below.

4.(iv).(1) Japanese phase I/II study (Study 1200.33)
4.(iv).(1).1) Phase I part
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out also occurred in all of the subjects (100%). Adverse events reported in ≥2 subjects in any group are as shown in the table below.

Adverse events reported in ≥2 subjects in any group

Event	Number of subjects (%)					
	20 mg (N = 3)		40 mg group (N = 3)		50 mg group (N = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	2 (66.7)	3 (100)	0	6 (100)	3 (50.0)
Diarrhoea	2 (66.7)	0	2 (66.7)	0	6 (100)	1 (16.7)
Dry skin	3 (100)	0	1 (33.3)	0	5 (83.3)	0
Fatigue	3 (100)	0	1 (33.3)	0	3 (50.0)	0
Nausea	1 (33.3)	0	3 (100)	0	3 (50.0)	0
Rash/acne	3 (100)	0	3 (100)	0	5 (83.3)	0
Stomatitis	1 (33.3)	0	3 (100)	0	5 (83.3)	1 (16.7)
Nail abnormality	1 (33.3)	0	2 (66.7)	0	5 (83.3)	0
Decreased appetite	2 (66.7)	0	2 (66.7)	0	3 (50.0)	0
Fall	2 (66.7)	0	0	0	0	0
Leukopenia	1 (33.3)	0	2 (66.7)	0	1 (16.7)	0
Mucosal dryness	1 (33.3)	0	2 (66.7)	0	0	0
Pyrexia	2 (66.7)	0	0	0	1 (16.7)	0
Blood urine present	0	0	0	0	3 (50.0)	0
Vomiting	0	0	1 (33.3)	0	3 (50.0)	0
Constipation	0	0	0	0	2 (33.3)	0
Epistaxis	0	0	1 (33.3)	0	2 (33.3)	0
Insomnia	0	0	0	0	2 (33.3)	0
Nasopharyngitis	0	0	0	0	2 (33.3)	0
Pruritus	1 (33.3)	0	0	0	2 (33.3)	0
Weight decreased	1 (33.3)	0	0	0	2 (33.3)	0

Serious adverse events were reported by 1 of 3 subjects (33.3%) in the 20 mg group and 2 of 6 subjects (33.3%) in the 50 mg group. The reported serious adverse events were bile duct cancer in 1 (33.3%) subject in the 20 mg group and enteritis and stomatitis in 1 subject each (16.7%) in the 50 mg group. Among these events, a causal relationship with the investigational drug could not be ruled out for enteritis and stomatitis in 1 subject each in the 50 mg group.

Adverse events leading to discontinuation of the investigational drug were reported by 1 of 3 subjects (33.3%) in the 20 mg group. The reported adverse events leading to discontinuation of the investigational drug were bile duct cancer in 1 subject (33.3%) in the 20 mg group. A causal relationship of this event to the investigational drug was ruled out.

4.(iv).(1).2) Phase II part

Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out also occurred in all of the subjects (100%). Adverse events with an incidence of ≥10% are as shown in the table below.

Adverse events with an incidence of ≥10%

Event	Number of subjects (%)	
	50 mg group (N = 62)	
	All Grades	Grade ≥3
All adverse events	62 (100)	51 (82.3)
Diarrhoea	62 (100)	23 (37.1)
Rash/acne	57 (91.9)	17 (27.4)
Stomatitis	52 (83.9)	6 (9.7)
Nail abnormality	43 (69.4)	7 (11.3)
Decreased appetite	38 (61.3)	3 (4.8)
Fatigue	25 (40.3)	5 (8.1)
Nausea	24 (38.7)	1 (1.6)
Weight decreased	19 (30.6)	0
Eye disorder	18 (29.0)	1 (1.6)
Epistaxis	17 (27.4)	0
Vomiting	17 (27.4)	1 (1.6)
Lip disorder	16 (25.8)	0
Dry skin	15 (24.2)	0
Dysgeusia	11 (17.7)	0
Dehydration	9 (14.5)	5 (8.1)
Nasal inflammation	8 (12.9)	0
Nasopharyngitis	7 (11.3)	0

Serious adverse events were reported by 16 of 62 subjects (25.8%). The reported serious adverse events were diarrhoea in 4 subjects (6.5%), dehydration in 2 subjects (3.2%), and blood creatinine increased, bronchitis, cholecystitis, decreased appetite, fatigue, hypoxia, ileus, interstitial lung disease, metastases to the central nervous system, metastatic pain, pneumonia bacterial, renal failure acute, sepsis, skeletal injury, spinal osteoarthritis, and syncope in 1 subject each (1.6%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (4 subjects), dehydration (2 subjects), and blood creatinine increased, decreased appetite, interstitial lung disease, renal failure acute, and sepsis (1 subject each).

Adverse events leading to discontinuation of the investigational drug were reported by 19 of 62 subjects (30.6%). The reported adverse events leading to discontinuation of the investigational drug were rash/acne in 7 subjects (11.3%), decreased appetite in 3 subjects (4.8%), and diarrhoea, interstitial lung disease, and stomatitis in 2 (3.2%) subjects each, cough, dehydration, fatigue, nail abnormality, and pyrexia in 1 subject each (1.6%). Among these events, a causal relationship with the investigational drug could not be ruled out for rash/acne (7 subjects), decreased appetite (3 subjects), diarrhoea, interstitial lung disease, and stomatitis (2 subjects each), and dehydration, fatigue, nail abnormality, and pyrexia (1 subject each).

4.(iv).(2) Global phase III study (Study 1200.32)

Adverse events were reported by 229 of 229 subjects (100%) in the afatinib group and 109 of 111 subjects (98.2%) in the CDDP/PEM group, and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported by 228 of 229 subjects (99.6%) in the afatinib group and 106 of 111 subjects (95.5%) in the CDDP/PEM group. Adverse events with an incidence of ≥10% in the afatinib group are as shown in the table below.

Adverse events with an incidence of ≥10% in the afatinib group

Event	Number of subjects (%)			
	Afatinib group (N = 229)		CDDP/PEM group (N = 111)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	229 (100)	139 (61.0)	109 (98.2)	63 (56.8)
Diarrhoea	220 (96.1)	34 (14.8)	25 (22.5)	0
Rash/acne	206 (90.0)	37 (16.2)	12 (10.8)	0
Stomatitis	168 (73.4)	20 (8.7)	19 (17.1)	0
Nail abnormality	141 (61.6)	27 (11.8)	0 (0.0)	0
Dry skin	69 (30.1)	1 (0.4)	2 (1.8)	1 (0.5)
Decreased appetite	66 (28.8)	10 (4.4)	61 (55.0)	3 (1.5)
Fatigue	62 (27.1)	7 (3.1)	55 (49.5)	0
Nausea	58 (25.3)	3 (1.3)	75 (67.6)	1 (0.5)
Eye disorder	52 (22.7)	1 (0.4)	8 (7.2)	0
Vomiting	52 (22.7)	10 (4.4)	52 (46.8)	0
Pruritus	46 (20.1)	1 (0.4)	1 (0.9)	0
Epistaxis	39 (17.0)	0	2 (1.8)	10 (5.1)
Weight decreased	39 (17.0)	2 (0.9)	16 (14.4)	6 (3.1)
Cough	35 (15.3)	0	21 (18.9)	0
Lip disorder	35 (15.3)	0	2 (1.8)	0
Insomnia	34 (14.8)	0	10 (9.0)	0
Headache	33 (14.4)	1 (0.4)	19 (17.1)	0
Back pain	32 (14.0)	0	13 (11.7)	2 (1.8)
Nasopharyngitis	32 (14.0)	0	9 (8.1)	0
Constipation	30 (13.1)	0	39 (35.1)	0
Alopecia	29 (12.7)	0	20 (18.0)	0
Pyrexia	28 (12.2)	0	7 (6.3)	0
ALT increased	25 (10.9)	4 (1.7)	4 (3.6)	0
Dizziness	25 (10.9)	1 (0.4)	12 (10.8)	0
Upper respiratory tract infection	25 (10.9)	1 (0.4)	4 (3.6)	0

ALT: Alanine aminotransferase

Serious adverse events were reported in 66 of 229 subjects (28.8%) in the afatinib group and 25 of 111 subjects (22.5%) in the CDDP/PEM group. Serious adverse events reported in ≥3 subjects in each group were diarrhoea in 15 subjects (6.6%), vomiting in 11 subjects (4.8%), dyspnoea, fatigue, and hypokalaemia in 4 subjects each (1.7%), and dehydration, metastases to the central nervous system, pneumonia, and stomatitis in 3 subjects each (1.3%) in the afatinib group and vomiting, fatigue, and pleural effusion in 3 subjects each (2.7%) in the CDDP/PEM group. Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (15 subjects), vomiting (8 subjects), fatigue and stomatitis (3 subjects each), decreased appetite, dehydration, hypokalaemia and pyrexia (2 subjects each), acute prerenal failure, acute respiratory distress syndrome, cholecystitis acute, death, dyspnoea, epilepsy, gastritis, interstitial lung disease, mitral valve incompetence, neoplasm malignant, pancreatitis acute, pulmonary embolism, rash/acne, and sepsis (1 subject each) in the afatinib group and vomiting and fatigue (3 subjects each) in the CDDP/PEM group.

Adverse events leading to discontinuation of the investigational drug were reported by 32 of 229 subjects (14.0%) in the afatinib group and 17 of 111 subjects (15.3%) in the CDDP/PEM group. Adverse events leading to discontinuation of the investigational drug reported by ≥2 subjects in each group were diarrhoea in 3 subjects (1.3%) and dyspnoea, interstitial lung disease, nail abnormality, pleural effusion, and pneumonia in 2 subjects each (0.9%) in the afatinib group and fatigue in 4 subjects (3.6%) in the CDDP/PEM group. Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (3 subjects), interstitial lung disease and nail abnormality (2 subjects each), and dyspnoea (1 subject) in the afatinib group and fatigue (3 subjects) in the CDDP/PEM group.

4.(iv).(3) Foreign phase I study (Study 1200.80)
Adverse events were reported in 2 of 12 subjects (16.7%) in the 20 mg group, 3 of 12 subjects (25.0%) in the 30 mg group, 1 of 12 subjects (8.3%) in the 40 mg group, and 2 of 12 subjects (16.7%) in the 50 mg group. Adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 1 of 12 subjects (8.3%) in the 30 mg group, 1 of 12 subjects (8.3%) in the 40 mg group, and 1 of 12 subjects (8.3%) in the 50 mg group.

There were no serious adverse events or adverse events leading to treatment discontinuation.

4.(iv).(4) Foreign phase I study (Study 1200.35)
Adverse events were reported in 1 of 3 subjects (33.3%) in the FF formulation/oral solution/TF2 formulation cohort (in which the FF formulation, oral solution, and TF2 formulation were administered in this order), 3 of 4 subjects (75.0%) in the FF formulation/TF2 formulation/oral solution cohort, 2 of 3 subjects (66.7%) in the oral solution/FF formulation/TF2 formulation cohort, 1 of 4 subjects (25.0%) in the oral solution/TF2 formulation/FF formulation cohort, 2 of 4 subjects (50.0%) in the TF2 formulation/FF formulation/oral solution cohort, and 3 of 4 subjects (75.0%) in the TF2 formulation/oral solution/FF formulation cohort. Adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 1 of 3 subjects (33.3%) in the oral solution/FF formulation/TF2 formulation cohort and 1 of 4 subjects (25.0%) in the TF2 formulation/oral solution/FF formulation cohort.

There were no serious adverse events or adverse events leading to treatment discontinuation.

4.(iv).(5) Foreign phase I study (Study 1200.25)
Adverse events were reported in 7 of 8 subjects (87.5%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 5 of 8 subjects (62.5%).

There were no serious adverse events or adverse events leading to treatment discontinuation.

4.(iv).(6) Foreign phase I study (Study 1200.79)
Adverse events were reported in 10 of 22 subjects (45.5%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 5 of 22 subjects (22.7%).

There were no serious adverse events or adverse events leading to treatment discontinuation.

4.(iv).(7) Foreign phase I study (Study 1200.151)
Adverse events were reported in 19 of 24 subjects (79.2%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported by 11 of 24 subjects (45.8%).

No serious adverse events occurred.

Adverse events leading to the investigational drug discontinuation were reported in 2 of 24 subjects (8.3%). The reported adverse event leading to the investigational drug discontinuation was lipase increased in 2 subjects (8.3%). A causal relationship of this event with the investigational drug could not be ruled out.

4.(iv).(8) Foreign phase I study (Study 1200.152)
Adverse events were reported in 8 of 22 subjects (36.4%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 1 of 22 subjects (4.5%).

There were no serious adverse events or adverse events leading to treatment discontinuation.

4.(iv).(9) Foreign phase I study (Study 1200.86)

Adverse events were reported in 1 of 16 healthy adult subjects (6.3%) at 50 mg, 3 of 8 patients (37.5%) with mild hepatic impairment at 50 mg, 1 of 3 patients (33.3%) with moderate hepatic impairment at 30 mg, and 1 of 8 patients (12.5%) with moderate hepatic impairment at 50 mg. Adverse events for which a causal relationship with the investigational drug could not be ruled out were reported by 3 of 8 patients (37.5%) with mild hepatic impairment at 50 mg.

There were no serious adverse events or adverse events leading to treatment discontinuation.

4.(iv).(10) Foreign phase I study (Study 1200.1)

Adverse events occurred in all of the subjects (100%) in the 10, 20, 30, 45, 70, 85, and 100 mg groups, and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 2 of 3 subjects (66.7%) in the 10 mg group, 3 of 3 subjects (100%) in the 20 mg group, 3 of 3 subjects (100%) in the 30 mg group, 3 of 3 subjects (100%) in the 45 mg group, 18 of 18 subjects (100%) in the 70 mg group, 6 of 6 subjects (100%) in the 85 mg group, and 2 of 2 subjects (100%) in the 100 mg group. Adverse events reported in ≥3 subjects in any group are as shown in the table below.

Adverse events reported in ≥3 subjects in any group

Event	Number of subjects (%)							
	10 mg group (N = 3)		20 mg group (N = 3)		30 mg group (N = 3)		45 mg group (N = 3)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	3 (100)	3 (100)	2 (66.7)	3 (100)	1 (33.3)	3 (100)	0
Diarrhoea	2 (66.7)	0	3 (100)	0	3 (100)	0	2 (66.7)	0
Epistaxis	1 (33.3)	0	1 (33.3)	0	1 (33.3)	0	2 (66.7)	0
Fatigue	3 (100)	0	3 (100)	0	2 (66.7)	0	2 (66.7)	0
Pyrexia	3 (100)	1 (33.3)	2 (66.7)	0	1 (33.3)	0	2 (66.7)	0
Rash/acne	1 (33.3)	0	3 (100)	0	3 (100)	0	3 (100)	0
Stomatitis	1 (33.3)	0	1 (33.3)	0	1 (33.3)	0	2 (66.7)	0
Abdominal pain	1 (33.3)	1 (33.3)	1 (33.3)	0	0	0	2 (66.7)	0
Anaemia	2 (66.7)	0	1 (33.3)	0	0	0	0	0
Back pain	0	0	0	0	2 (66.7)	0	1 (33.3)	0
Cough	2 (66.7)	0	0	0	1 (33.3)	0	1 (33.3)	0
Nausea	2 (66.7)	0	2 (66.7)	1 (33.3)	0	0	1 (33.3)	0
Pruritus	1 (33.3)	0	2 (66.7)	0	0	0	0	0
Vomiting	1 (33.3)	1 (33.3)	2 (66.7)	0	1 (33.3)	0	2 (66.7)	0
Abdominal pain upper	1 (33.3)	0	0	0	1 (33.3)	0	1 (33.3)	0
Decreased appetite	1 (33.3)	0	1 (33.3)	1 (33.3)	1 (33.3)	0	1 (33.3)	0
Dehydration	0	0	1 (33.3)	0	0	0	0	0
Dry skin	0	0	1 (33.3)	0	1 (33.3)	0	0	0
Hypokalaemia	1 (33.3)	0	0	0	0	0	0	0
Oropharyngeal pain	0	0	0	0	0	0	0	0
Paraesthesia	1 (33.3)	0	0	0	0	0	0	0
Weight decreased	1 (33.3)	0	0	0	0	0	0	0

Adverse events reported in ≥3 subjects in any group (continued)

Event	Number of subjects (%)					
	70 mg group (N = 18)		85 mg group (N = 6)		100 mg group (N = 2)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	18 (100)	11 (61.1)	6 (100)	2 (33.3)	2 (100)	2 (100)
Diarrhoea	15 (83.3)	7 (38.9)	6 (100)	1 (16.7)	2 (100)	2 (100)
Epistaxis	9 (50.0)	0	4 (66.7)	0	2 (100)	0
Fatigue	10 (55.6)	2 (11.1)	3 (50.0)	1 (16.7)	1 (50.0)	0
Pyrexia	3 (16.7)	1 (5.6)	0	0	1 (50.0)	0
Rash/acne	18 (100)	0	6 (100)	0	2 (100)	1 (50.0)
Stomatitis	15 (83.3)	0	5 (83.3)	0	2 (100)	0
Abdominal pain	4 (22.2)	0	2 (33.3)	0	0	0
Anaemia	0	0	0	0	0	0
Back pain	3 (16.7)	1 (5.6)	2 (33.3)	0	0	0
Cough	3 (16.7)	0	2 (33.3)	0	0	0
Nausea	8 (44.4)	2 (11.1)	3 (50.0)	0	1 (50.0)	0
Pruritus	6 (33.3)	0	0	0	0	0
Vomiting	8 (44.4)	2 (11.1)	4 (66.7)	0	1 (50.0)	0
Abdominal pain upper	3 (16.7)	0	1 (16.7)	0	1 (50.0)	1 (50.0)
Decreased appetite	7 (38.9)	0	3 (50.0)	0	0	0
Dehydration	5 (27.8)	4 (22.2)	2 (33.3)	0	0	0
Dry skin	6 (33.3)	0	2 (33.3)	0	0	0
Hypokalaemia	5 (27.8)	2 (11.1)	1 (16.7)	0	0	0
Oropharyngeal pain	3 (16.7)	0	2 (33.3)	0	0	0
Paraesthesia	4 (22.2)	0	1 (16.7)	0	0	0
Weight decreased	4 (22.2)	0	1 (16.7)	0	0	0

Serious adverse events were reported in 3 of 3 subjects (100%) in the 10 mg group, 2 of 3 subjects (66.7%) in the 20 mg group, 1 of 3 subjects (33.3%) in the 30 mg group, 11 of 18 subjects (61.1%) in the 70 mg group, 2 of 6 subjects (33.3%) in the 85 mg group, and 1 of 2 subjects (50.0%) in the 100 mg group. The reported serious adverse events were pyrexia in 2 subjects (66.7%) and abdominal pain, constipation, pneumonia, and sinusitis in 1 subject each (33.3%) in the 10 mg group, dehydration, nausea, flank pain, neoplasm malignant, renal function disorder, and tumor pain in 1 subject each (33.3%) in the 20 mg group, neoplasm malignant in 1 subject (33.3%) in the 30 mg group, diarrhoea and dehydration in 5 subjects each (27.8%), neoplasm malignant and vomiting in 2 subjects each (11.1%), and nausea, cerebrovascular accident, cholangitis, pain in extremity, and pulmonary haemorrhage in 1 subject each (5.6%) in the 70 mg group, dehydration in 2 subjects (33.3%) and constipation in 1 subject (16.7%) in the 85 mg group, and abdominal pain upper in 1 subject (50.0%) in the 100 mg group. Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (5 subjects), dehydration (4 subjects), vomiting (2 subjects), and nausea (1 subject) in the 70 mg group.

Adverse events leading to discontinuation of the investigational drug were reported in 10 of 18 subjects (55.6%) in the 70 mg group, 2 of 6 subjects (33.3%) in the 85 mg group, and 1 of 2 subjects (50.0%) in the 100 mg group. The reported adverse events leading to discontinuation of the investigational drug were diarrhoea in 5 subjects (27.8%), decreased appetite and dehydration in 2 subjects each (11.1%), and stomatitis, ALT increased, cerebrovascular accident, cholangitis, epistaxis, fatigue, nausea, oedema peripheral, pulmonary haemorrhage, and rash/acne in 1 subject each (5.6%) in the 70 mg group, complex partial seizures and stomatitis in 1 subject each (16.7%) in the 85 mg group, and diarrhoea in 1 subject (50.0%) in the 100 mg group. Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (5 subjects), decreased appetite and dehydration (2 subjects each), and stomatitis, ALT increased, epistaxis, and rash/acne (1 subject each) in the 70 mg group, stomatitis (1 subject) in the 85 mg group, and diarrhoea (1 subject) in the 100 mg group.

4.(iv).(11) Foreign phase I study (Study 1200.2)

Adverse events occurred in all of the subjects (100%) in the 10, 20, 40, 55, and 65 mg groups. Adverse events for which a causal relationship with the investigational drug could not be ruled

out were reported in 2 of 3 subjects (66.7%) in the 10 mg group, 6 of 6 subjects (100%) in the 20 mg group, 7 of 8 subjects (87.5%) in the 40 mg group, 19 of 20 subjects (95.0%) in the 55 mg group, and 6 of 6 subjects (100%) in the 65 mg group. Adverse events reported in ≥3 subjects in any group are as shown in the table below.

Adverse events reported by ≥3 subjects in any group

Event	Number of subjects (%)									
	10 mg group (N = 3)		20 mg group (N = 6)		40 mg group (N = 8)		55 mg group (N = 20)		65 mg group (N = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	0	6 (100)	3 (50.0)	8 (100)	5 (62.5)	20 (100)	15 (75.0)	6 (100)	5 (83.3)
Diarrhoea	1 (33.3)	0	1 (16.7)	0	5 (62.5)	1 (12.5)	18 (90.0)	5 (25.0)	6 (100)	2 (33.3)
Rash/acne	1 (33.3)	0	4 (66.7)	0	7 (87.5)	1 (12.5)	17 (85.0)	1 (5.0)	5 (83.3)	0
Fatigue	2 (66.7)	0	1 (16.7)	0	3 (37.5)	1 (12.5)	7 (35.0)	1 (5.0)	5 (83.3)	3 (50.0)
Stomatitis	0	0	3 (50.0)	0	5 (62.5)	0	14 (70.0)	2 (10.0)	5 (83.3)	0
Decreased appetite	0	0	1 (16.7)	0	4 (50.0)	0	7 (35.0)	2 (10.0)	4 (66.7)	0
Dyspnoea	2 (66.7)	0	0	0	0	0	4 (20.0)	0	1 (16.7)	0
Epistaxis	0	0	2 (33.3)	0	1 (12.5)	0	9 (45.0)	0	4 (66.7)	0
Pruritus	2 (66.7)	0	0	0	2 (25.0)	0	4 (20.0)	0	4 (66.7)	0
Nausea	1 (33.3)	0	3 (50.0)	0	4 (50.0)	2 (25.0)	11 (55.0)	0	3 (50.0)	1 (16.7)
Abdominal pain	0	0	0	0	0	0	2 (10.0)	0	3 (50.0)	0
Urinary tract infection	0	0	3 (50.0)	0	1 (12.5)	0	2 (10.0)	0	1 (16.7)	0
Vomiting	1 (33.3)	0	3 (50.0)	0	4 (50.0)	1 (12.5)	9 (45.0)	1 (5.0)	2 (33.3)	1 (16.7)
Dry skin	0	0	1 (16.7)	0	0	0	8 (40.0)	0	2 (33.3)	0
Dysgeusia	0	0	1 (16.7)	0	0	0	8 (40.0)	0	0	0
Abdominal pain upper	0	0	1 (16.7)	0	3 (37.5)	0	1 (5.0)	0	2 (33.3)	0
Dehydration	0	0	0	0	3 (37.5)	1 (12.5)	4 (20.0)	2 (10.0)	2 (33.3)	2 (33.3)
Oral pain	0	0	0	0	3 (37.5)	0	1 (5.0)	0	0	0
Back pain	1 (33.3)	0	0	0	1 (12.5)	0	3 (15.0)	0	1 (16.7)	0
Eye disorder	0	0	1 (16.7)	0	1 (12.5)	0	5 (25.0)	1 (5.0)	0	0
Rhinorrhoea	0	0	0	0	0	0	5 (25.0)	0	0	0

Serious adverse events were reported in 1 of 6 subjects (16.7%) in the 20 mg group, 2 of 8 subjects (25.0%) in the 40 mg group, 11 of 20 subjects (55.0%) in the 55 mg group, and 3 of 6 subjects (50.0%) in the 65 mg group. The reported serious adverse events were large intestine ulcer and rectal haemorrhage in 1 subject each (16.7%) in the 20 mg group, dehydration, nausea, vomiting, bacteraemia, pyrexia, and tachycardia in 1 (12.5%) subject each in the 40 mg group, diarrhoea in 4 subjects (20.0%), death and stomatitis in 2 subjects each (10.0%), and dehydration, hyponatraemia, vomiting, acute myocardial infarction, acute respiratory distress syndrome, cellulitis, decreased appetite, disease progression, herpes zoster, hypercalcaemia, hyperuricaemia, intestinal obstruction, eye disorder, pneumonia, rash/acne, small intestinal obstruction, and spinal cord compression in 1 subject each (5.0%) in the 55 mg group, and diarrhoea, dehydration, and fatigue in 2 subjects each (33.3%) and dyspnoea, hyponatraemia, nausea, night blindness, peripheral sensory neuropathy, renal failure, and vomiting in 1 subject each (16.7%) in the 65 mg group. Among these events, a causal relationship with the investigational drug could not be ruled out for dehydration, nausea, and vomiting (1 subject each) in the 40 mg group, diarrhoea (4 subjects), stomatitis (2 subjects), and dehydration, hyponatraemia, vomiting, decreased appetite, and rash/acne (1 subject each) in the 55 mg group, and diarrhoea and dehydration (2 subjects each) and fatigue, hyponatraemia, nausea, and vomiting (1 subject each) in the 65 mg group.

Adverse events leading to discontinuation of the investigational drug were reported in 3 of 8 subjects (37.5%) in the 40 mg group, 9 of 20 subjects (45.0%) in the 55 mg group, and 5 of 6 subjects (83.3%) in the 65 mg group. The reported adverse events leading to discontinuation of the investigational drug were diarrhoea, dehydration, and nausea in 1 subject each (12.5%) in the 40 mg group, dehydration in 2 subjects (10.0%), and diarrhoea, acute myocardial infarction, deep vein thrombosis, hypercalcaemia, hyponatraemia, intestinal obstruction, and stomatitis in 1 subject each (5.0%) in the 55 mg group, and defaecation urgency, diarrhoea, dehydration,

dyspnoea, muscular weakness, and renal failure in 1 subject each (16.7%) in the 65 mg group. Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea, dehydration, and nausea (1 subject each) in the 40 mg group, dehydration (2 subjects), and diarrhoea and stomatitis (1 subject each) in the 55 mg group, and defaecation urgency, diarrhoea, and dehydration (1 subject each) in the 65 mg group.

4.(iv).(12) Foreign phase I study (Study 1200.3)

Adverse events were reported in 3 of 3 subjects (100%) in the 10 mg group, 4 of 4 subjects (100%) in the 20 mg group, 7 of 7 subjects (100%) in the 30 mg group, 25 of 26 subjects (96.2%) in the 40 mg group, and 13 of 13 subjects (100%) in the 50 mg group. Adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 2 of 3 subjects (66.7%) in the 10 mg group, 3 of 4 subjects (75.0%) in the 20 mg group, 6 of 7 subjects (85.7%) in the 30 mg group, 23 of 26 subjects (88.5%) in the 40 mg group, and 10 of 13 subjects (76.9%) in the 50 mg group. Adverse events reported in ≥3 subjects in any group are as shown in the table below.

Adverse events reported in ≥3 subjects in any group

Event	Number of subjects (%)									
	10 mg group (N = 3)		20 mg group (N = 4)		30 mg group (N = 7)		40 mg group (N = 26)		50 mg group (N = 13)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	0	4 (100)	2 (50.0)	7 (100)	7 (100)	25 (96.2)	13 (50.0)	13 (100)	8 (61.5)
Nausea	0	0	4 (100)	0	1 (14.3)	0	11 (42.3)	0	4 (30.8)	0
Rash/acne	2 (66.7)	0	3 (75.0)	0	5 (71.4)	0	21 (80.8)	1 (3.8)	9 (69.2)	1 (7.7)
Diarrhoea	1 (33.3)	0	2 (50.0)	0	3 (42.9)	0	20 (76.9)	2 (7.7)	9 (69.2)	1 (7.7)
Dizziness	0	0	3 (75.0)	0	0	0	1 (3.8)	0	1 (7.7)	0
Fatigue	1 (33.3)	0	3 (75.0)	1 (25.0)	5 (71.4)	0	10 (38.5)	0	9 (69.2)	0
Dyspnoea	0	0	1 (25.0)	0	4 (57.1)	1 (14.3)	5 (19.2)	1 (3.8)	3 (23.1)	2 (15.4)
Stomatitis	0	0	1 (25.0)	0	4 (57.1)	0	7 (26.9)	0	3 (23.1)	0
Decreased appetite	0	0	2 (50.0)	0	3 (42.9)	0	9 (34.6)	0	6 (46.2)	0
Anaemia	0	0	1 (25.0)	0	3 (42.9)	1 (14.3)	1 (3.8)	0	1 (7.7)	0
Arthralgia	0	0	0	0	3 (42.9)	0	1 (3.8)	0	1 (7.7)	0
Chest pain	0	0	0	0	3 (42.9)	1 (14.3)	1 (3.8)	0	1 (7.7)	0
Vomiting	0	0	1 (25.0)	0	2 (28.6)	0	10 (38.5)	0	3 (23.1)	0
Dry skin	0	0	0	0	1 (14.3)	0	3 (11.5)	0	4 (30.8)	0
Urinary tract infection	0	0	0	0	2 (28.6)	1 (14.3)	2 (7.7)	1 (3.8)	4 (30.8)	0
Constipation	0	0	1 (25.0)	0	1 (14.3)	0	3 (11.5)	0	3 (23.1)	0
Epistaxis	0	0	1 (25.0)	0	0	0	3 (11.5)	0	2 (15.4)	0

Serious adverse events were reported in 1 of 3 subjects (33.3%) in the 10 mg group, 2 of 4 subjects (50.0%) in the 20 mg group, 5 of 7 subjects (71.4%) in the 30 mg group, 12 of 26 subjects (46.2%) in the 40 mg group, and 7 of 13 subjects (53.8%) in the 50 mg group. The reported serious adverse events were disease progression in 1 subject (33.3%) in the 10 mg group, condition aggravated, malignant ascites, and upper gastrointestinal haemorrhage in 1 subject each (25.0%) in the 20 mg group, disease progression, abdominal distension, anaemia, blood creatinine increased, chest pain, dyspnoea, pneumonia, pneumonitis, and respiratory failure in 1 subject each (14.3%) in the 30 mg group, pericardial effusion in 2 subjects (7.7%), and disease progression, condition aggravated, malignant ascites, dyspnoea, intestinal obstruction, urinary tract infection, urosepsis, atrial fibrillation, clot retraction, fatigue, hydronephrosis, metastases to the central nervous system, myocardial infarction, oesophageal stenosis, pain, pleural effusion, vaginal haemorrhage, and visual impairment in 1 subject each (3.8%) in the 40 mg group, lower respiratory tract infection in 2 subjects (15.4%), and disease progression, dyspnoea, diarrhoea, infection, intestinal obstruction, rash/acne, renal function disorder, small intestinal obstruction, somnolence, ureteric obstruction, urinary tract infection, urosepsis, and weight decreased in 1 subject each (7.7%) in the 50 mg group. Among these events, a causal relationship with the investigational drug could

not be ruled out for pneumonitis and respiratory failure (1 subject each) in the 30 mg group and diarrhoea and rash/acne (1 subject each) in the 50 mg group.

Adverse events leading to discontinuation of the investigational drug were reported in 1 of 4 subjects (25.0%) in the 20 mg group, 3 of 7 subjects (42.9%) in the 30 mg group, 7 of 26 subjects (26.9%) in the 40 mg group, and 7 of 13 subjects (53.8%) in the 50 mg group. The reported adverse events leading to discontinuation of the investigational drug were upper gastrointestinal haemorrhage in 1 subject (25.0%) in the 20 mg group, dyspnoea, pneumonia, pneumonitis, and respiratory failure in 1 subject each (14.3%) in the 30 mg group, diarrhoea, condition aggravated, disease progression, metastases to the central nervous system, myocardial infarction, rash/acne, and urosepsis in 1 subject each (3.8%) in the 40 mg group, dyspnoea and lower respiratory tract infection in 2 subjects each (15.4%), and diarrhoea, fatigue, intestinal obstruction, small intestinal obstruction, and vomiting in 1 subject each (7.7%) in the 50 mg group. Among these events, a causal relationship with the investigational drug could not be ruled out for pneumonitis and respiratory failure (1 subject each) in the 30 mg group, diarrhoea and rash/acne (1 subject each) in the 40 mg group, and diarrhoea (1 subject) in the 50 mg group.

4.(iv).(13) Foreign phase I study (Study 1200.4)

Adverse events occurred in all of the subjects (100%) in the 10, 20, 40, and 60 mg groups, and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 4 of 5 subjects (80.0%) in the 10 mg group, 3 of 3 subjects (100%) in the 20 mg group, 19 of 19 subjects (100%) in the 40 mg group, and 3 of 3 subjects (100%) in the 60 mg group. Adverse events reported in ≥3 subjects in any group are as shown in the table below.

Adverse events reported in ≥3 subjects in any group

Event	Number of subjects (%)							
	10 mg group (N = 5)		20 mg group (N = 3)		40 mg group (N = 19)		60 mg group (N = 3)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	5 (100)	2 (40.0)	3 (100)	3 (100)	19 (100)	7 (36.8)	3 (100)	2 (66.7)
Diarrhoea	3 (60.0)	0	3 (100)	0	15 (78.9)	2 (10.5)	3 (100)	2 (66.7)
Headache	0	0	3 (100)	1 (33.3)	0	0	1 (33.3)	0
Rash/acne	0	0	3 (100)	0	17 (89.5)	0	3 (100)	0
Stomatitis	1 (20.0)	0	1 (33.3)	0	16 (84.2)	0	3 (100)	0
Fatigue	4 (80.0)	2 (40.0)	1 (33.3)	0	7 (36.8)	1 (5.3)	1 (33.3)	1 (33.3)
Constipation	0	0	2 (66.7)	0	2 (10.5)	0	0	0
Cough	2 (40.0)	0	2 (66.7)	0	3 (15.8)	0	0	0
Decreased appetite	1 (20.0)	0	1 (33.3)	1 (33.3)	5 (26.3)	1 (5.3)	2 (66.7)	0
Epistaxis	0	0	0	0	4 (21.1)	0	2 (66.7)	0
Mood altered	0	0	2 (66.7)	0	0	0	0	0
Nausea	3 (60.0)	0	2 (66.7)	1 (33.3)	6 (31.6)	0	2 (66.7)	0
Vomiting	0	0	1 (33.3)	1 (33.3)	6 (31.6)	0	2 (66.7)	0
Dehydration	1 (20.0)	1 (20.0)	0	0	3 (15.8)	1 (5.3)	1 (33.3)	0
Nasal dryness	0	0	1 (33.3)	0	3 (15.8)	0	1 (33.3)	0
Dysgeusia	0	0	0	0	4 (21.1)	0	0	0

Serious adverse events were reported in 2 of 5 subjects (40.0%) in the 10 mg group, 2 of 3 subjects (66.7%) in the 20 mg group, 5 of 19 subjects (26.3%) in the 40 mg group, and 1 of 3 subjects (33.3%) in the 60 mg group. The reported serious adverse events were dehydration, fatigue, hydronephrosis, hypotension, lung infiltration, and NSCLC in 1 subject each (20.0%) in the 10 mg group, disease progression, headache, nausea, and vomiting in 1 subject each (33.3%) in the 20 mg group, dehydration, pneumonia, pleural effusion, abdominal pain, functional gastrointestinal disorder, nephrolithiasis, and bile duct obstruction in 1 subject each (5.3%) in the 40 mg group, and diarrhoea in 1 subject (33.3%) in the 60 mg group. Among these events, a causal relationship with the investigational drug could not be ruled out for nausea (1 subject) in the 20 mg group and diarrhoea (1 subject) in the 60 mg group.

Adverse events leading to discontinuation of the investigational drug were reported in 2 of 5 subjects (40.0%) in the 10 mg group, 4 of 19 subjects (21.1%) in the 40 mg group, and 2 of 3 subjects (66.7%) in the 60 mg group. The reported adverse events leading to discontinuation of the investigational drug were fatigue in 2 subjects (40.0%), and decreased appetite, dehydration, diplopia, dyspnoea, hyperglycaemia, hypocalcaemia, hypotension, lung infiltration, nausea, and tumor pain in 1 subject each (20.0%) in the 10 mg group, diarrhoea, fatigue, decreased appetite, dehydration, bile duct obstruction, and pneumonia in 1 subject each (5.3%) in the 40 mg group, and diarrhoea in 2 subjects (66.7%), fatigue, decreased appetite, dehydration, hypokalaemia, nail abnormality, and stomatitis in 1 subject each (33.3%) in the 60 mg group. Among these events, a causal relationship with the investigational drug could not be ruled out for diplopia and nausea (1 subject each) in the 10 mg group, diarrhoea, decreased appetite, dehydration, and fatigue (1 subject each) in the 40 mg group, diarrhoea (2 subjects), and decreased appetite, dehydration, fatigue, nail abnormality, and stomatitis (1 subject each) in the 60 mg group.

4.(iv).(14) Foreign phase II study (Study 1200.22)

Adverse events were reported in 23 of 23 subjects (100%) in the treated group with afatinib as first-line therapy at a starting dose of 40 mg (first-line 40 mg group), 30 of 30 subjects (100%) in the first-line 50 mg group, 7 of 7 subjects (100%) in the treated group with afatinib as second-line therapy at a starting dose of 40 mg (second-line 40 mg group), and 68 of 69 subjects (98.6%) in the second-line 50 mg group. Adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 23 of 23 subjects (100%) in the first-line 40 mg group, 30 of 30 subjects (100%) in the first-line 50 mg group, 7 of 7 subjects (100%) in the second-line 40 mg group, and 68 of 69 subjects (98.6%) in the second-line 50 mg group. Adverse events with an incidence of ≥20% in any group are as shown in the table below.

Adverse events with an incidence of ≥20% in any group

Event	Number of subjects (%)							
	First-line 40 mg group (N = 23)		First-line 50 mg group (N = 30)		Second-line 40 mg group (N = 7)		Second-line 50 mg group (N = 69)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	23 (100)	14 (60.9)	30 (100)	23 (76.7)	7 (100)	2 (28.6)	68 (98.6)	49 (71.0)
Diarrhoea	22 (95.7)	1 (4.3)	28 (93.3)	10 (33.3)	7 (100)	1 (14.3)	65 (94.2)	14 (20.3)
Rash/acne	21 (91.3)	2 (8.7)	30 (100)	6 (20.0)	6 (85.7)	0	64 (92.8)	22 (31.9)
Stomatitis	11 (47.8)	0	27 (90.0)	3 (10.0)	4 (57.1)	0	63 (91.3)	5 (7.2)
Nail abnormality	18 (78.3)	2 (8.7)	25 (83.3)	3 (10.0)	6 (85.7)	0	61 (88.4)	5 (7.2)
Pruritus	11 (47.8)	0	17 (56.7)	0	4 (57.1)	0	43 (62.3)	1 (1.4)
Rhinorrhoea	9 (39.1)	0	15 (50.0)	0	2 (28.6)	0	31 (44.9)	0
Dry skin	4 (17.4)	0	14 (46.7)	0	3 (42.9)	0	21 (30.4)	0
Cough	8 (34.8)	0	9 (30.0)	0	1 (14.3)	0	30 (43.5)	0
Dizziness	10 (43.5)	0	4 (13.3)	1 (3.3)	0	0	18 (26.1)	0
Decreased appetite	8 (34.8)	2 (8.7)	12 (40.0)	1 (3.3)	2 (28.6)	0	27 (39.1)	2 (2.9)
Epistaxis	9 (39.1)	0	10 (33.3)	0	1 (14.3)	0	16 (23.2)	0
Eye disorder	4 (17.4)	0	8 (26.7)	0	2 (28.6)	0	25 (36.2)	0
Fatigue	8 (34.8)	3 (13.0)	8 (26.7)	2 (6.7)	2 (28.6)	0	21 (30.4)	1 (1.4)
Insomnia	2 (8.7)	0	3 (10.0)	0	1 (14.3)	0	22 (31.9)	0
Vomiting	7 (30.4)	1 (4.3)	2 (6.7)	0	1 (14.3)	0	15 (21.7)	3 (4.3)
Urinary tract infection	5 (21.7)	1 (4.3)	8 (26.7)	0	0	0	10 (14.5)	0
Oedema peripheral	6 (26.1)	0	3 (10.0)	0	1 (14.3)	0	8 (11.6)	0
Upper respiratory tract infection	6 (26.1)	0	1 (3.3)	0	0	0	16 (23.2)	0
Lip disorder	2 (8.7)	0	7 (23.3)	0	0	0	7 (10.1)	0
Weight decreased	3 (13.0)	0	7 (23.3)	0	0	0	12 (17.4)	1 (1.4)
Constipation	2 (8.7)	0	5 (16.7)	0	1 (14.3)	0	16 (23.2)	0
Dyspnoea	4 (17.4)	0	5 (16.7)	1 (3.3)	0	0	16 (23.2)	2 (2.9)
Oropharyngeal pain	1 (4.3)	0	6 (20.0)	0	1 (14.3)	0	16 (23.2)	0
Alopecia	5 (21.7)	0	5 (16.7)	0	0	0	6 (8.7)	0
Headache	5 (21.7)	0	6 (20.0)	0	1 (14.3)	0	11 (15.9)	1 (1.4)
Abdominal pain upper	2 (8.7)	0	2 (6.7)	0	0	0	14 (20.3)	0
Nausea	4 (17.4)	0	4 (13.3)	1 (3.3)	1 (14.3)	0	14 (20.3)	2 (2.9)

Serious adverse events were reported in 7 of 23 subjects (30.4%) in the first-line 40 mg group, 11 of 30 subjects (36.7%) in the first-line 50 mg group, 1 of 7 subjects (14.3%) in the second-line 40 mg group, and 32 of 69 subjects (46.4%) in the second-line 50 mg group. Serious adverse events reported in ≥2 subjects in each group were neoplasm malignant and pneumothorax in 2 subjects each (8.7%) in the first-line 40 mg group, dyspnoea, intracranial pressure increased, and rash/acne in 2 subjects each (6.7%) in the first-line 50 mg group, and dyspnoea in 4 subjects (5.8%), rash/acne, pneumonia, and pneumonitis in 3 subjects each (4.3%), and neoplasm malignant, intracranial pressure increased, septic shock, duodenal ulcer, gastric ulcer, headache, interstitial lung disease, nephrolithiasis, obstructive airways disorder, and renal failure in 2 subjects each (2.9%) in the second-line 50 mg group. Among these events, a causal relationship with the investigational drug could not be ruled out for decreased appetite, fatigue, nausea, pneumothorax, and vomiting (1 subject each) in the first-line 40 mg group, rash/acne, abscess, cellulitis, cyst rupture, and diarrhoea (1 subject each) in the first-line 50 mg group, and rash/acne (3 subjects), interstitial lung disease and renal failure (2 subjects each), fatigue, cellulitis, diarrhoea, cystitis, dehydration, duodenal ulcer, gastric ulcer, gastric ulcer haemorrhage, gastritis, gastrooesophageal reflux disease, lung infiltration, nephrolithiasis, pain of skin, pruritus, and stomatitis (1 subject each) in the second-line 50 mg group.

Adverse events leading to discontinuation of the investigational drug were reported in 7 of 23 subjects (30.4%) in the first-line 40 mg group, 5 of 30 subjects (16.7%) in the first-line 50 mg group, 2 of 7 subjects (28.6%) in the second-line 40 mg group, and 12 of 69 subjects (17.4%) in the second-line 50 mg group. The reported adverse events leading to discontinuation of the investigational drug were interstitial lung disease and neoplasm malignant in 2 subjects each (8.7%), and metastases to the central nervous system, multiple myeloma, and pneumothorax in 1 subject each (4.3%) in the first-line 40 mg group, abscess, cardiac tamponade, cerebral infarction, chest discomfort, cyst rupture, hepatic congestion, musculoskeletal pain, and rash/acne in 1 subject each (3.3%) in the first-line 50 mg group, disease progression and nail abnormality in 1 subject each (14.3%) in the second-line 40 mg group, and interstitial lung disease, dyspnoea, and vomiting in 2 subjects each (2.9%), and metastases to the central nervous system, rash/acne, gastritis erosive, intracranial pressure increased, lung infiltration, metastases to meninges, obstructive airways disorder, pneumonitis, proteinuria, and wheezing in 1 subject each (1.4%) in the second-line 50 mg group. Among these events, a causal relationship with the investigational drug could not be ruled out for interstitial lung disease (2 subjects), pneumothorax (1 subject) in the first-line 40 mg group, abscess, cyst rupture, and rash/acne (1 subject each [3.3%]) in the first-line 50 mg group, nail abnormality (1 subject) in the second-line 40 mg group, and interstitial lung disease and vomiting (2 subjects each), and rash/acne, lung infiltration, and proteinuria (1 subject each) in the second-line 50 mg group.

4.(iv).(15) Foreign phase II study (Study 1200.24)

Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 58 of 60 subjects (96.7%). Adverse events with an incidence of ≥10% are as shown in the table below.

Adverse events with an incidence of ≥10%

Event	Number of subjects (%)	
	Afatinib group (N = 60)	
	All Grades	Grade ≥3
All adverse events	60 (100)	40 (66.7)
Diarrhoea	51 (85.0)	13 (21.7)
Rash/acne	47 (78.3)	8 (13.3)
Fatigue	31 (51.7)	6 (10.0)
Nausea	31 (51.7)	3 (5.0)
Stomatitis	28 (46.7)	3 (5.0)
Decreased appetite	24 (40.0)	1 (1.7)
Vomiting	21 (35.0)	3 (5.0)
Dehydration	11 (18.3)	4 (6.7)
Constipation	10 (16.7)	0
Epistaxis	9 (15.0)	0
Cough	8 (13.3)	0
Dry skin	8 (13.3)	0
Dyspnoea	8 (13.3)	2 (3.3)
Lower respiratory tract infection	8 (13.3)	2 (3.3)
Nail abnormality	8 (13.3)	1 (1.7)
Eye disorder	8 (13.3)	0
Palmar-plantar erythrodysaesthesia syndrome	8 (13.3)	2 (3.3)
Abdominal pain	7 (11.7)	1 (1.7)
Pyrexia	7 (11.7)	0
Urinary tract infection	7 (11.7)	0

Serious adverse events were reported in 34 of 60 subjects (56.7%). Serious adverse events reported in ≥2 subjects were diarrhoea in 7 subjects (11.7%), dehydration and vomiting in 5 subjects each (8.3%), lower respiratory tract infection and neoplasm malignant in 4 subjects each (6.7%), nausea and renal failure acute in 3 subjects each (5.0%), and anaemia, dyspnoea, pleural effusion, rash/acne, and urinary tract infection in 2 subjects each (3.3%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (7 subjects), dehydration and nausea (3 subjects each), rash/acne, renal failure acute, and vomiting (2 subjects each).

Adverse events leading to discontinuation of the investigational drug were reported in 17 of 60 subjects (28.3%). Adverse events leading to discontinuation of the investigational drug reported in ≥2 subjects were diarrhoea, fatigue, and rash/acne in 4 subjects each (6.7%), nausea in 3 subjects (5.0%), and dehydration, dyspnoea, lower respiratory tract infection, and vomiting in 2 subjects each (3.3%). Among these events, a causal relationship with the investigational drug could not be ruled out for rash/acne (4 subjects), diarrhoea, fatigue, and nausea (3 subjects each), vomiting (2 subjects), and dehydration (1 subject).

4.(iv).(16) Foreign phase III study (Study 1200.23)

Adverse events were reported in 384 of 390 subjects (98.5%) in the afatinib group and 169 of 195 subjects (86.7%) in the placebo group, and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 372 of 390 subjects (95.4%) in the afatinib group and 74 of 195 subjects (37.9%) in the placebo group. Adverse events with an incidence of ≥10% in the afatinib group are as shown in the table below.

Adverse events with an incidence of ≥10% in the afatinib group

Event	Number of subjects (%)			
	Afatinib group (N = 390)		Placebo group (N = 195)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	384 (98.5)	223 (66.7)	169 (86.7)	50 (66.7)
Diarrhoea	339 (86.9)	67 (17.2)	18 (9.2)	0
Rash/acne	305 (78.2)	56 (14.4)	31 (15.9)	0
Stomatitis	237 (60.8)	11 (2.8)	5 (2.6)	0
Nail abnormality	153 (39.2)	20 (5.1)	2 (1.0)	0
Decreased appetite	120 (30.8)	14 (3.6)	22 (11.3)	1 (0.5)
Fatigue	116 (29.7)	23 (5.9)	43 (22.1)	3 (1.5)
Nausea	93 (23.8)	8 (2.1)	39 (20.0)	0
Vomiting	79 (20.3)	9 (2.3)	26 (13.3)	1 (0.5)
Epistaxis	73 (18.7)	0	1 (0.5)	0
Pruritus	72 (18.5)	1 (0.3)	11 (5.6)	0
Dry skin	61 (15.6)	1 (0.3)	14 (7.2)	0
Dyspnoea	60 (15.4)	18 (4.7)	26 (13.3)	10 (5.1)
Cough	54 (13.8)	3 (0.8)	38 (19.5)	6 (3.1)
Eye disorder	52 (13.3)	2 (0.5)	5 (2.6)	0
Constipation	43 (11.0)	1 (0.3)	24 (12.3)	0
Rhinorrhoea	42 (10.8)	0	2 (1.0)	0
Pyrexia	40 (10.3)	1 (0.3)	7 (3.6)	0

Serious adverse events were reported in 135 of 390 subjects (34.6%) in the afatinib group and 37 of 195 subjects (19.0%) in the placebo group. Serious adverse events reported in ≥3 subjects in each group were diarrhoea in 18 subjects (4.6%), neoplasm malignant in 16 subjects (4.1%), pleural effusion in 14 subjects (3.6%), metastases to the central nervous system in 11 subjects (2.8%), pneumonia in 10 subjects (2.6%), respiratory failure in 9 subjects (2.3%), dehydration and dyspnoea in 8 subjects each (2.1%), pyrexia and renal failure acute in 7 subjects each (1.8%), deep vein thrombosis, fatigue, hypokalaemia, pulmonary embolism, septic shock, and vomiting in 5 subjects each (1.3%), blood creatinine increased, lung infection, nausea, and pancreatitis acute in 4 subjects each (1.0%), and death, decreased appetite, dizziness, muscular weakness, and stomatitis in 3 subjects each (0.8%) in the afatinib group, and neoplasm malignant and pleural effusion in 7 subjects each (3.6%), pneumonia and dyspnoea in 4 subjects each (2.1%), metastases to the central nervous system, cough, and dysphagia in 3 subjects each (1.5%) in the placebo group. Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (17 subjects), hypokalaemia (5 subjects), blood creatinine increased and dehydration (4 subjects each), fatigue, renal failure acute, stomatitis, and vomiting (3 subjects each), decreased appetite, hypocalcaemia, nausea, pancreatitis acute, rash/acne, and rectal haemorrhage (2 subjects each), abdominal pain, acute hepatic failure, acute left ventricular failure, acute prerenal failure, chest discomfort, deep vein thrombosis, dyspnoea, nail abnormality, oliguria, pneumonia, proctalgia, pulmonary embolism, renal failure, renal function disorder, and SJS (1 subject each) in the afatinib group, and pulmonary embolism (1 subject) in the placebo group.

Adverse events leading to discontinuation of the investigational drug were reported in 70 of 390 subjects (17.9%) in the afatinib group and 12 of 195 subjects (6.2%) in the placebo group. Adverse events leading to discontinuation of the investigational drug reported in ≥2 subjects in each group were diarrhoea in 14 subjects (3.6%), neoplasm malignant and rash/acne in 7 subjects each (1.8%), nausea, respiratory failure, and vomiting in 5 subjects each (1.3%), decreased appetite and lung infection in 4 subjects each (1.0%), fatigue, pleural effusion, and pneumonia in 3 subjects each (0.8%), and dyspnoea, reduced general condition, metastases to the central nervous system, and renal failure acute in 2 subjects each (0.5%) in the afatinib group, and neoplasm malignant in 3

subjects (1.5%) and dysphagia in 2 subjects (1.0%) in the placebo group. Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (14 subjects), rash/acne (7 subjects), vomiting (4 subjects), decreased appetite and nausea (3 subjects each), fatigue (2 subjects), abdominal pain, acute left ventricular failure, drug hypersensitivity, dysphagia, gingivitis, localised infection, neuralgia, oedema peripheral, pancreatitis acute, renal failure, SJS, and stomatitis (1 subject each) in the afatinib group, and pulmonary embolism (1 subject) in the placebo group.

4.(iv).(17) Foreign phase I study (Study 1200.6)
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out also occurred in all of the subjects (100%).

Serious adverse events were reported in 17 of 31 subjects (54.8%). The observed serious adverse events were febrile neutropenia in 6 subjects (19.4%), urinary tract infection in 2 subjects (6.5%), and dyspnoea, large intestinal obstruction, cardiac failure congestive, diarrhoea, small intestinal obstruction, dysphagia, gastrointestinal haemorrhage, abdominal pain, anaemia, ascites, confusional state, haematuria, pneumonia, pyrexia, rectal haemorrhage, renal failure, vena cava thrombosis, deep vein thrombosis, dehydration, hydronephrosis, and proctalgia in 1 subject each (3.2%). Among these events, a causal relationship with the investigational drug could not be ruled out for febrile neutropenia (4 subjects), and urinary tract infection, cardiac failure congestive, and diarrhoea (1 subject each).

Adverse events leading to discontinuation of the investigational drug were reported in 9 of 31 subjects (29.0%). The observed adverse events leading to discontinuation of the investigational drug were diarrhoea in 3 subjects (9.7%), and dyspnoea, large intestinal obstruction, atrial fibrillation, small intestinal obstruction, urinary retention, dysphagia, anaemia, confusional state, pneumonia, renal failure, and vena cava thrombosis in 1 subject each (3.2%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (3 subjects), and atrial fibrillation and urinary retention (1 subject each).

4.(iv).(18) Foreign phase I study (Study 1200.20)
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 37 of 40 subjects (92.5%).

Serious adverse events were reported in 21 of 40 subjects (52.5%). The observed serious adverse events were reduced general condition in 13 subjects (32.5%), neutropenia in 6 subjects (15.0%), pyrexia in 5 subjects (12.5%), neoplasm malignant in 4 subjects (10.0%), septic shock, diarrhoea, vomiting, dehydration, and cholangitis in 2 subjects each (5.0%), and pulmonary embolism, renal pain, urinary retention, infection, hypercalcaemia, anaemia, bronchitis, campylobacter intestinal infection, chills, deep vein thrombosis, dizziness, epilepsy, fatigue, grand mal convulsion, hypotension, syncope, ascites, decreased appetite, diverticulitis, febrile neutropenia, intestinal obstruction, rash/acne, dyspnoea, pleural effusion, and renal failure in 1 subject each (2.5%). Among these events, a causal relationship with the investigational drug could not be ruled out for neutropenia (6 subjects), diarrhoea (2 subjects), and pulmonary embolism, infection, anaemia, septic shock, decreased appetite, diverticulitis, febrile neutropenia, rash/acne, and vomiting (1 subject each).

Adverse events leading to discontinuation of the investigational drug were reported in 3 of 40 subjects (7.5%). The observed adverse events leading to discontinuation of the investigational drug were neutropenia in 1 subject, and dizziness, neoplasm malignant, syncope, renal failure,

and septic shock in 1 subject each (2.5%). Among these events, a causal relationship with the investigational drug could not be ruled out for neutropenia in 1 subject.

4.(iv).(19) Foreign phase I/II study (Study 1200.36)

4.(iv).(19).1) Phase I part

Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 29 of 33 subjects (87.9%).

Serious adverse events were reported in 12 of 32 subjects (37.5%). The observed serious adverse events were convulsion in 3 subjects (9.4%), haemorrhage intracranial and hemiparesis in 2 subjects each (6.3%), and delirium, aphasia, bacteraemia, brain oedema, cerebrovascular accident, deep vein thrombosis, diarrhoea, disease progression, fatigue, grand mal convulsion, headache, muscular weakness, nephrolithiasis, paralysis, pneumonia, pyelonephritis, respiratory distress, thrombosis, and urinary tract infection in 1 subject each (3.1%). Among these events, a causal relationship with the investigational drug could not be ruled out for haemorrhage intracranial, diarrhoea, and fatigue (1 subject each).

Adverse events leading to discontinuation of the investigational drug were reported in 13 of 32 subjects (40.6%). The observed adverse events leading to discontinuation of the investigational drug were convulsion, diarrhoea, fatigue, and hemiparesis in 2 subjects each (6.3%), and haemorrhage intracranial, thrombocytopenia, aphasia, bacteraemia, brain oedema, cerebrovascular accident, dehydration, disease progression, headache, mental status changes, muscular weakness, pancreatitis, paralysis, peroneal nerve palsy, pyelonephritis, rash/acne, respiratory distress, urinary tract infection, and vasogenic cerebral oedema in 1 subject each (3.1%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (2 subjects), and haemorrhage intracranial, thrombocytopenia, dehydration, fatigue, pancreatitis, and rash/acne (1 subject each).

4.(iv).(19).2) Phase II part

Adverse events were reported in 41 of 41 subjects (100%) in the afatinib group and 38 of 39 subjects (97.4%) in the afatinib/TMZ group, and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 35 of 41 subjects (85.4%) in the afatinib group and 36 of 39 subjects (92.3%) in the afatinib/TMZ group.

Serious adverse events were reported in 10 of 41 subjects (24.4%) in the afatinib group and 13 of 39 subjects (33.3%) in the afatinib/TMZ group. The observed serious adverse events were convulsion in 3 subjects (7.3%), mental status changes and neoplasm malignant in 2 subjects each (4.9%), cellulitis, anaemia, dysphagia, headache, hyponatraemia, muscular weakness, necrotizing fasciitis, neurological decompensation, palpitations, rash/acne, and spontaneous haematoma in 1 subject each (2.4%) in the afatinib group, and confusional state, dehydration, diarrhoea, thrombocytopenia, and vomiting in 2 subjects each (5.1%), and convulsion, neoplasm malignant, abdominal pain, acute prerenal failure, cellulitis, cerebral haemorrhage, cerebrovascular accident, cholecystitis, fatigue, febrile neutropenia, femoral neck fracture, reduced general condition, hemiparesis, respiratory failure, and somnolence in 1 subject each (2.6%) in the afatinib/TMZ group. Among these events, a causal relationship with the investigational drug could not be ruled out for rash/acne (1 subject) in the afatinib group and diarrhoea and vomiting (2 subjects each) and acute prerenal failure, cerebral haemorrhage, and dehydration (1 subject each) in the afatinib/TMZ group.

Adverse events leading to discontinuation of the investigational drug were reported in 8 of 41 subjects (19.5%) in the afatinib group and 15 of 39 subjects (38.5%) in the afatinib/TMZ group. The observed adverse events leading to discontinuation of the investigational drug were mental

status changes, muscular weakness, neoplasm malignant, and neurological decompensation in 2 subjects each (4.9%), and diarrhoea, rash/acne, confusional state, ataxia, gait disturbance, headache, memory impairment, speech disorder, and urinary incontinence in 1 subject each (2.4%) in the afatinib group and diarrhoea in 4 subjects (10.3%), dehydration, rash/acne, and thrombocytopenia in 2 subjects each (5.1%), and neoplasm malignant, balance disorder, cerebral haemorrhage, cholecystitis, confusional state, dysgeusia, fatigue, hemiparesis, hypersensitivity, nausea, oedema, urticaria, and vomiting in 1 subject each (2.6%) in the afatinib/TMZ group. Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea and rash/acne (1 subject each) in the afatinib group and diarrhoea (4 subjects), rash/acne and thrombocytopenia (2 subjects each), cerebral haemorrhage, dysgeusia, fatigue, hypersensitivity, nausea, oedema, urticaria, and vomiting (1 subject each) in the afatinib/TMZ group.

4.(iv).(20) Foreign phase III study (Study 1200.42)

Adverse events were reported in 1142 of 1154 subjects (99.0%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 1087 of 1154 subjects (94.2%). Adverse events with an incidence of ≥10% are as shown in the table below.

Adverse events with an incidence of ≥10%

Event	Number of subjects (%)	
	Afatinib group (N = 1154)	
	All Grades	Grade ≥3
All adverse events	1142 (99.0)	736 (63.8)
Diarrhoea	986 (85.4)	207 (17.9)
Rash/acne	809 (70.1)	125 (10.8)
Stomatitis	595 (51.6)	60 (5.2)
Nail abnormality	395 (34.2)	56 (4.9)
Fatigue	375 (32.5)	84 (7.3)
Decreased appetite	332 (28.8)	44 (3.8)
Nausea	267 (23.1)	16 (1.4)
Dyspnoea	265 (23.0)	96 (8.3)
Vomiting	231 (20.0)	27 (2.3)
Cough	216 (18.7)	12 (1.0)
Pruritus	182 (15.8)	8 (0.7)
Dry skin	164 (14.2)	1 (0.1)
Epistaxis	162 (14.0)	1 (0.1)
Eye disorder	141 (12.2)	6 (0.5)

Serious adverse events were reported in 485 of 1154 subjects (42.0%). Serious adverse events reported in ≥5 subjects were dyspnoea in 69 subjects (6.0%), diarrhoea in 62 subjects (5.4%), neoplasm malignant in 56 subjects (4.9%), reduced general condition and pleural effusion in 50 subjects each (4.3%), pneumonia in 42 subjects (3.6%), pulmonary embolism in 19 subjects (1.6%), dehydration and vomiting in 18 subjects each (1.6%), fatigue in 12 subjects (1.0%), decreased appetite in 11 subjects (1.0%), chest pain, pyrexia, and respiratory failure in 10 subjects each (0.9%), back pain, lung infection, nausea, and renal failure acute in 9 subjects each (0.8%), abdominal pain and interstitial lung disease in 8 subjects each (0.7%), acute respiratory distress syndrome, convulsion, haemoptysis, metastases to the central nervous system, and pneumothorax in 7 subjects each (0.6%), deep vein thrombosis, lower respiratory tract infection, and respiratory tract infection in 6 subjects each (0.5%), and ascites, disease progression, dizziness, sepsis, and stomatitis in 5 subjects each (0.4%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (60 subjects), vomiting (14 subjects), dehydration (12 subjects), interstitial lung disease and renal failure acute (8 subjects each), decreased appetite (7 subjects), dyspnoea (6 subjects), stomatitis (5 subjects), pneumonia (4 subjects), fatigue and nausea (3 subjects each), reduced general condition, pyrexia, and abdominal

pain (2 subjects each), and pulmonary embolism, deep vein thrombosis, and sepsis (1 subject each).

Adverse events leading to discontinuation of the investigational drug were reported in 304 of 1154 subjects (26.3%). Adverse events leading to discontinuation of the investigational drug reported in ≥5 subjects were diarrhoea in 57 subjects (4.9%), dyspnoea in 31 subjects (2.7%), fatigue and reduced general condition in 23 subjects each (2.0%), rash/acne in 17 subjects (1.5%), decreased appetite, pleural effusion, and vomiting in 12 subjects each (1.0%), stomatitis in 11 subjects (1.0%), pneumonia in 10 subjects (0.9%), interstitial lung disease in 9 subjects (0.8%), nail abnormality, neoplasm malignant, and pulmonary embolism in 6 subjects each (0.5%), and nausea in 5 subjects (0.4%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (57 subjects), rash/acne (17 subjects), fatigue (16 subjects), decreased appetite and stomatitis (11 subjects each), vomiting (10 subjects), interstitial lung disease (9 subjects), nail abnormality (6 subjects), nausea (4 subjects), dyspnoea and reduced general condition (3 subjects each), and pneumonia (2 subjects).

4.(iv).(21) Foreign phase I study (Study 1200.37)
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out also occurred in all of the subjects.

Serious adverse events were reported in 15 of 21 subjects (71.4%) in the afatinib/CDDP/5-FU group (in which afatinib, CDDP, and 5-FU were concomitantly administered) and 18 of 26 subjects (69.2%) in the afatinib/CDDP/PTX group (in which afatinib, CDDP, and PTX were concomitantly administered). Serious adverse events reported in ≥2 subjects in each group were decreased appetite in 10 subjects (47.6%), vomiting in 7 subjects (33.3%), nausea in 6 subjects (28.6%), diarrhoea in 5 subjects (23.8%), reduced general condition, dehydration, and fatigue in 2 (9.5%) subjects each in the afatinib/CDDP/5-FU group, and diarrhoea in 9 subjects (34.6%), renal failure and nausea in 5 subjects each (19.2%), fatigue and dehydration in 4 subjects each (15.4%), vomiting, febrile neutropenia, neutropenia, dyspnoea, pyrexia, and anaemia in 3 subjects each (11.5%), sepsis, abdominal pain, and decreased appetite in 2 subjects each (7.7%) in the afatinib/CDDP/PTX group. Among these events, a causal relationship with the investigational drug could not be ruled out for decreased appetite (10 subjects), diarrhoea (5 subjects), nausea and vomiting (5 subjects each), dehydration and fatigue (2 subjects each) in the afatinib/CDDP/5-FU group, and diarrhoea (8 subjects), renal failure (5 subjects), nausea and dehydration (4 subjects each), vomiting, febrile neutropenia, neutropenia, and fatigue (3 subjects each), pyrexia and anaemia (2 subjects each), abdominal pain, decreased appetite, and dyspnoea (1 subject each) in the afatinib/CDDP/PTX group.

Adverse events leading to discontinuation of the investigational drug were reported in 10 of 21 subjects (47.6%) in the afatinib/CDDP/5-FU group and 10 of 26 subjects (38.5%) in the afatinib/CDDP/PTX group. The observed adverse events leading to discontinuation of the investigational drug were decreased appetite in 4 subjects (19.0%), nausea in 3 subjects (14.3%), vomiting and reduced general condition in 2 subjects each (9.5%), anaemia, rash/acne, ejection fraction decreased, flushing, hypokalaemia, hypomagnesaemia, diarrhoea, blood creatinine increased, dehydration, fatigue, peripheral motor neuropathy, and stomatitis in 1 subject each (4.8%) in the afatinib/CDDP/5-FU group, and fatigue in 3 subjects, diarrhoea in 2 subjects, duodenal obstruction, sepsis, vomiting, nausea, ALT increased, anaemia, AST increased, blood ALP increased, blood LDH increased, dyspnoea, gamma-glutamyltransferase increased, neutropenia, rash/acne, thrombocytopenia, acute pulmonary oedema, acute respiratory distress syndrome, atrial fibrillation, neurotoxicity, and febrile neutropenia in 1 subject each in the afatinib/CDDP/PTX group. Among these events, a causal relationship with the investigational drug could not be ruled out for decreased appetite (4 subjects), nausea (2 subjects), rash/acne, ejection fraction decreased, flushing, diarrhoea, blood creatinine increased, dehydration, fatigue,

peripheral motor neuropathy, and stomatitis (1 subject each) in the afatinib/CDDP/5-FU group, and fatigue (3 subjects), nausea, ALT increased, AST increased, blood ALP increased, blood LDH increased, gamma-glutamyltransferase increased, neutropenia, rash/acne, diarrhoea, acute pulmonary oedema, acute respiratory distress syndrome, atrial fibrillation, neurotoxicity, and febrile neutropenia (1 subject each) in the afatinib/CDDP/PTX group.

4.(iv).(22) Foreign phase I study (Study 1200.68)
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 17 of 18 subjects (94.4%).

Serious adverse events were reported in 3 of 18 subjects (16.7%). The observed serious adverse events were diarrhoea, pulmonary embolism, and renal failure acute in 1 subject each (5.6%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea in 1 subject.

Adverse events leading to discontinuation of the investigational drug were reported in 7 of 18 subjects (38.9%). The observed adverse events leading to discontinuation of the investigational drug were diarrhoea in 4 subjects (22.2%), ejection fraction decreased in 2 subjects (11.1%), and pulmonary embolism in 1 subject (5.6%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea in 4 subjects and ejection fraction decreased in 2 subjects.

4.(iv).(23) Foreign phase II study (Study 1239.1)
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 25 of 28 subjects (89.3%).

Serious adverse events were reported in 8 of 28 subjects (28.6%). The observed serious adverse events were dehydration in 3 subjects (10.7%), nausea, AST increased, and mental status changes in 2 subjects each (7.1%), and accidental overdose, anaemia, fatigue, hypokalaemia, neoplasm malignant, pain, pericardial effusion, vomiting, ALT increased, diarrhoea, and peritonitis bacterial in 1 (3.8%) subject each. Among these events, a causal relationship with the investigational drug could not be ruled out for dehydration (2 subjects), and hypokalaemia, nausea, ALT increased, AST increased, and diarrhoea (1 subject each).

Adverse events leading to discontinuation of the investigational drug were reported in 12 of 28 subjects (42.9%). The observed adverse events leading to discontinuation of the investigational drug were nausea, ALT increased, AST increased, and diarrhoea in 4 subjects each (14.3%), fatigue, vomiting, and dehydration in 2 subjects each (7.1%), decreased appetite, dysphagia, lymphadenopathy, posterior reversible encephalopathy syndrome, blood magnesium decreased, hypokalaemia, hypophosphataemia, hypotension, and hypovolaemia each in 1 subject (3.8%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (4 subjects), nausea, ALT increased, and AST increased (3 subjects each), dehydration (2 subjects), decreased appetite, fatigue, vomiting, blood magnesium decreased, hypokalaemia, hypophosphataemia, hypotension, and hypovolaemia (1 subject each).

4.(iv).(24) Foreign phase II study (Study 1239.2)
Adverse events occurred in all (100%) of the subjects, and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 42 of 46 subjects (91.3%).

Serious adverse events were reported in 22 of 46 subjects (47.8%). The observed serious adverse events were fatigue in 5 subjects (10.9%), vomiting and reduced general condition in 4 subjects each (8.7%), diarrhoea in 3 subjects (6.5%), pyrexia, dehydration, jaundice, neoplasm malignant, pain in extremity, and renal failure in 2 (4.3%) subjects each, and dyspnoea, subileus, abdominal pain, arthralgia, ascites, bladder dilatation, cardio-respiratory arrest, cholestasis, circulatory collapse, convulsion, decreased appetite, electrolyte imbalance, female genital tract fistula, gastrointestinal obstruction, haematemesis, hepatitis, hypercreatininaemia, hypokalaemia, intestinal obstruction, nausea, neoplasm progression, oedema peripheral, paraplegia, pelvic pain, portal vein thrombosis, prostatic adenoma, pruritus, pulmonary haemorrhage, purpura, renal function disorder, respiratory distress, small intestinal obstruction, urinary retention, weight decreased, anaemia, dyspnoea, epistaxis, fatigue, gamma-glutamyltransferase increased, malnutrition, pain, pyrexia, rectal haemorrhage, respiratory failure, subileus, and thrombocytopenia in 1 subject each (2.2%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (3 subjects), fatigue (2 subjects), arthralgia, hypercreatininaemia, nausea, pain in extremity, purpura, pyrexia, renal failure, vomiting, epistaxis, gamma-glutamyltransferase increased, and rectal haemorrhage (1 subject each).

Adverse events leading to discontinuation of the investigational drug were reported in 15 of 46 subjects (32.6%). The observed adverse events leading to discontinuation of the investigational drug were diarrhoea in 4 subjects (8.7%), fatigue in 3 subjects (6.5%), ascites, AST increased, convulsion, dyspnoea, electrolyte imbalance, hepatitis, jaundice, neoplasm malignant, oedema peripheral, pain in extremity, pulmonary haemorrhage, renal failure, subileus, vomiting, and reduced general condition in 1 subject each (2.2%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (4 subjects), and AST increased and fatigue (1 subject each).

4.(iv).(25) Foreign phase II study (Study 1239.3)
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 38 of 39 subjects (97.4%).

Serious adverse events were reported in 6 of 39 subjects (15.4%). The observed serious adverse events were pain in extremity, prostate cancer, prostate cancer metastatic, spinal cord compression, death, muscular weakness, pancytopenia, cauda equina syndrome, and spinal cord compression in 1 subject each (2.6%). Among these events, a causal relationship with the investigational drug could not be ruled out for pancytopenia in 1 subject.

Adverse events leading to discontinuation of the investigational drug were reported in 11 of 39 subjects (28.2%). The observed adverse events leading to discontinuation of the investigational drug were diarrhoea in 5 subjects (12.9%), rash/acne in 3 subjects (7.7%), stomatitis and decreased appetite in 2 subjects each (5.1%), depression, dyspnoea, renal function disorder, ageusia, dry skin, mucosal haemorrhage, muscular weakness, nasal inflammation, nasal mucosal disorder, spinal cord compression, stomatitis, dysgeusia, and fatigue in 1 subject each (2.6%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea in 5 subjects (12.9%), rash/acne in 3 subjects (7.7%), stomatitis and decreased appetite in 2 subjects each (5.1%), ageusia, dry skin, mucosal haemorrhage, nasal inflammation, nasal mucosal disorder, dysgeusia, and fatigue in 1 subject each (2.6%).

4.(iv).(26) Foreign phase III study (Study 1200.34)
Adverse events were reported in 239 of 239 subjects (100%) in the afatinib group and 112 of 113 subjects (99.1%) in the CDDP/GEM group, and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 236 of 239 subjects (98.7%)

in the afatinib group and 112 of 113 subjects (99.1%) in the CDDP/GEM group. Adverse events with an incidence of ≥10% in the afatinib group are as shown in the table below.

Adverse events with an incidence of ≥10% in the afatinib group

Event	Number of subjects (%)			
	Afatinib group (N = 239)		CDDP/GEM group (N = 113)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	239 (100)	112 (46.9)	112 (99.1)	70 (61.9)
Diarrhoea	214 (89.5)	14 (5.9)	17 (15.0)	0
Rash/acne	193 (80.8)	35 (14.6)	11 (9.7)	0
Stomatitis	125 (52.3)	13 (5.4)	6 (5.3)	0
Nail abnormality	82 (34.3)	0	0	0
ALT increased	55 (23.0)	5 (2.1)	18 (15.9)	3 (2.7)
AST increased	43 (18.0)	1 (0.4)	12 (10.6)	2 (1.8)
Cough	42 (17.6)	0	8 (7.1)	0
Fatigue	41 (17.2)	5 (2.1)	44 (38.9)	1 (0.9)
Decreased appetite	37 (15.5)	6 (2.5)	48 (42.5)	2 (1.8)
Epistaxis	36 (15.1)	1 (0.4)	2 (1.8)	0
Vomiting	32 (13.4)	3 (1.3)	91 (80.5)	23 (20.4)
Weight decreased	30 (12.6)	0	6 (5.3)	0
Back pain	28 (11.7)	1 (0.4)	9 (8.0)	0
Headache	28 (11.7)	3 (1.3)	8 (7.1)	0
Nausea	28 (11.7)	1 (0.4)	85 (75.2)	9 (8.0)
Hypokalaemia	27 (11.3)	11 (4.6)	26 (23.0)	13 (11.5)
Pruritus	27 (11.3)	1 (0.4)	0	0
Chest pain	25 (10.5)	0	8 (7.1)	0

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Serious adverse events were reported in 36 of 239 subjects (15.1%) in the afatinib group and 12 of 113 subjects (10.6%) in the CDDP/GEM group. Serious adverse events reported in ≥3 subjects in each group were respiratory failure in 5 subjects (2.1%), dyspnoea in 4 subjects (1.7%), headache and rash/acne in 3 subjects each (1.3%) in the afatinib group and thrombocytopenia in 2 subjects (1.8%) in the CDDP/GEM group. Among these events, a causal relationship with the investigational drug could not be ruled out for rash/acne in 3 subjects and headache and dyspnoea in 1 subject each in the afatinib group and thrombocytopenia in 2 subjects in the CDDP/GEM group.

Adverse events leading to discontinuation of the investigational drug were reported in 23 of 239 subjects (9.6%) in the afatinib group and 45 of 113 subjects (39.8%) in the CDDP/GEM group. Adverse events leading to discontinuation of the investigational drug reported in ≥3 subjects were rash/acne in 5 subjects (2.1%) in the afatinib group, and vomiting in 16 subjects (14.2%), nausea in 11 subjects (9.7%), neutropenia in 10 subjects (8.8%), leukopenia in 8 subjects (7.1%), fatigue in 5 subjects (4.4%), anaemia and thrombocytopenia in 4 subjects each (3.5%), and platelet count decreased in 3 subjects (2.7%) in the CDDP/GEM group. Among these events, a causal relationship with the investigational drug could not be ruled out for rash/acne (5 subjects) in the afatinib group and vomiting (16 subjects), nausea (11 subjects), neutropenia (10 subjects), leukopenia (8 subjects), fatigue, anaemia, and thrombocytopenia (4 subjects each), platelet count decreased (3 subjects), and white blood cell count decreased (2 subjects) in the CDDP/GEM group.

4.(iv).(27) Foreign phase II study (Study 1200.40)

Adverse events were reported in 69 of 70 subjects (98.6%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 64 of 70 subjects (91.4%).

Serious adverse events were reported in 33 of 70 subjects (47.1%). Serious adverse events

reported in ≥2 subjects were diarrhoea and neoplasm malignant in 4 (5.7%) subjects each, death, dyspnoea, and pleural effusion in 3 subjects each (4.3%), and dehydration, renal failure acute, and respiratory failure in 2 subjects each (2.9%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (4 subjects) and dehydration (1 subject).

Adverse events leading to discontinuation of the investigational drug were reported in 25 of 70 subjects (35.7%). Adverse events leading to discontinuation of the investigational drug reported in ≥2 subjects were diarrhoea and rash/acne in 6 subjects each (8.6%), fatigue in 3 subjects (4.3%), and decreased appetite, neoplasm malignant, respiratory failure, and vomiting in 2 subjects each (2.9%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (6 subjects), rash/acne (5 subjects), fatigue and vomiting (2 subjects each).

4.(iv).(28) Foreign phase II study (Study 1200.72)
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 38 of 42 subjects (90.5%).

Serious adverse events were reported in 17 of 42 subjects (40.5%). The observed serious adverse events were pneumonia in 5 subjects (11.9%), febrile neutropenia and pleural effusion in 2 subjects each (4.8%), and blood creatinine increased, dyspnoea, gastrointestinal obstruction, haemoptysis, headache, melaena, muscular weakness, musculoskeletal pain, myalgia, pneumonia aspiration, pneumothorax, pulmonary embolism, pyrexia, and vomiting in 1 subject each (2.4%). A causal relationship with the investigational drug was ruled out for all of these events.

Adverse events leading to discontinuation of the investigational drug were reported in 7 of 42 subjects (16.7%). The observed adverse events leading to discontinuation of the investigational drug were pneumonia in 2 subjects (4.8%), and decreased appetite, gastrointestinal obstruction, haemoptysis, nail abnormality, pulmonary embolism, rash/acne, and stomatitis in 1 subject each (2.4%). Among these events, a causal relationship with the investigational drug could not be ruled out for decreased appetite, nail abnormality, rash/acne, and stomatitis (1 subject each).

4.(iv).(29) Foreign phase II study (Study 1200.26)
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 19 of 20 subjects (95.0%).

Serious adverse events were reported in 6 of 20 subjects (30.0%). The observed serious adverse events were dyspnoea and neoplasm malignant in 2 subjects each (10.0%), and dehydration, diarrhoea, escherichia bacteraemia, female genital tract fistula, and pleural effusion in 1 subject each (5.0%). Among these events, a causal relationship with the investigational drug could not be ruled out for dehydration, diarrhoea, and dyspnoea (1 subject each).

Adverse events leading to discontinuation of the investigational drug were reported in 5 of 20 subjects (25.0%). The observed adverse events leading to discontinuation of the investigational drug were AST increased, blood ALP increased, blood creatinine increased, fatigue, female genital tract fistula, haematuria, hyperbilirubinaemia, neoplasm malignant, and weight decreased in 1 subject each (5.0%). Among these events, a causal relationship with the investigational drug could not be ruled out for AST increased, blood ALP increased, blood creatinine increased, fatigue, haematuria, hyperbilirubinaemia, and weight decreased (1 subject each).

4.(iv).(30) Foreign phase II study (Study 1200.10)
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 48 of 50 subjects (96.0%).

Serious adverse events were reported in 20 of 50 subjects (40.0%). Serious adverse events reported in ≥2 subjects were diarrhoea and reduced general condition in 5 (10.0%) subjects each, neoplasm malignant in 4 subjects (8.0%), dehydration in 3 subjects (6.0%), and nausea and vomiting in 2 subjects (4.0%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (5 subjects), dehydration (3 subjects), nausea (2 subjects), and reduced general condition and vomiting (1 subject each).

Adverse events leading to discontinuation of the investigational drug were reported in 23 of 50 subjects (46.0%). Adverse events leading to discontinuation of the investigational drug reported in ≥2 subjects were diarrhoea in 12 subjects (24.0%), rash/acne in 7 subjects each (14.0%), stomatitis and vomiting in 5 subjects each (10.0%), nausea in 4 subjects (8.0%), reduced general condition in 3 subjects (6.0%), and dysphagia, fatigue, hypokalaemia, and neoplasm malignant in 2 subjects each (4.0%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (12 subjects), rash/acne (7 subjects), stomatitis and vomiting (5 subjects each), nausea (4 subjects), and dysphagia, fatigue, reduced general condition, and hypokalaemia (2 subjects each).

4.(iv).(31) Foreign phase II study (Study 1200.11)
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 40 of 41 subjects (97.6%).

Serious adverse events were reported in 8 of 41 subjects (19.5%). The observed serious adverse events were vomiting in 3 subjects (7.3%), dehydration, nausea, and neoplasm malignant in 2 subjects each (4.9%), and asthma, biliary colic, constipation, diarrhoea, diarrhoea infectious, dyspnoea, headache, hyponatraemia, prothrombin-international normalized ratio decreased, and leukocytoclastic vasculitis in 1 subject each (2.4%). Among these events, a causal relationship with the investigational drug could not be ruled out for dehydration and vomiting (2 subjects each), and diarrhoea, hyponatraemia, and leukocytoclastic vasculitis (1 subject each).

Adverse events leading to discontinuation of the investigational drug were reported in 10 of 41 subjects (24.4%). The observed adverse events leading to discontinuation of the investigational drug were diarrhoea in 4 subjects (9.8%), rash/acne in 2 subjects (4.9%), hyponatraemia, leukocytoclastic vasculitis, nausea, neoplasm malignant, stomatitis, and vomiting in 1 subject each (2.4%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (4 subjects), rash/acne (2 subjects), and hyponatraemia, leukocytoclastic vasculitis, nausea, stomatitis, and vomiting (1 subject each).

4.(iv).(32) Foreign phase II study (Study 1200.44)
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out also occurred in all of the subjects (100%).

No serious adverse events occurred.

Adverse events leading to discontinuation of the investigational drug were reported in 1 of 10 subjects (10.0%). The observed adverse events leading to discontinuation of the investigational

drug were rash/acne in 1 subject (10.0%). A causal relationship with the investigational drug could not be ruled out for this event.

4.(iv).(33) Foreign phase II study (Study 1200.5)
Adverse events occurred in all of the subjects (100%), and adverse events for which a causal relationship with the investigational drug could not be ruled out also occurred in all of the subjects (100%).

Serious adverse events were reported in 9 of 28 subjects (32.1%). The observed serious adverse events were dehydration and vomiting in 2 subjects each (7.1%), and arthralgia, depression, fatigue, mood altered, nausea, neoplasm malignant, neoplasm progression, pain in extremity, spinal disorder, arthritis bacterial, diarrhoea, disseminated intravascular coagulation, jugular vein thrombosis, obstruction, oedema peripheral, pneumococcal sepsis, post procedural sepsis, renal failure acute, stomatitis, erysipelas, melanocytic naevus, and sinusitis in 1 subject each (3.8%). Among these events, a causal relationship with the investigational drug could not be ruled out for dehydration (2 subjects), and fatigue, nausea, arthritis bacterial, diarrhoea, pneumococcal sepsis, renal failure acute, stomatitis, and vomiting (1 subject each).

Adverse events leading to discontinuation of the investigational drug were reported in 14 of 28 subjects (50.0%). The observed adverse events leading to discontinuation of the investigational drug were diarrhoea in 8 subjects (28.6%), rash/acne and fatigue in 4 subjects (14.3%), stomatitis in 3 subjects (10.7%), dehydration, nausea, neoplasm malignant, and nail abnormality in 2 subjects each (7.1%), and arthritis bacterial, disseminated intravascular coagulation, lip disorder, pneumococcal sepsis, renal failure acute, vomiting, and cystitis in 1 subject each (3.8%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (8 subjects), rash/acne (4 subjects), fatigue and stomatitis (3 subjects each), dehydration and nail abnormality (2 subjects each), nausea, arthritis bacterial, lip disorder, pneumococcal sepsis, renal failure acute, vomiting, and cystitis (1 subject each).

4.(iv).(34) Foreign phase II study (Study 1200.74)
Adverse events were reported in 75 of 77 subjects (97.4%), and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 71 of 77 subjects (92.2%).

Serious adverse events were reported in 31 of 77 subjects (40.3%). Serious adverse events reported in ≥2 subjects were nausea in 8 subjects (10.4%), vomiting in 7 subjects (9.1%), diarrhoea and disease progression in 6 subjects each (7.8%), dehydration in 4 subjects (5.2%), dyspnoea in 3 subjects (3.9%), and abdominal pain, fatigue, neoplasm progression, pneumonia, pyrexia, and rash/acne in 2 subjects each (2.6%). Among these events, a causal relationship with the investigational drug could not be ruled out for vomiting (6 subjects), diarrhoea and nausea (4 subjects each), abdominal pain, dehydration, dyspnoea, and rash/acne (2 subjects each), and fatigue (1 subject).

Adverse events leading to discontinuation of the investigational drug were reported in 15 of 77 subjects (19.5%). Adverse events leading to discontinuation of the investigational drug reported in ≥2 subjects were diarrhoea in 6 subjects (7.8%), fatigue in 3 subjects (3.9%), and dyspnoea and vomiting in 2 subjects (2.6%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (6 subjects), fatigue (3 subjects), vomiting (2 subjects), and dyspnoea (1 subject).

4.(iv).(35) Foreign phase II study (Study 1200.28)
Adverse events occurred in all (100%) of the subjects, and adverse events for which a causal relationship with the investigational drug could not be ruled out were reported in 90 of 97 subjects (92.8%).

Serious adverse events reported in 56 of 97 subjects (57.7%). Serious adverse events reported in ≥2 subjects were reduced general condition in 13 subjects (13.4%), diarrhoea in 11 subjects (11.3%), dehydration in 8 subjects (8.2%), dysphagia in 6 subjects (6.2%), dyspnoea and pneumonia in 5 subjects each (5.2%), malnutrition, pneumonia aspiration, and renal failure acute in 4 subjects each (4.1%), fatigue, renal failure, respiratory failure, and vomiting in 3 subjects each (3.1%), and anaemia, cardiopulmonary failure, decreased appetite, haemorrhage, hypercalcaemia, hypernatraemia, hypotension, mouth haemorrhage, pain, pleural effusion, post procedural haemorrhage, pyrexia, rash/acne, stomatitis, and tumor haemorrhage in 2 subjects each (2.1%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (10 subjects); dehydration (7 subjects); reduced general condition, renal failure, and renal failure acute (3 subjects each); dysphagia, rash/acne, and stomatitis (2 subjects each); and cardiopulmonary failure, decreased appetite, hypernatraemia, hypotension, malnutrition, and pyrexia (1 subject each).

Adverse events leading to discontinuation of the investigational drug were reported in 33 of 97 subjects (34.0%). Adverse events leading to discontinuation of the investigational drug reported in ≥2 subjects were diarrhoea in 6 subjects (6.2%), reduced general condition in 5 subjects (5.2%), dysphagia and stomatitis in 4 subjects each (4.1%), decreased appetite and rash/acne in 3 subjects each (3.1%), and anaemia, dehydration, dyspnoea, fatigue, malnutrition, pneumonia, and tumor haemorrhage in 2 subjects each (2.1%). Among these events, a causal relationship with the investigational drug could not be ruled out for diarrhoea (6 subjects); rash/acne (3 subjects); decreased appetite, dysphagia, fatigue, and stomatitis (2 subjects each); and anaemia, dehydration, and reduced general condition (1 subject each).

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

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

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

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

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.3.2-9, 5.3.5.2-1, 5.3.5.1-1). As a result, the following irregularities were revealed in some clinical trial sites: (i) protocol deviations (enrollment of subjects who met the exclusion criteria); (ii) a clinical research coordinator who provided patients with supplementary information failed to fill in the date and his or her seal/name or signature in the informed consent form. Although the inspection revealed these irregularities that should be corrected, the data from the relevant patients were appropriately handled. PMDA therefore concluded that the clinical studies had been conducted generally in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted product application documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of afatinib in treating *EGFR* mutation-positive inoperable or recurrent NSNLC has been demonstrated, and the safety of afatinib is acceptable in view of its observed benefits. Afatinib is a drug with a new active ingredient considered to inhibit phosphorylation of tyrosine kinases including EGFR, HER2, and HER4, resulting in inhibition of tumor growth, and has a clinical significance as a treatment option for patients with *EGFR* mutation-positive inoperable or recurrent NSNLC. The indication, dosage and administration, and post-marketing investigation of afatinib will be further discussed at the Expert Discussion.

PMDA considers that afatinib may be approved if the drug is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

October 31, 2013

I. Product Submitted for Registration

[Brand name]	Giotrif Tablets 20 mg, 30 mg, 40 mg, and 50 mg
[Non-proprietary name]	Afatinib Maleate
[Name of applicant]	Nippon Boehringer Ingelheim Co., Ltd.
[Date of application]	November 30, 2012

II. Content of the Review

The outline of the comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions, etc., by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

As a result of the review described in "4.(iii).B.(2) Efficacy" of the Review Report (1), PMDA has concluded that afatinib maleate (hereinafter referred to as afatinib) showed efficacy in chemotherapy-naive patients with epidermal growth factor receptor (EGFR) mutation-positive inoperable or recurrent non-small cell lung cancer (NSCLC), because the global phase III study (Study 1200.32) conducted in this patient population demonstrated the superiority of afatinib to the combination of cisplatin and pemetrexed sodium hydrate (CDDP/PEM), the control agents, in the primary endpoint of progression-free survival (PFS) assessed by the Independent Review Committee.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- In Study 1200.32, afatinib prolonged the median PFS by 4.24 months with the hazard ratio (95% confidence interval [CI]) of 0.577 [0.425, 0.784], but the hazard ratio [95% CI] of the median overall survival (OS) was 0.907 [0.660, 1.246], with almost no difference between the 2 groups. To discuss the cause for the failure in demonstrating the efficacy in the OS, the details of post-treatment should be provided.

Details of post-treatment after discontinuation of the study treatment in Study 1200.32 are as shown below (data cut-off on January 21, 2013).

Details of post-treatment after discontinuation of the study treatment (ITT population, data cut-off on January 21, 2013)

	Afatinib group Number of subjects (%)	CDDP/PEM group Number of subjects (%)
Number of subjects	230	115
Patients who underwent post-treatment	149 (76.0)	99 (86.1)
Antineoplastic drugs	145 (74.0)	99 (86.1)
EGFR-TKIs	68 (34.7)	83 (72.2)
Erlotinib hydrochloride monotherapy	50 (25.5)	49 (42.6)
Gefitinib monotherapy	24 (12.2)	46 (40.0)
Afatinib monotherapy	0	7 (6.1)*
Combination therapy including erlotinib hydrochloride	2 (1.0)	7 (6.1)
Combination therapy including gefitinib	0	2 (1.7)
Treatment without EGFR-TKIs	130 (66.3)	50 (43.5)
Combination therapy with cytotoxic antineoplastic drugs including platinum antineoplastic drugs	100 (51.0)	15 (13.0)
Monotherapy with a cytotoxic antineoplastic drug	64 (32.7)	38 (33.0)
Combination therapy with cytotoxic antineoplastic drugs including platinum antineoplastic drugs + Bev	22 (11.2)	0
Combination therapy with cytotoxic antineoplastic drugs + Bev	5 (2.6)	1 (0.9)
Combination therapy with other antineoplastic drugs	3 (1.5)	4 (3.5)
Others	3 (1.5)	5 (4.3)
Radiation therapy	25 (12.8)	16 (13.9)

EGFR-TKI, EGFR tyrosine kinase inhibitor; Bev, Bevacizumab (recombinant).
* Afatinib was administered under the named-patient use programme

Taking account of comments raised in the Expert Discussion, PMDA instructed the applicant to provide the information about the above post-treatment using materials, and the applicant accepted it.

(2) Safety

As a result of the review described in "4.(iii).B.(3) Safety" of the Review Report (1), PMDA has concluded that adverse events requiring attention during the treatment with afatinib were interstitial lung disease, liver disorder, diarrhoea, rash/acne (including Stevens-Johnson syndrome), stomatitis, nail abnormality (including paronychia), eye disorder (keratitis), cardiac failure, gastrointestinal perforation (including severe gastrointestinal ulcer/haemorrhage of digestive tract), and pancreatitis acute.

PMDA has concluded that although attention should be paid to the occurrence of these adverse events during use of afatinib, the drug is tolerable if it is used properly and safety measures (e.g., monitoring and management of adverse events as well as the treatment interruption, discontinuation, or dose reduction) are taken by physicians with sufficient knowledge and experience of cancer chemotherapy.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- In patients receiving approved EGFR tyrosine kinase inhibitors (EGFR-TKIs) (gefitinib and erlotinib hydrochloride), it is important to ensure early diagnosis and treatment of interstitial lung disease. Therefore, during the initial phase of treatment, patients are hospitalized or receive equivalent care to be monitored for adverse drug reactions. Healthcare professionals should be informed of this and thoroughly cautioned about interstitial lung disease associated

with afatinib, in the same manner as they are cautioned about the disease associated with the approved EGFR-TKIs.

Taking account of comments raised in the Expert Discussion, PMDA instructed the applicant to provide the above cautions, and the applicant accepted it.

(3) Clinical positioning and indication

As a result of the review described in "4.(iii).B.(4) Clinical positioning and indication" of the Review Report (1), PMDA has concluded that afatinib is positioned as a treatment option for patients with *EGFR* mutation-positive inoperable or recurrent NSCLC who have not received chemotherapy, and thus that afatinib should be indicated for "*EGFR* mutation-positive inoperable or recurrent NSNLC," with the following precautionary statements in the "Precautions for Indications" section.

- An *EGFR* mutation test should be performed. Afatinib should be administered referring to the latest information such as the "Lung Cancer Clinical Practice Guidelines" issued by the Japan Lung Cancer Society, including how to handle patients with unknown *EGFR* mutation.
- The efficacy and safety of afatinib used in adjuvant chemotherapy have not been established.
- The eligibility of a patient should be determined by physicians who are familiar with the applicable history of cancer chemotherapy presented in the "Clinical Studies" section and thoroughly understand the efficacy and safety of afatinib.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion. The following comments were raised from the expert advisors:

- In Study 1200.32, the therapeutic effect was reversed in patients with inoperable or recurrent NSCLC who had *EGFR* mutation other than deletion mutation in Exon 19 (Del 19) or point mutation in Exon 21 (L858R) [see "4.(iii).B.(4).5) EGFR mutation types" of Review Report (1)]. In addition to this finding, the event occurred in 81% of the patients, and the therapeutic effect in patients with Del 19 was comparable to that in patients with L858R, suggesting an interaction between the therapeutic effect and *EGFR* mutation type, although the applicable patients were limited. The data by *EGFR* mutation type therefore should be provided.

PMDA considers as follows:

It is difficult to evaluate the efficacy of afatinib in patients with NSCLC positive for *EGFR* mutations other than Del 19 or L858R who participated in Study 1200.32, because very few patients had such mutations. The *EGFR* mutation types applicable to afatinib therapy should be determined based on the latest information such as the "Lung Cancer Clinical Practice Guidelines" issued by the Japan Lung Cancer Society [see "4.(iii).B.(4).5) EGFR mutation types" of Review Report (1)]. Furthermore, in light of the discussion at the Expert Discussion, it is appropriate to determine whether or not to administer afatinib based on the results by *EGFR* mutation type in Study 1200.32; the results should therefore be provided to healthcare professionals.

Based on the above, PMDA instructed the applicant to include data on PFS by *EGFR* mutation type in Study 1200.32 in the "Clinical Studies" section in the package insert, and to include the following statements in the Indication section and the "Precautions for Indications" section. The applicant accepted the instruction.

[Indication]

EGFR mutation-positive inoperable or recurrent non-small cell lung cancer

[Precautions for Indications]

- An *EGFR* mutation test should be performed. Afatinib should be administered referring to the latest information such as the "Lung Cancer Clinical Practice Guidelines" issued by the Japan

Lung Cancer Society, including how to handle patients with unknown *EGFR* mutation.
- The efficacy and safety of afatinib used in adjuvant chemotherapy have not been established.
- The eligibility of a patient should be determined by physicians who are familiar with the applicable history of cancer chemotherapy presented in the "Clinical Studies" section and thoroughly understand the efficacy and safety of afatinib.

(4) Dosage and administration

As a result of the review in "4.(iii).B.(5) Dosage and administration" of the Review Report (1), PMDA concluded that the dosage and administration of afatinib should be set as follows: "The usual adult dosage is 40 mg of afatinib orally administered once daily in the fasted state. The dose may be adjusted according to the conditions of the patient as appropriate. The dose may be increased up to 50 mg once daily." Furthermore, the following information should be included in the "Precautions for Dosage and Administration" section of the package insert:

- Dose adjustment criteria based on the criteria used in Study 1200.32.
- It is reported that C_{max} and AUC decrease after administration of afatinib in the fed state. Afatinib should not be administered between 1 hour before and 3 hours after a meal to avoid food effect.
- The efficacy and safety of the combination therapy of afatinib with other antineoplastic drugs have not been established.

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

Based on the above, PMDA instructed the applicant to use the following wording for the sections of "Dosage and Administration" and "Precautions for Dosage and Administration". The applicant accepted the instruction.

[Dosage and Administration]

The usual adult dosage is 40 mg of afatinib orally administered once daily in the fasted state. The dose may be adjusted according to the conditions of the patient as appropriate. The dose may be increased up to 50 mg once daily.

[Precautions for Dosage and Administration]

- If an adverse drug reaction occurs, the dose of afatinib should be reduced or treatment with afatinib should be interrupted or discontinued according to its symptom and severity and in consideration of the following criteria.

Grade of adverse drug reaction[Note 1)]	Criteria for treatment interruption and dose reduction
Grade 1 or 2	Maintain the same dose.
Grade 2 (persistent symptom[Note 2)] or intolerable) or Grade ≥3	Interrupt afatinib until the symptom improved to Grade ≤1. Resume afatinib after recovery by decreasing 10 mg from the previous dose.[Note 3), 4)]

Note 1) Grade is in accordance with NCI-CTCAE 3.0.
Note 2) Diarrhoea for >48 hours or skin disorder for >7 days
Note 3) If afatinib is not tolerable at a dose of 20 mg once daily, treatment discontinuation should be considered.
Note 4) The dose should not be increased once it has been reduced.

- The dose may be increased to 50 mg once daily in patients who have continued the once-daily treatment at a dose of 40 mg for ≥3 weeks without diarrhoea, skin disorder, stomatitis, or other adverse drug reactions of Grade ≥2.
- It is reported that C_{max} and AUC decrease after administration of afatinib in the fed state. Afatinib should not be administered between 1 hour before and 3 hours after a meal to avoid food effect.

- The efficacy and safety of the combination therapy of afatinib with other antineoplastic drugs have not been established.

(5) Risk management plan (draft)
In order to verify the safety of afatinib in routine clinical use, the applicant plans to conduct a post-marketing surveillance in patients with *EGFR* mutation-positive inoperable or recurrent NSCLC who have received afatinib, using a surveillance that enrolls patients sequentially, with a sample size for analysis of 800 patients and a 12-month follow-up period. The proposed priority investigation items for the post-marketing surveillance include diarrhoea, rash/acne, nail abnormality, and interstitial lung disease [see "4.(iii).B.(6) Post-marketing investigations" of Review Report (1)].

As a result of its review described in "4.(iii).B.(6) Post-marketing investigations" of the Review Report (1), PMDA concluded that the post-marketing surveillance should be conducted to collect safety information under routine use of afatinib in Japan. In addition, PMDA concluded that the planned sample size for the surveillance should be reconsidered so that the risk of interstitial lung disease can also be estimated at a certain precision, because the incidence of this event following treatment with afatinib and approved EGFR-TKIs was higher in Japanese patients than in non-Japanese patients.

At the Expert Discussion, the above conclusion of PMDA was supported by the expert advisors including the decision that the post-marketing surveillance would not include all patients who have received afatinib (i.e., all-case surveillance will not be conducted). The following comments were raised by expert advisors.

- In Study 1200.32, the incidence of interstitial lung disease-like events in Japanese patients was higher than that in non-Japanese patients, and severe diarrhoea, skin disorder, liver disorder, and peptic ulcer/haemorrhage of digestive tract occurred. An all-case surveillance may therefore be an option. However, in light of the following points, the omission of all-case surveillance is acceptable.
  - Experience with approved EGFR-TKIs in Japanese NSCLC patients has been accumulated.
  - In Japanese patients, the incidence of interstitial lung disease-like events associated with afatinib was not particularly higher than that associated with approved EGFR-TKIs [see "4.(iii).B.(3).3) Interstitial lung disease-like events" of Review Report (1)].
  - The events of diarrhoea, skin disorder, liver disorder, and peptic ulcer/haemorrhage of the digestive tract are also observed in patients treated with approved EGFR-TKIs.

The following comments were raised from the expert advisors:
- The target sample size in the surveillance should be set so as to detect Grade ≥3 interstitial lung disease.

Taking the discussion at the Expert Discussion into account, PMDA instructed the applicant to reconsider the target sample size in the surveillance so as to evaluate adverse events in Japanese patients including Grade ≥3 interstitial lung disease.

The applicant responded as follows:
The target sample size will be set at 1500 patients to ensure that at least 1 event of Grade ≥3 interstitial lung disease is detected for afatinib in routine clincal use with a probability of 99%, assuming that the incidence of the event associated with afatinib in routine clinical use is comparable to the incidence (0.3%) in all the unblinded clinical studies in cancer patients (in which, 12 of 3865 [0.3%] patients treated with afatinib experienced Grade ≥3 interstitial lung disease for which a causal relationship with afatinib could not be ruled out). Data from a total of

1500 patients would allow thorough investigation of the priority investigation items such as diarrhoea, rash/acne, and nail abnormality of Grade ≥3.

The proposed follow-up period of 12 months was considered acceptable because interstitial lung disease in 3865 patients receiving afatinib occurred within 12 months after the beginning of treatment.

PMDA accepted the applicant's response.

Taking the above discussion into account, PMDA concluded that the risk management plan for afatinib should include the following safety and efficacy specifications, additional pharmacovigilance activities, surveillance/study for the efficacy, and additional risk minimization activities, as shown in the tables below.

Outline of drug risk management plan

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• Diarrhoea • Skin disorder • Interstitial lung disease • Liver disorder • Gastrointestinal ulcer/haemorrhage • Left ventricular ejection fraction (LVEF) decreased/cardiac failure	• Pancreatitis • Reproductive and developmental toxicity • Corneal perforation/ulcer	• Safety in patients with renal impairment
Efficacy specifications		
• Efficacy under routine use of afatinib • Efficacy in patients with *EGFR* mutation-positive inoperable or recurrent non-small cell lung cancer (post-marketing clinical study)		

Outline of pharmacovigilance plan, surveillance/study plan for the efficacy, and additional risk minimization plan

Additional pharmacovigilance activity	Surveillance/study for the efficacy	Additional risk minimization activity
• Early post-marketing phase vigilance • Post-marketing surveillance (see the outline of the post-marketing surveillance plan [draft] in the table below) • Post-marketing clinical study (extended treatment following Study 1200.32)	• Post-marketing surveillance (see the outline of the post-marketing surveillance plan [draft] in the table below) • Post-marketing clinical study (extended treatment following Study 1200.32)	• Provision of information obtained from early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals (guidance for proper use) • Preparation and distribution of materials for patients • Cautions before use (check list for eligibility)

Outline of the post-marketing surveillance plan (draft)

Objective	To evaluate the safety, etc. of afatinib under long-term routine use
Surveillance method	Surveillance by sequential enrollment
Population	Patients with *EGFR* mutation-positive inoperable or recurrent NSCLC
Follow-up period	12 months
Planned sample size	1500
Priority investigation items	Interstitial lung disease, diarrhoea, rash/acne, and nail abnormality

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication and dosage and administration statements as shown below, with the

following conditions: (i) appropriate cautions must be included in the package insert; (ii) information concerning the proper use of afatinib must be provided appropriately after the market launch; and (iii) afatinib must be used properly under the supervision of physicians with sufficient knowledge and experience with cancer chemotherapy at a medical institution well equipped to cope with emergencies. The re-examination period is 8 years, both the drug substance and the drug product are classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indication] *EGFR* mutation-positive inoperable or recurrent non-small cell lung cancer

[Dosage and Administration] The usual adult dosage is 40 mg of afatinib orally administered once daily in the fasted state.
The dose may be adjusted according to the conditions of the patient as appropriate. The dose may be increased up to 50 mg once daily.

[Warnings]

1. Afatinib should be administered only to patients considered eligible for the therapy in accordance with the descriptions in the package insert, under the supervision of a physician with sufficient knowledge and experience with cancer chemotherapy at medical institutions well equipped to cope with emergencies. Prior to the initiation of treatment, consent should be obtained from the patient or his/her family member who has been provided with a thorough explanation of the benefits and risks of the therapy (especially, information about initial symptoms of interstitial lung disease, cautions during the treatment, and the fact that some patients died during the treatment).
2. Interstitial lung disease resulting in death has been reported in patients treated with afatinib. Patients should therefore be carefully monitored for initial symptoms (dyspnoea, cough, pyrexia, etc.) and undergo periodic chest imaging and other examinations. If any abnormalities are observed, afatinib should be discontinued and appropriate measures should be taken. During the initial phase of treatment, patients should be hospitalized or receive equivalent care to be carefully monitored for serious adverse drug reactions such as interstitial lung disease.

[Contraindications]

Patients with a history of hypersensitivity to any ingredient of afatinib maleate

[Precautions for Indications]

1. An *EGFR* mutation test should be performed. Afatinib should be administered referring to the latest information such as the “Lung Cancer Clinical Practice Guidelines” issued by the Japan Lung Cancer Society, including how to handle patients with unknown *EGFR* mutation.
2. The efficacy and safety of afatinib used in adjuvant chemotherapy have not been established.
3. The eligibility of a patient should be determined by physicians who are familiar with the applicable history of cancer chemotherapy presented in the “Clinical Studies” section and thoroughly understand the efficacy and safety of afatinib.

[Precautions for Dosage and Administration]

1. If an adverse drug reaction occurs, the dose of afatinib should be reduced or treatment with afatinib should be interrupted or discontinued according to its symptom and severity and in consideration of the following criteria.

Grade of the adverse drug reaction[Note 1)]	Criteria for treatment interruption and dose reduction
Grade 1 or 2	Maintain the same dose.
Grade 2 (persistent symptom[Note 2)] or intolerable) or Grade ≥3	Interrupt afatinib until the symptom improves to Grade ≤1. Resume afatinib after recovery by decreasing 10 mg from the previous dose.[Note 3), 4)]

Note 1) Grade is in accordance with NCI-CTCAE 3.0.
Note 2) Diarrhoea for >48 hours or skin disorder for >7 days
Note 3) If afatinib is not tolerable at a dose of 20 mg once daily, treatment discontinuation should be considered.
Note 4) The dose should not be increased once it has been reduced.

2. The dose may be increased to 50 mg once daily in patients who have continued the once-daily treatment at a dose of 40 mg for ≥3 weeks without diarrhoea, skin disorder, stomatitis, or other adverse drug reactions of Grade ≥2.
3. It is reported that C_{max} and AUC decrease after administration of afatinib in the fed state. Afatinib should not be administered between 1 hour before and 3 hours after a meal to avoid food effect.
4. The efficacy and safety of the combination therapy of afatinib with other antineoplastic drugs have not been established.