Report on the Deliberation Results

March 3, 2016

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

[Brand name]	Tagrisso Tablets 40 mg Tagrisso Tablets 80 mg
[Non-proprietary name]	Osimertinib Mesilate (JAN*)
[Applicant]	AstraZeneca K.K.
[Date of application]	August 21, 2015

[Results of deliberation]
In the meeting held on February 26, 2016, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

[Conditions for approval]
The applicant is required to:

1. Develop and appropriately implement a risk management plan;
2. Conduct a drug use-results survey covering all patients treated with the product after market launch until data from a certain number of patients have been accumulated, to identify the characteristics of the patients treated with the product and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product, since an extremely limited number of patients participated in the clinical studies conducted in Japan; and
3. Take necessary measures before market launch to ensure that the product is used only under the supervision of physicians well versed in the diagnosis of lung cancer and chemotherapy at a medical institution capable of handling the risks associated with treatment in cooperation with a pharmacy with a supervising pharmacist.

**Japanese Accepted Name (modified INN)*

Review Report

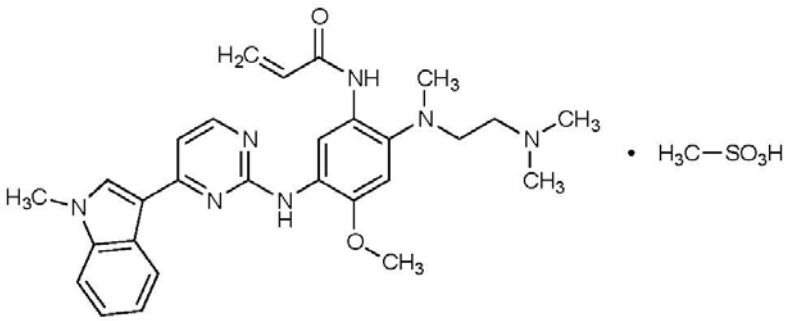
February 17, 2016

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]	Tagrisso Tablets 40 mg Tagrisso Tablets 80 mg
[Non-proprietary name]	Osimertinib Mesilate
[Applicant]	AstraZeneca K.K.
[Date of application]	August 21, 2015
[Dosage form/Strength]	Tablets, each tablet containing 47.7 or 95.4 mg of Osimertinib Mesilate (equivalent to 40 or 80 mg of osimertinib, respectively).
[Application classification]	Prescription drug, (1) Drugs with a new active ingredient

[Chemical structure]



Molecular formula: $C_{28}H_{33}N_7O_2 \bullet CH_4O_3S$
Molecular weight: 595.71
Chemical name:
N-(2-{[2-(Dimethylamino)ethyl](methyl)amino}-4-methoxy-5-{[4-(1-methyl-1*H*-indol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide monomethanesulfonate

[Items warranting special mention]
Priority Review (Notification No.0930-9 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated September 30, 2015)

[Reviewing office] Office of New Drug V

Review Results

February 17, 2016

[Brand name]	Tagrisso Tablets 40 mg Tagrisso Tablets 80 mg
[Non-proprietary name]	Osimertinib Mesilate
[Applicant]	AstraZeneca K.K.
[Date of application]	August 21, 2015

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that a certain level of the efficacy of the product in the treatment of patients with inoperable or recurrent epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer resistant to EGFR tyrosine kinase inhibitors has been demonstrated, and its safety is acceptable in view of its observed benefits. Events such as interstitial lung disease, QT interval prolonged, haematotoxicity, liver disorder, cardiac disorder (except for QT interval prolonged), thromboembolism, infection, and corneal disorder need to be further investigated in the post-marketing surveillance.

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

[Indication]	Inoperable or recurrent EGFR T790M mutation-positive non-small cell lung cancer resistant to EGFR tyrosine kinase inhibitors
[Dosage and administration]	The usual adult dosage is 80 mg of osimertinib administered orally once daily. The dose may be reduced as appropriate according to the patient's condition.
[Conditions for approval]	The applicant is required to: 1. Develop and appropriately implement a risk management plan; 2. Conduct a drug use-results survey covering all patients treated with the product after market launch until data from a certain number of patients have been accumulated, to identify the characteristics of the patients treated with the product and to promptly collect safety and efficacy data, so that necessary measures are taken to ensure proper use of the product since an extremely limited number of patients participated in the clinical studies conducted in Japan; and 3. Take necessary measures before market launch to ensure that the product is used only under the supervision of physicians well versed in the diagnosis of lung cancer and chemotherapy at a medical institution capable of handling the risks associated with treatment in cooperation with a pharmacy with a supervising pharmacist.

Review Report (1)

January 13, 2016

I. Product Submitted for Registration

[Brand name]	Tagrisso Tablets 40 mg Tagrisso Tablets 80 mg
[Non-proprietary name]	Osimertinib Mesilate
[Applicant]	AstraZeneca K.K.
[Date of application]	August 21, 2015
[Dosage form/Strength]	Tablets, each containing 47.7 or 95.4 mg of Osimertinib Mesilate (equivalent to 40 or 80 mg of osimertinib, respectively)
[Proposed indication]	Unresectable, advanced or recurrent EGFR T790M mutation-positive non-small cell lung cancer that progressed during or after EGFR tyrosine kinase inhibitor treatment
[Proposed dosage and administration]	The usual adult dosage is 80 mg of osimertinib administered orally once daily.

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

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

1.(1) Outline of the product submitted for registration

EGFR forms its homodimer or heterodimer with human epidermal growth factor receptor (HER) 2 or HER4, both of which belong to the EGFR family, and thereby activates its downstream signal transduction pathway and thus regulates cell proliferation and differentiation.

Osimertinib mesilate (hereinafter referred to as osimertinib) is an EGFR tyrosine kinase inhibitor (EGFR-TKI) discovered by AstraZeneca PLC (UK) and is considered to suppress proliferation of EGFR T790M mutation-positive cancer. In this mutation, threonine (T) at position 790 in exon 20 of EGFR gene is substituted by methionine (M), resulting in resistance to the existing EGFR-TKIs.*

*: In Japan, gefitinib, erlotinib hydrochloride, and afatinib maleate are approved for the indication of unresectable advanced or recurrent EGFR gene mutation-positive non-small cell lung cancer.

1.(2) Development history etc.

A phase I/II study (Study D5160C00001 [AURA study]) in patients with unresectable, advanced or recurrent EGFR activating mutation-positive non-small cell lung cancer (NSCLC) was initiated in March 2013 by AstraZeneca PLC (UK) as a global clinical study involving Japan. In addition, a phase II study (Study D5160C00002 [AURA2 study]) in patients with unresectable, advanced or recurrent EGFR T790M mutation-positive NSCLC that progressed after EGFR-TKI therapy was initiated in April 2014 as a global clinical study involving Japan. Furthermore, a phase III study (Study D5160C00003 [AURA3 study]) in patients with unresectable advanced or recurrent EGFR T790M mutation-positive NSCLC that progressed after EGFR-TKI therapy was initiated in August 2014 as a global clinical study involving Japan, and it is currently ongoing.

In the US and EU, applications for Tagrisso were submitted in June 2015 with the results from the AURA and AURA2 studies as the pivotal data. In the US, Tagrisso was approved under accelerated approval in November 2015 for the following indication: "TAGRISSO is indicated for the treatment of patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed during or after EGFR tyrosine kinase inhibitor (TKI) therapy. This indication is approved under accelerated approval

based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials." Tagrisso is currently under review in the EU.

As of November 2015, Tagrisso is approved only in the US for the indication of unresectable advanced or recurrent EGFR T790M mutation-positive NSCLC.

In Japan, this marketing application for Tagrisso was submitted in August 2015, based on the results from the AURA and AURA2 studies 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 brown powder and its description, solubility, dissociation constant, partition coefficient, melting point, optical rotation, and hygroscopicity have been determined.

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

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

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

[redacted]*3 [redacted] are identified as critical steps. Moreover, [redacted], [redacted],*4 and [redacted]*5 are controlled as critical intermediates.

*1: [redacted]
*2: [redacted]
*3: [redacted]
*4: [redacted]
*5: [redacted]

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

The proposed specifications for the drug substance include content, description, identification (IR), purity (organic impurities [redacted], mutagenic impurities [redacted], and residual solvents [gas chromatography]), residue on ignition, [redacted], and assay ([redacted]).

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

The stability studies of the drug substance are shown in the table below. The photostability study has shown that the drug substance is photostable.

Stability studies of the drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot scale batches	25°C	60%RH	Low-density polyethylene bag (double-layered) + hard container	12 months
Accelerated g	3 pilot scale batches	40°C	75%RH		6 months

On the basis of above study results, a retest period of [redacted] months has been proposed for the drug substance when stored at room temperature in a double-layered low-density polyethylene bag and placed in a hard container, in accordance with the "Guideline on Evaluation of Stability Data" (PMSB/ELD Notification

No. 0603004 dated June 3, 2003 [ICH Q1E Guideline]). The long-term testing will be continued for [redacted] months.

2.A.(2) Drug product

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

The drug product is an immediate-release film-coated tablet containing 47.7 or 95.4 mg of the drug substance (40.0 or 80.0 mg as osimertinib, respectively). The drug product contains D-mannitol, microcrystalline cellulose, low substituted hydroxypropylcellulose, sodium stearyl fumarate, and Opadry II beige as excipients.

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

The drug product is manufactured through a process consisting of [redacted], [redacted], sizing, [redacted], tableting, film-coating, and packaging.

[redacted] is defined as the critical step, and process control parameters and their action limits are specified in [redacted], [redacted], and [redacted].

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

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

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

The stability study results of the drug product are shown in the table below. The photostability study showed that the drug product is photostable.

Stability studies of drug product

Strength	Study	Primary batch	Temperature	Humidity	Storage form	Storage period
40 mg	Long-term	1 pilot scale batch 2 small scale* batches	25°C	60%RH	Aluminum foil blister package	12 months
	Accelerated		40°C	75%RH		6 months
80 mg	Long-term	3 small scale* batches	25°C	60%RH		12 months
	Accelerated		40°C	75%RH		6 months

*: < pilot scale (≥1/10 the commercial scale and <100,000-tablet scale)

On the basis of above study results, a shelf life of 18 months has been proposed for the drug product when stored at room temperature in aluminum foil blister package, in accordance with the ICH Q1E Guideline. The long-term testing will be continued for [redacted] months.

2.B Outline of the review by PMDA

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

Shelf life of the drug product

At least 2 of 3 batches provided in formal stability studies of a drug product are required to be manufactured at a pilot scale or larger (PMSB/ELD Notification No. 0603001 dated June 3, 2003 [ICH Q1A Guideline]). The applicant, however, proposed a shelf life of 18 months for both 40 mg and 80 mg drug products based on data from a stability study including 2 batches or more at a scale smaller than the pilot scale [see "2.A.(2).4) Stability of drug product]. PMDA asked the applicant to explain the impact of the difference in manufacturing scale on stability of the drug product.

The applicant's response:

The manufacturing processes of the batches used for the formal drug product stability studies and the commercial production are based on the same operation principle. In light of this, the difference in manufacturing scale between these processes is considered to have no impact on the stability of the drug product.

PMDA's view:
In principle, shelf life of a drug product should be proposed based on data from a stability study in compliance with the ICH Q1A guideline. However, PMDA has concluded that a shelf life of 18 months can be proposed for the drug product based on data from the above stability studies, because (a) the manufacturing scale for the batches in the formal stability studies was at least one tenth of the commercial production scale; and (b) the applicant's claim is acceptable in that the difference in manufacturing scale has no impact on the stability of the drug product.

3. Non-clinical data

In this section, the doses and concentrations of osimertinib mesilate are expressed as free-base equivalent unless otherwise specified.

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) Inhibitory effects on EGFR (Reports; Pharmacology Report [redacted], Pharmacology Report [redacted], Pharmacology Report [redacted], and Pharmacology Report [redacted])

Inhibitory effects of osimertinib and its metabolites (AZ5104 and AZ7550) [see "3.(ii).A.(3) Metabolism"] on phosphorylation of wild-type and mutant* EGFR ($EGFR_{wt}$ and $EGFR_{mut}$, respectively) (recombinant proteins) were investigated by measuring the uptake of [γ-^{33}P]-adenosine triphosphate (ATP) into the substrate. The IC_{50} values of osimertinib and its metabolites [95% confidence interval (CI)] are shown in the table below.

* L858R mutation, a substitution of arginine (R) for leucine (L) at position 858 in exon 21 of EGFR gene; L861Q mutation, a substitution of glutamine (Q) for L at position 861 in exon 21 (both activating mutants); T790M mutation, a substitution of methionine (M) for threonine (T) at position 790 in exon 20 of EGFR gene (resistant mutant); and others, such as exon 19 deletion (Ex19del) mutation (activating mutant) are known.

Inhibitory effects of osimertinib and its metabolites on phosphorylation of EGFR (recombinant protein)

EGFR	IC_{50} value [95% CI] (nmol/L)		
	Osimertinib	AZ5104	AZ7550
Wild-type	80 [10, 629]	15 [5, 49]	330 [61, 1792]
L858R/T790M	2 [0.1, 49]	<1, <1, 4*	10 [0.6, 179]
L858R	20 [6, 62]	9 [4, 24]	83 [33, 212]
L861Q	10 [1, 84]	2 [0.2, 28]	66 [7.4, 581]

Geometric mean; n = 3; *, Geometric mean was not calculated since results from 2 measurements were <1 (below the detection limit).

Inhibitory effects of osimertinib and its metabolites (AZ5104 and AZ7550) on phosphorylation of EGFR were investigated by enzyme-linked immunoassay (ELISA) in human NSCLC cell lines H3255, PC9, H1650, H1975, and PC9VanR* that express $EGFR_{mut}$, as well as human colorectal adenocarcinoma LOVO, human skin squamous cell carcinoma A431, and human NSCLC cell line H2073 that express $EGFR_{wt}$. The IC_{50} values [95% CI] are shown in the table below.

*: Vandetanib-resistant PC9 cell line

Inhibitory effects of osimertinib and its metabolites on phosphorylation of EGFR

Cell line	EGFR	IC_{50} value [95% CI] (nmol/L)		
		Osimertinib	AZ5104	AZ7550
H3255	L858R	60, 49	-	-
PC9	Ex19del	17 [13, 22]	2 [2, 3]	26 [10, 65]
H1650	Ex19del	14, 12	-	-
H1975	L858R/T790M	15 [10, 20]	2 [2, 4]	45 [34, 59]
PC9VanR	Ex19del/T790M	6 [3, 13]	1 [0.04, 8]	29 [8, 108]
LOVO*	Wild-type	480 [320, 720]	33 [24, 45]	786 [480, 1292]
A431*	Wild-type	2376, 1193	-	-
H2073*	Wild-type	1865 [872, 3988]	53, 66	2356, 2367

Geometric mean (individual values if n = 2); n = 2-16; *, EGFR phosphorylation induced by epidermal growth factor; -, Not investigated

The binding site of osimertinib to EGFR (recombinant protein) was investigated by mass spectrometry. Osimertinib has been shown to be bound to cysteine residue covalently at position 797 (C797) within the catalytic site of EGFR tyrosine kinase.

Duration of the inhibitory effect of osimertinib on phosphorylation of EGFR was investigated in H1975, PC9, and LOVO cell lines. In any cell line, the IC_{50} value decreased over the course of osimertinib treatment period (1-10 hours).

H1975 cell line was treated with osimertinib or AZ5104 for 2 hours and then rinsed off to investigate reversibility of the inhibitory effect on phosphorylation. The inhibitory effects of osimertinib and AZ5104 on phosphorylation were observed up to 48 hours after rinsing, indicating that their inhibitory effects are irreversible.

3.(i).A.(1).2) Inhibitory effect on kinases other than EGFR (Reports; Pharmacology Report [redacted], 3129SV, 3285SV, 3284SV, and Pharmacology Report [redacted])

The inhibitory effect of osimertinib on phosphorylation of 298 kinases (recombinant proteins) was investigated by measuring the uptake of [γ-^{33}P]-ATP into the substrate. Osimertinib at 1000 nmol/L inhibited 18 kinases by >60%. The IC_{50} values of osimertinib were determined for these 18 kinases in a separate study, and the results are shown in the table below. Moreover, inhibitory effects of osimertinib metabolites (AZ5104 and AZ7550) on phosphorylation of 265 kinases (recombinant proteins) were investigated. Osimertinib metabolites, AZ5104 and AZ7550, at 1000 nmol/L inhibited 23 and 6 kinases, respectively, by >60%.

Inhibitory effect of osimertinib on phosphorylation of various kinases (recombinant proteins)

Kinase	IC_{50} value (nmol/L)	Kinase	IC_{50} value (nmol/L)
ACK1	71, 128	HER2	116
ALK	231, 1622	IGF1R	941, 1775
BLK	168, 442	INSR	432, 880
BRK	255, 258	LRRK2	375
BTK	699, 989	MLK1	85, 409
ERBB4	67, 46	MNK2	95, 155
FAK	598, 774	TEC	420, 497
FGFR1	>10,000	TXK	1590, 2519
FLT4	678, 983	YES	8193

Individual values (n = 1 or 2)

Inhibitory effects of osimertinib and its metabolites (AZ5104 and AZ7550) on phosphorylation of human insulin-like growth factor 1 receptor (IGF1R) and human insulin receptor (INSR) (recombinant proteins for both) were investigated, as measured by phosphorylation of the substrate. The IC_{50} values [95% CI] are shown in the table below.

Inhibitory effects of osimertinib and its metabolites on phosphorylation of IGF1R and INSR (recombinant proteins for both)

Kinase	IC_{50} value [95% CI] (nmol/L)		
	Osimertinib	AZ5104	AZ7550
IGF1R	2360, 3460	238 [181, 313]	1710 [990, 2940]
INSR	1200 [620, 2290]	90, 130	1020, 530

Geometric mean (individual values if n = 2), n = 2-5

Inhibitory effects of osimertinib and its metabolites (AZ5104 and AZ7550) on phosphorylation of IGF1R were investigated by ELISA in mouse embryonic fibroblast NIH-3T3 cell line expressing human IGF1R at a high level. The IC_{50} values [95% CI] (nmol/L) of osimertinib, AZ5104, and AZ7550 were 4614 [1997, 10,664], 1915 [1350, 2714], and >10,000, respectively.

Inhibitory effects of osimertinib and its metabolite (AZ5104) on phosphorylation of HER2 were investigated by ELISA in NIH-3T3 cell line expressing HER2 at a high level (NIH-3T3/HER2) as well as human breast cancer cell lines BT474c and MCF7 expressing HER2 endogenously. The IC_{50} values [95% CI] are shown in the table below.

Inhibitory effects of osimertinib and its metabolites on phosphorylation of HER2

Cell line	IC_{50} value [95% CI] (nmol/L)	
	Osimertinib	AZ5104
NIH3T3/HER2	93 [39, 221]	18 [9, 35]
BT474c	119 [55, 257]	17 [12, 23]
MCF7	118, 63	16, 11

Geometric mean (individual values if n = 2), n = 2 or 3

3.(i).A.(1).3) Inhibitory effects on EGFR signal transduction pathway (AKT and ERK) (Report; Pharmacology Report [redacted])

The inhibitory effect of osimertinib on phosphorylation of EGFR signal transduction pathways (AKT and ERK) in tumor tissues was investigated in athymic mice (nude mice) and severe combined immunodeficiency (SCID) mice subcutaneously implanted, respectively, with $EGFR_{mut}$-expressing H1975 (L858R/T790M) and PC9 (Ex19del) cell lines. When the volume of subcutaneously implanted tumor reached 500 mm^3 (H1975) or 800 mm^3 (PC9), mice were randomized, and on the following day a single oral dose of osimertinib 0.5, 1, 5, or 25 mg/kg was administered. At 1 to 48 hours post-dose, phosphorylation of EGFR, AKT, and ERK in tumor tissues was examined by ELISA, electrochemiluminescence immunoassay, and immunohistochemical staining. Osimertinib inhibited phosphorylation of EGFR, AKT, and ERK in a dose dependent manner, and the maximum inhibition was found at 6 hours post-dose.

The same investigation was performed in nude mice subcutaneously implanted with $EGFR_{wt}$-expressing A431 cell line. Osimertinib 25 mg/kg inhibited phosphorylation of EGFR and AKT.

3.(i).A.(1).4) Effect on malignant tumors (Reports; Pharmacology Report [redacted], Pharmacology Report [redacted], Pharmacology Report [redacted], Pharmacology Report [redacted], Pharmacology Report [redacted], Pharmacology Report [redacted], Pharmacology Report [redacted], and Pharmacology Report [redacted])

i) *in vitro*

Antiproliferative effects of osimertinib and its metabolites (AZ5104 and AZ7550) were determined by counting dead cells in $EGFR_{mut}$-expressing H1975 (L858R/T790M), PC9VanR (Ex19del/T790M), and PC9 (Ex19del) cell lines as well as $EGFR_{wt}$-expressing human NSCLC cell lines CALU3, CALU6, and H2073. The IC_{50} values [95% CI] of osimertinib and its metabolites are shown in the table below.

Antiproliferative effects of osimertinib and its metabolites on human NSCLC cell lines

Cell line	EGFR	IC_{50} value [95% CI] (nmol/L)		
		Osimertinib	AZ5104	AZ7550
H1975	L858R/T790M	11 [6, 19]	3 [2, 5]	26, 33
PC9VanR	Ex19del/T790M	40 [30, 54]	7 [3, 17]	-
PC9	Ex19del	8 [7, 9]	3 [2, 3]	10, 26
CALU3	Wild-type	650 [457, 924]	80 [28, 231]	2460, 370
CALU6	Wild-type	4089 [3551, 4708]	2041 [1650, 2525]	3850, 4060
H2073	Wild-type	461 [230, 924]	28 [7, 107]	1361

Geometric mean [95% CI] (individual values if n = 1 or 2); n = 1-17; -, Not investigated

ii) *in vivo*

The tumor growth inhibitory effects of osimertinib on $EGFR_{mut}$-expressing H3255 (L858R), H1975 (L858R/T790M), PC9 (Ex19del), and PC9VanR (Ex19del/T790M) cell lines as well as $EGFR_{wt}$-expressing A431 and LOVO cell lines were investigated in nude mice (H1975, A431, and LOVO) or SCID mice (H3255, PC9, and PC9VanR) (n = 6-8/group) subcutaneously implanted with these cell lines. Starting from the day when the volume of subcutaneously implanted tumor reached 200 mm^3 (nude mice) or 400 mm^3 (SCID mice), osimertinib was orally administered (5 mg/kg for H3255 and PC9VanR, 0.5-25 mg/kg for H1975, 0.1-25 mg/kg for PC9 and A431, 5 and 25 mg/kg for LOVO) once daily (QD) for 14 days, and then the tumor volume was measured.

As a result, compared with vehicle (1% polysorbate 80), osimertinib inhibited tumor growth of all the cell lines with a statistical significance ($P < 0.001$ or 0.05, t-test). In H3255, H1975, PC9, and PC9VanR cell lines, the tumor growth inhibition rate* was ≥100% (211%, 116% or 107%, 103%, and 171%, respectively) after osimertinib 5, 2.5, 0.5, and 5 mg/kg was administered, respectively, while in A431

and LOVO cell lines, the rate was 102% and 56%, respectively, after osimertinib 25 mg/kg was administered. The above findings suggested that the antiproliferative effects of osimertinib on $EGFR_{wt}$-expressing cell lines were weaker than those against $EGFR_{mut}$-expressing cell lines. In the same manner, the tumor growth inhibitory effects of AZ5104, an osimertinib metabolite, were investigated 2.5-50 mg/kg in mice subcutaneously implanted with H1975, PC9, and A431 cell lines and AZ5104 inhibited tumor growth of all the cell lines statistically significantly compared with vehicle.

*: The tumor growth inhibition rate was calculated by the following formula, where tumor volume ratio was defined as the ratio of tumor volume at the end of the study to that at baseline: Tumor growth inhibition rate (%) = (tumor volume ratio in the vehicle group - tumor volume ratio in the osimertinib group) × 100/(tumor volume ratio in the vehicle group - 1).

The tumor growth inhibitory effects of osimertinib following long-term administration was investigated in nude mice (n = 10-12/group) subcutaneously implanted with $EGFR_{mut}$-expressing H1975 (L858R/T790M) cell line. Starting from the day when the volume of subcutaneously implanted tumor reached 200 mm^3, osimertinib was orally administered at a dose of 1 (25 mg/kg from Day 100 onward), 5, or 25 mg/kg QD for 200 days, and then the tumor volume was measured. Eleven days after initiation of study treatment, all osimertinib groups showed statistically significant anti-tumor growth effect compared with the vehicle (1% polysorbate 80)-treated group. The relevant effect continued during repeated dose of osimertinib, and no re-growth of tumor was observed during the subsequent observation period (100 days). The same was performed in SCID mice subcutaneously implanted with PC9 cell line (Ex19del) or H3255 cell line (L858R). The anti-tumor growth effect of osimertinib 5 or 25 mg/kg administered orally was continued during the treatment period (200 days in PC9, 75 days in H3255).

Osimertinib 1 or 5 mg/kg QD was orally administered for 28 days to transgenic mice designed to develop NSCLC due to $EGFR_{mut}$ (L858R/T790M) expressed in the lung tissue. Then, the lung tissue sections were subjected to hematoxylin-eosin staining and immunohistochemical staining to investigate the tumor growth inhibitory effect of osimertinib and the inhibitory effect of osimertinib on EGFR phosphorylation. Osimertinib was shown to inhibit tumor growth and EGFR phosphorylation in a dose-dependent manner.

Nude mice (n = 8-9/group) were implanted in the brain with $EGFR_{mut}$ (Ex19del)-expressing PC9 cells transfected with luciferase gene by internal carotid artery injection. Osimertinib was orally administered to them at a dose of 5 or 25 mg/kg QD for 60 days to investigate the tumor growth inhibitory effect and survival. When luciferase luminescence was used as an indicator, osimertinib groups tended to suppress tumor growth and increased the survival statistically significantly ($P < 0.05$, t-test) compared with vehicle (1% polysorbate 80)-treated group.

3.(i).A.(1).5) Mechanism of development of resistance to osimertinib (Reports; Pharmacology Report [redacted] and Pharmacology Report [redacted])

The mechanism of development of resistance to osimertinib as well as gefitinib and afatinib maleate (afatinib), the existing EGFR tyrosine kinase inhibitors (EGFR-TKIs), was investigated in $EGFR_{mut}$ (Ex19del)-expressing PC9 cell lines by next generation sequencing etc. As a result, 8 and 5 PC9 cell specimens developed resistance to gefitinib and afatinib, respectively, and 7 and 4 cell specimens of those were found to have EGFR T790M mutation, while none of the PC9 cell specimens (n = 8) that developed resistance to osimertinib were found to have EGFR T790M mutation. Furthermore, it took 65 to 135 days* to develop resistance to osimertinib, which was longer than that to gefitinib and afatinib (26-117 days and 28-128 days, respectively).

*: Time until the resistant cells reached 80% confluence in a culture flask.

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

3.(i).A.(2).1) Effects on various receptors, ion channels, transporters, and enzymes (Reports; 1112SY [Reference data], 1120SY [Reference data], 1121SY [Reference data], 3129SV, 3285SV, 3284SV, and 3273KR [Reference data])

Effects of osimertinib on 181 different receptors, ion channels, transporters, and enzymes were investigated in radiolabeled-ligand binding, function, and enzyme activity studies. For a total of 21 types of molecules including $EGFR_{wt}$, IC_{50} value or binding constant (Ki) of osimertinib was ≤100 fold the IC_{50} value for $EGFR_{mut}$ (≤12 nmol/L). Effects of AZ5104 and AZ7550, osimertinib metabolites, on 189 different molecules were investigated in the same way. As a result, for 12 and 40 types of molecules

including $EGFR_{wt}$, the IC_{50} values of AZ5104 and AZ7550, respectively, were ≤100 fold the IC_{50} values for $EGFR_{mut}$ (≤6 nmol/L and 56 nmol/L, respectively). The IC_{50} values of osimertinib and its metabolites for $EGFR_{wt}$ were found to be the lowest among those against the molecules investigated, and the relevant IC_{50} value of osimertinib was 14 nmol/L. The IC_{50} values of osimertinib for other target molecules were all ≥15 fold the value for EGFR, except for 5-HT_{2C} receptor (IC_{50} value, 18 nmol/L). On the basis of the above, although it is difficult to predict effects mediated by target molecules in routine clinical use, no findings related to the target molecules were noted in safety pharmacology studies [see "3.(i).A.(3) Safety pharmacology"]. Moreover, findings of the skin and cornea in repeat-dose toxicity studies as well as adverse events frequently reported in clinical studies such as diarrhoea and rash are considered mainly attributable to inhibition against $EGFR_{wt}$.

Effects of osimertinib on IGF1R and INSR were investigated in rats receiving a single oral dose of osimertinib 200 mg/kg by measuring plasma insulin and blood glucose values up to 24 hours post-dose. As a result, no effects of osimertinib on plasma insulin or blood glucose levels were found. In repeat-dose toxicity studies in rats and dogs, no clear effects on the plasma insulin or blood glucose levels were observed [see "3.(iii).A.(2) Repeat-dose toxicity"], and thus osimertinib and its metabolites do not exert a clear impact on IGF1R or INSR.

3.(i).A.(2).2) Effects on various myocardial ion channels (Reports; 1112SY [Reference data], 3535SV, 1120SY [Reference data], 3473SV, 1121SY [Reference data], and 3472SV)

Effects of osimertinib and its metabolites (AZ5104 and AZ7550) on 8 human voltage-dependent myocardial ion channels (recombinant proteins) were investigated electrophysiologically. Osimertinib did not affect any channel except *human ether-a-go-go*-related gene (hERG) channel. In addition, AZ5104 and AZ7550 inhibited $hCa_v3.2$ channel with IC_{50} values of 37.5 and 31.9 μmol/L, respectively.

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

3.(i).A.(3).1) Effects on the central nervous system (Report; 3464SR)

A single oral dose of osimertinib 10, 40, or 100 mg/kg was administered to rats (n = 6/group) to evaluate effects of osimertinib on the central nervous system, body temperature, and body weight. No effects of osimertinib were observed except for slightly decreased body weight at the doses of 40 and 100 mg/kg.

3.(i).A.(3).2) Effects on the cardiovascular system

i) Effects on hERG-related gene potassium channel (Report; VKS0795)

In Chinese hamster ovary cell line CHO (n = 4) transfected with hERG, effects of osimertinib (mesilate) at 135 to 1980 nmol/L on hERG potassium channel were investigated. The IC_{50} value of osimertinib was 690 nmol/L.

ii) Effects on blood pressure, heart rate, and electrocardiogram (Reports; 1352ZD, PH/E/14191 [non-GLP study], and 0264SG [non-GLP study])

Single oral doses of osimertinib 6, 20, and 60 mg/kg were sequentially administered to dogs (n = 4) to investigate the effects of osimertinib on arterial blood pressure, heart rate, left ventricular pressure, and electrocardiogram (PR, QT, and QTcR intervals, QRS duration, and waveform). Transiently and slightly prolonged QTcR interval and mildly decreased heart rate occurred after administration of osimertinib.

A single oral dose of osimertinib 20, 50, or 100 mg/kg was administered to rats (n = 4/group) to evaluate the effects of osimertinib on blood pressure and heart rate. Systolic and diastolic blood pressure increased dose-dependently after administration of osimertinib 50 and 100 mg/kg. Blood pressure increased transiently at the dose of 50 mg/kg.

Although a report indicated that the blood pressure increase was related to an effect on the left ventricular ejection fraction associated with inhibitory effects on HER2 (*Clin Breast Cancer.* 2007;7:600-607), the applicant explained that the blood pressure increase after administration of osimertinib is unlikely to raise safety issues in routine clinical use on the following grounds:

- No effect of osimertinib on blood pressure was observed at a single dose of 60 mg/kg in dogs, which led to C_{max} higher than that (0.78 μmol/L) in Japanese NSCLC patients orally receiving osimertinib 80 mg QD [see "4.(ii).B.(1) Differences in PK between Japanese and non-Japanese patients"].

- In the phase II part of a global phase I/II study (Study D5160C00001 [AURA study]) and a global phase II study (Study D5160C00002 [AURA2 study]), no effect of osimertinib on blood pressure was observed.

A single intravenous dose of osimertinib 5 or 40 mg/kg was administered to guinea pigs (n = 6/group) to investigate effects on arterial blood pressure, heart rate, left ventricular pressure, and electrocardiogram (PR, QT, and QTcB intervals and QRS duration). Consequently, mildly decreased heart rate and dP/dt max, and increased left ventricular systolic pressure as well as prolonged PR interval, QTcB interval, and QRS duration were observed in animals receiving 40 mg/kg of osimertinib. C_{max} in guinea pigs receiving osimertinib at 40 mg/kg (22.87 μmol/L) was approximately 29 fold C_{max} (0.78 μmol/L) in Japanese NSCLC patients orally receiving osimertinib 80 mg QD [see "4.(ii).B.(1) Differences in PK between Japanese and non-Japanese patients"].

The risk of QT interval prolonged and cardiac disorder after administration of osimertinib is described in "4.(iii).B.(3).4) QT interval prolonged" and "4.(iii).B.(3).7) Cardiac disorder (except for QT interval prolonged)," on the basis of clinical study results.

3.(i).A.(3).3) Effects on the respiratory system (Report; 3464SR)

A single oral dose of osimertinib 10, 40, or 100 mg/kg was administered to rats (n = 8/group) to investigate effects of osimertinib on respiratory rate, tidal volume, minute ventilation, inspiratory time, expiratory time, inspiratory capacity, and peak expiratory flow rate. No effects of osimertinib were observed.

3.(i).A.(3).4) Effects on the visual and gastrointestinal systems (Report; 3464SR)

A single oral dose of osimertinib 10, 40, or 100 mg/kg was administered to rats (n = 6/group) to investigate effects of osimertinib on vision and behavior. No effects of osimertinib were observed.

A single oral dose of osimertinib 10, 40, or 100 mg/kg was administered to rats (n = 8/group) to investigate effects of osimertinib on the gastric emptying and small intestinal transit. Osimertinib decreased the gastric emptying capacity and suppressed the small intestinal transit in a dose-dependent manner.

The applicant explained that the decreased gastric emptying capacity and suppressed small intestinal transit, findings in animals treated with osimertinib, are unlikely to raise clinical safety issues considering the following points:

- Although decreased gastric emptying capacity and suppressed small intestinal transit in rats are considered attributable to the inhibition against $EGFR_{wt}$, whether events related to these findings occur or not in routine clinical use remains unknown (*Neurogastroenterol Motil.* 2014;26:980-989).
- Although events such as stomach fullness and abdominal discomfort occurred in the phase II part of the AURA study and the AURA2 study, many of them were Grade 1 or 2 events [see "4.(iii).B.(3).11) Gastrointestinal disorders (excluding diarrhoea)].

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

Based on the submitted data and the following review, PMDA has concluded that the efficacy of osimertinib can be expected in the treatment of EGFR T790M mutation-positive NSCLC that progressed after EGFR-TKI therapy.

Mechanism of action and efficacy of osimertinib against EGFR T790M mutation-positive NSCLC

The applicant's explanation on the mechanism of action and efficacy of osimertinib against EGFR T790M mutation-positive NSCLC:

Many patients with NSCLC in which active mutation has occurred in EGFR gene (EGFR activating mutation-positive) were reported to develop resistance to the existing EGFR-TKIs (gefitinib, erlotinib hydrochloride, and afatinib) (*Clin Cancer Res.* 2011;17:1616-1622, etc.). The major part of the mechanism responsible for such resistance has been reported to be EGFR T790M mutation, which was identified in approximately 60% of patients with NSCLC resistant to EGFR-TKIs (*Clin Cancer Res.* 2013;19:2240-2247, etc.).

Osimertinib is a EGFR-TKI that covalently binds to the ATP binding site of EGFR tyrosine kinase as with the existing EGFR-TKIs, but unlike these inhibitors, it inhibits EGFR tyrosine kinase irreversibly even in the presence of EGFR T790M mutation [see "3.(i).A.(1).1) Inhibitory effect on EGFR"] and thus suppresses growth of EGFR T790M mutation-positive cancer [see "3.(i).A.(1).4) Effect on malignant tumors"].

Consequently, the applicant considered that the efficacy of osimertinib can be expected in the treatment of EGFR T790M mutation-positive NSCLC resistant to the existing EGFR-TKIs.

PMDA's view:
PMDA accepted the applicant's explanation. However, since information on developing resistance to osimertinib should be useful in selecting patients eligible for osimertinib therapy, it is necessary to continue collecting relevant information and provide it appropriately to healthcare professionals in clinical settings when new findings become available.

3.(ii) Summary of pharmacokinetic studies

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

The pharmacokinetics (PK) of osimertinib in animals was investigated in mice, rats, and dogs. Plasma protein binding, drug-metabolizing enzymes, and transporters etc., of osimertinib were investigated in human and animal biological samples.

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

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

Plasma osimertinib concentrations were determined in animals subcutaneously implanted with H1975 cell line after a single dose of osimertinib (i) at 5 or 25 mg/kg orally to female SCID mice under fed conditions, (ii) at 10 mg/kg orally to male and female rats under fed conditions, or (iii) at 2 mg/kg intravenously to male and female rats (the table below). After oral administration of osimertinib to mice, AUC_t increased almost dose-proportionally, but C_{max} increased less than dose-proportionally. The applicant explained the reason for this difference as follows: the solubility of osimertinib was higher in the suspension used for 5 mg/kg dose than in that for 25 mg/kg dose, resulting in a higher absorption rate of osimertinib at 5 mg/kg than at 25 mg/kg. Clearance after intravenous administration of osimertinib to rats was lower in females than in males, and C_{max} and AUC_t after oral administration of osimertinib were higher in females than in males. Bioavailability (BA) of osimertinib in male and female rats was 24% and 37%, respectively.

PK parameters of osimertinib in various animal species (single intravenous or oral administration)

Animal species	Dose (route of administration)	Sex	C_{max} (μmol/L)	t_{max} (h)	AUC_t (μmol·h/L)	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
Mouse*1	5 mg/kg (oral)	Female	1.92	0.5	4.82	-	-	2.85
	25 mg/kg (oral)		2.98	0.5	23.8	-	-	2.81
Rat	2 mg/kg (intravenous)	Male*2	1.00, 0.80	-	1.45, 1.43	2.51, 2.63	12.7, 11.8	3.23, 2.96
		Female	1.00 ± 0.68	-	1.98 ± 0.59	1.78 ± 0.61	13.0 ± 3.0	4.69 ± 1.71
	10 mg/kg (oral)	Male	0.15 ± 0.05	4*3 (4, 4)	1.74 ± 0.53	-	-	5.18 ± 0.55
		Female	0.29 ± 0.05	4*3 (2, 8)	3.61 ± 0.94	-	-	8.59 ± 1.58

Arithmetic mean ± standard deviation (SD); n = 3 (individual values if n = 2); *1, PK parameters were calculated from mean plasma osimertinib concentration (n = 3) at each time point; *2, n = 2; *3, Median (range); -, Not calculated

A single dose of ^{14}C-labeled osimertinib (^{14}C-osimertinib) was administered orally at 2 mg/kg or intravenously at 1 mg/kg to male dogs under fed conditions to determine plasma radioactivity and osimertinib concentrations (the table below). BA of osimertinib in dogs was 115%.

PK parameters of radioactivity and osimertinib (male dogs, single oral or intravenous administration)

Dose (administration route)	Analyte	C_{max} (μmol/L)	t_{max}*1 (h)	AUC_t (μmol·h/L)	CL (L/h/kg)	V_{ss} (L/kg)	$t_{1/2}$ (h)
2 mg/kg (oral)	Radioactivity	0.54 ± 0.00	4 (2, 4)	53.0 ± 15.5	-	-	179*2 ± 4.97
	Osimertinib	0.20 ± 0.04	2 (2, 2)	3.74 ± 1.81	-	-	13.1 ± 4.48
1 mg/kg (intravenous)	Radioactivity	0.46 ± 0.04	-	30.3 ± 4.48	-	-	197*2 ± 34.8
	Osimertinib	0.20 ± 0.01	-	1.55 ± 0.46	1.28 ± 0.41	18.2 ± 1.58	10.3 ± 2.12

Arithmetic mean ± SD; n = 3; *1, Median (range); *2, PK data on the terminal phase are not available; -, Not calculated

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

Osimertinib 4, 10, or 40 mg/kg QD was administered orally to male rats under fed conditions and osimertinib 4, 10, or 20 mg/kg QD was administered orally to female rats under fed conditions for 4 weeks to determine plasma osimertinib concentrations (the table below). In the dose range investigated, C_{max} and AUC_t increased almost dose-proportionally. C_{max} and AUC_t did not indicate accumulation. In male rats given 40 mg/kg/day, C_{max} and AUC_t on Day 28 were lower than those on Day 1. The applicant explained that the decrease was considered attributable to toxicity caused by osimertinib administration [see "3.(iii).A.(2).1) One-month repeated oral dose toxicity study in rats"]. C_{max} and AUC_t were higher in females than in males. The applicant explained that this difference was potentially related to a gender-related difference in cytochrome P450 (CYP) isoforms in rats, because CYP 3A4 isoform is involved in the metabolism of osimertinib [see 3.(ii).A.(3) Metabolism"]; and gender-related difference in expression of oxidases such as CYPs has been reported in rats (*Pharmacol Ther.* 1988;38:269-304, etc.).

PK parameters of osimertinib (male and female rats, 4-week repeated oral administration)

Dose (mg/kg/day)	Time point (Day)	C_{max} (μmol/L)		t_{max} (h)*		AUC_t (μmol·h/L)	
		Male	Female	Male	Female	Male	Female
4	1	0.12 ± 0.03	0.14 ± 0.03	2 (2, 4)	4 (2, 4)	1.31 ± 0.42	1.56 ± 0.36
	28	0.13 ± 0.04	0.20 ± 0.05	4 (2, 4)	2 (2, 4)	1.66 ± 0.55	2.47 ± 0.49
10	1	0.25 ± 0.05	0.40 ± 0.06	2 (2, 4)	2 (2, 4)	2.54 ± 0.61	4.05 ± 0.27
	28	0.22 ± 0.04	0.33 ± 0.05	2 (2, 2)	2 (2, 4)	2.50 ± 0.31	3.41 ± 0.37
20	1	-	0.61 ± 0.05	-	2 (2, 4)	-	8.03 ± 0.82
	28	-	0.62 ± 0.11	-	4 (4, 8)	-	9.98 ± 2.91
40	1	0.95 ± 0.12	-	2 (2, 4)	-	14.0 ± 3.75	-
	28	0.55 ± 0.08	-	4 (2, 4)	-	9.53 ± 0.87	-

Arithmetic mean ± SD; n = 3; *, Median (range)

Osimertinib 2, 6, or 20 mg/kg QD was administered orally to male and female dogs under fed conditions for 4 weeks to determine plasma osimertinib concentrations (the table below). In the dose range investigated, C_{max} and AUC_t increased almost dose-proportionally. No clear gender-related differences were observed in exposure to osimertinib. C_{max} and AUC_t on Day 28 increased to approximately twice those on Day 1.

PK parameters of osimertinib (male and female dogs, 4-week repeated oral administration)

Dose (mg/kg/day)	n	Time point (Day)	C_{max} (μmol/L)		t_{max} (h)*1		AUC_t (μmol·h/L)	
			Male	Female	Male	Female	Male	Female
2	3	1	0.16 ± 0.04	0.20 ± 0.18	4 (4, 4)	2 (2, 4)	1.82 ± 0.24	2.28 ± 1.70
		15	0.22 ± 0.06	0.23 ± 0.11	4 (2, 4)	4 (2, 4)	2.76 ± 0.99	2.55 ± 1.07
		28	0.21 ± 0.09	0.25 ± 0.15	4 (2, 4)	2 (2, 4)	2.61 ± 1.34	2.72 ± 1.23
6	3	1	0.39 ± 0.20	0.28 ± 0.16	4 (2, 4)	4 (2, 4)	4.08 ± 1.92	3.54 ± 1.52
		15	0.77 ± 0.66	0.49 ± 0.31	2 (2, 4)	4 (2, 4)	8.50 ± 6.24	5.77 ± 3.35
		28	0.86 ± 0.43	0.53 ± 0.19	2 (2, 4)	2 (2, 2)	8.15 ± 3.86	6.40 ± 2.62
20	6	1	1.23 ± 0.49	1.52 ± 0.90	3 (2, 4)	4 (2, 8)	14.8 ± 5.68	18.3 ± 9.08
		11*2	1.21 ± 0.52	1.41 ± 0.44	2 (2, 4)	2 (2, 4)	13.8 ± 6.57	14.9 ± 4.28
		15*2	1.33 ± 0.49	1.34 ± 0.33	2 (2, 4)	4 (2, 4)	15.8 ± 5.61	16.1 ± 3.42
		28*2	0.97 ± 0.67	1.14 ± 0.45	3 (2, 8)	4 (4, 4)	12.3 ± 8.45	12.0 ± 2.99

Arithmetic mean ± SD; *1, Median (range); *2, administration was discontinued on Day 7 or Day 8 due to toxicity, and resumed at a reduced dose of 12 mg/kg/day on Day 11.

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

Membrane permeability of osimertinib was investigated in human colon carcinoma cell line Caco-2. The apparent permeation coefficient of osimertinib at 10 and 50 μmol/L from the apical surface to the

basolateral surface ($P_{app\ A\rightarrow B}$) was 2.58×10^{-6} and 3.35×10^{-6} cm/sec, respectively. The applicant explained that osimertinib has moderate membrane permeability because $P_{app\ A\rightarrow B}$ of minimally or moderately permeable atenolol (10 μmol/L) and highly permeable minoxidil (10 μmol/L) are 0.45×10^{-6} and 7.21×10^{-6} cm/sec, respectively.

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

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

A single oral dose of ^{14}C-osimertinib 4 mg/kg was administered to male pigmented rats and male and female albino rats to investigate tissue distribution of radioactivity by quantitative whole-body autoradiography.

After oral administration, the radioactivity was widely distributed across tissues in male pigmented rats and tissue radioactivity concentrations peaked at 6 hours post-dose in most of the tissues including blood. Maximum radioactivity concentrations in all tissues, including the brain and spinal cord and excluding lens, white fat, and seminal vesicle, were higher than the maximum concentration in blood (0.552 nmol Eq./g). The applicant explained that high affinity of osimertinib or its metabolites to melanin was suggested, because in the melanin-containing uvea and retinal pigment epithelium in the eyes, the radioactivity was detectable at 60 days post-dose and tens of times higher than that in albino rats. Tissue distribution of the radioactivity in male pigmented rats was similar to that in male albino rats except for melanin-containing tissues. No clear gender-related differences were observed in the trend of distribution in albino rats.

A single oral dose of osimertinib 5 or 25 mg/kg was administered to female SCID mice subcutaneously implanted with H1975 cell line to investigate concentrations of osimertinib and its metabolites (AZ5104 and AZ7550) in plasma, brain, and tumors by liquid chromatography-tandem mass spectrometry (LC-MS/MS). After single oral doses of osimertinib 5 and 25 mg/kg, the ratio of AUC_t in tissue to that in plasma in the brain was 1.8 and 2.8 for osimertinib, not calculated* at either dose for AZ5104, and not calculated* and 0.1 for AZ7550, respectively, while the ratio in the tumors was 1.7 and 2.8 for osimertinib, 0.26 and 0.86 for AZ5104, and 0.63 and 2.0 for AZ7550, respectively.

*: AZ5104 or AZ7550 concentration in the brain was below the lower limit of quantitation (0.08 and 0.02 μmol/L, respectively).

3.(ii).A.(2).2) Plasma protein binding

Plasma samples from mice, rats, guinea pigs, rabbits, dogs, and humans were mixed with osimertinib or its metabolites (AZ5104 or AZ7550) 100 μmol/L each, then were centrifuged at 37°C for 15 minutes, to determine plasma protein binding of osimertinib and its metabolites by ultrafiltration. Plasma protein binding rates of osimertinib and AZ7550 were not able to be calculated due to non-specific binding. On the other hand, the plasma protein binding rate of AZ5104 was 97.9%, 96.4%, 98.3%, 98.0%, 98.6%, and 98.0% in the respective samples.

Human serum albumin (45 mg/mL) or human α1-acid glycoprotein (0.9 mg/mL) was mixed with osimertinib or its metabolites (AZ5104 or AZ7550) 100 μmol/L each, then was centrifuged at 37°C for 15 minutes, to determine binding of osimertinib or its metabolites to human serum albumin and α1-acid glycoprotein by ultrafiltration. Binding rates of osimertinib, AZ5104, and AZ7550 to human serum albumin were 82.3%, 69.0%, and 83.7%, respectively, and those to α1-acid glycoprotein were 15.9%, 29.5%, and 21.5%, respectively.

The above results revealed that plasma protein binding rates of osimertinib and AZ7550 were not able to be calculated while those of osimertinib and AZ7550 to human serum albumin were higher than that of AZ5104. The applicant therefore explained that the plasma protein binding rates of osimertinib and AZ7550 were considered to be higher than that of AZ5104.

3.(ii).A.(2).3) Distribution in blood cells

A single oral dose of ^{14}C-osimertinib 10 mg/kg was administered to male and female rats and a single intravenous or oral dose of ^{14}C-osimertinib was administered at 1 mg/kg or 2 mg/kg, respectively, to male dogs to investigate distribution of osimertinib in blood cells. The applicant explained that the ratio

of blood radioactivity concentration to plasma radioactivity concentration was ≥1 at any time point, suggesting that radioactivity is distributed in blood cells.

3.(ii).A.(2).4) Covalent binding to hepatocyte protein

Rat and human hepatocytes were incubated with ^{14}C-osimertinib at 10 μmol/L at 37°C for 4 hours to investigate covalent binding of osimertinib or its metabolites to hepatocyte protein. The amount of covalent binding in rat and human hepatocytes was 217 and 677 pmol/mg protein, and the covalent binding rate calculated from the percentage of unchanged osimertinib not recovered (71% and 15%, respectively) was 0.020 and 0.29, respectively.

3.(ii).A.(2).5) Placental permeability and placental to fetal transfer

After repeated oral administration of osimertinib 20 mg/kg QD to pregnant rats, fetal plasma concentrations of osimertinib and AZ7550 on gestation day 16 were 0.28 and 0.0020 μmol/L, respectively. Consequently, the applicant explained that osimertinib and its metabolite are considered to cross the placenta.

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

Mouse, rat, dog, and human hepatocytes were incubated with osimertinib at 5 μmol/L at 37°C for 1 hour to investigate metabolites of osimertinib. In hepatocytes of humans and all animal species, AZ5104, AZ7550, M1 (oxidant), M4 (oxidant), and M10 (glutathione conjugate) were detected. Also, M2 (dealkylated form) was detected in hepatocytes of humans and all animal species except mice, and M8 (cysteine-glycine conjugate) in hepatocytes of rats and humans.

CYP isoforms involved in metabolism of osimertinib in humans were investigated. On the basis of the investigation results, the applicant explained that CYP3A4 isoform is mainly involved in the metabolism of osimertinib in humans. CYP1A2, CYP2A6, CYP2C9, CYP2E1, and CYP3A5 isoforms are also involved, although their contribution is limited.

- Membrane vesicles prepared from *Escherichia coli* expressing CYP isoforms (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4) were incubated with osimertinib at 2 μmol/L for 30 minutes. Osimertinib was metabolized in CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 expression systems, and the contribution of each CYP isoform to metabolism of osimertinib was 3.2%, 8.9%, 1.4%, 1.3%, and 85.2%, respectively, based on the intrinsic clearance.

- Microsomes prepared from insect ovary cell line Sf9 expressing CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, or CYP3A5) were incubated with osimertinib at 1 μmol/L for 30 minutes. Osimertinib was metabolized in CYP1A2, CYP2A6, CYP2C9, CYP2E1, CYP3A4, and CYP3A5 expression systems, and the contribution of each CYP isoform to metabolism of osimertinib was 12.0%, 15.5%, 15.5%, 3.0%, 44.4%, and 9.6%, respectively, based on the intrinsic clearance.

- Human hepatocytes were incubated with osimertinib at 1 μmol/L for 120 minutes in the presence of CYP2C8, CYP2C9, CYP2C19, and CYP3A inhibitors, a CYP isoform non-specific inhibitor as well as a flavin-containing monooxygenase inhibitor. The mean formation rate of AZ5104 (0.044 pmol/min/10^6 cells) decreased in the presence of a CYP3A inhibitor (ketoconazole) and a CYP isoform non-specific inhibitor (1-aminobenzotriazole) (0.028 and 0.013 pmol/min/10^6 cells, respectively). In addition, the mean formation rate of AZ7550 (0.231 pmol/min/10^6 cells) decreased in the presence of a CYP3A inhibitor and a CYP isoform non-specific inhibitor (0.092 and 0.010 pmol/min/10^6 cells, respectively). Meanwhile, other inhibitors did not inhibit the metabolism of osimertinib remarkably.

CYP isoforms involved in metabolism of osimertinib metabolites (AZ5104 and AZ7550) were investigated as below. On the basis of the investigation results, the applicant explained that CYP3A4, CYP3A5, and CYP3A4 isoforms are mainly involved in metabolism of AZ5104 and AZ7550 in humans.

- Membrane vesicles prepared from insect ovary cell line Sf9 expressing CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, or CYP3A5)

were incubated with AZ5104 and AZ7550 at 2 μmol/L for 30 minutes. AZ5104 was metabolized in CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5 expression systems, and the contribution of each CYP isoform to metabolism of osimertinib was 0.373%, 3.19%, 0.160%, 0.958%, 0.285%, 67.0%, and 28.1%, respectively, based on the intrinsic clearance. AZ7550 was metabolized in CYP2C8 and CYP3A4 expression systems, and the contribution of each CYP isoform to metabolism of osimertinib was 0.129% and 99.9%, respectively, based on the intrinsic clearance.

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

3.(ii).A.(4).1) Urinary and fecal excretion

A single intravenous or oral dose of ^{14}C-osimertinib was administered at 2 or 10 mg/kg, respectively, to female and male rats; and a single intravenous or oral dose was administered at 1 or 2 mg/kg, respectively, to male dogs to investigate urinary and fecal excretion rates (percentage of the administered radioactivity excreted), yielding the following results. On the basis of the results, the applicant explained that osimertinib is mainly excreted into feces through bile.

- Urinary and fecal excretion rates up to 168 hours after intravenous administration to rats were 3.8% and 84.4% in males and 2.8% and 80.9% in females, respectively. The respective rates after oral administration were 2.3% and 93.4% in males and 2.3% and 87.4% in females. No clear gender-related differences were observed in urinary or fecal excretion rate following either intravenous or oral administration.

- Urinary and fecal excretion rates up to 168 hours after intravenous administration to male dogs were 3.1% and 81.4%, respectively. The respective rates after oral administration were 2.9% and 83.3%.

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

Although excretion of osimertinib in milk has not been investigated, the applicant explained that the possibility of excretion in milk could not be ruled out, because lower mean body weight of offspring were observed when lactating female rats were treated with osimertinib [see "3.(iii).A.(5).2) Study for effects on embryo-fetal development and pre- and postnatal development"].

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

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

In the presence of osimertinib, AZ5104, or AZ7550 (0.1-30 μmol/L), substrates* of CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A) were incubated with human liver microsomes to investigate effects of osimertinib and its metabolites on metabolism of the substrate of each CYP isoform, yielding the following results.

*: Phenacetin, coumarin, bupropion, amodiaquine, diclofenac, S-mephenytoin, bufuralol, chlorzoxazone and midazolam and nifedipine, respectively, were used.

- Osimertinib inhibited metabolism of substrates of CYP1A2, CYP2C8, and CYP3A (IC_{50} value; 25.7,* 22.8, and 5.14-26.2 μmol/L, respectively). In addition, osimertinib at 30 μmol/L inhibited activity of CYP2E1 by 14.8%. Osimertinib at the highest concentration investigated did not clearly inhibit metabolism of the substrates of CYP2A6, CYP2B6, CYP2C9, CYP2C19, or CYP2D6.

- AZ5104 inhibited metabolism of substrates of CYP1A2, CYP2C8, and CYP3A (IC_{50} value; 29.5,* 27.9,* and 17.9-19.9 μmol/L). AZ5104 at the highest concentration investigated did not clearly inhibit metabolism of the substrates of CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP2E1.

- AZ7550 inhibited metabolism of substrates of CYP1A2 and CYP3A (IC_{50} value; 25.2 and 18.7-30* μmol/L). AZ7550 at the highest concentration investigated did not clearly inhibit metabolism of the substrates of CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, or CYP2E1.

*: Mean, n = 3 (if individual values were >30 μmol/L, they were regarded as 30 μmol/L to calculate the mean).

Osimertinib (10 or 50 μmol/L), AZ5104 (10 or 50 μmol/L), or AZ7550 (50 μmol/L) was pre-incubated with human liver microsomes followed by incubation with substrates* of CYP isoforms (CYP1A2, CYP2C9, CYP2C19, or CYP3A) to investigate time-dependent inhibition of osimertinib and its metabolites against various CYP isoforms. Osimertinib and AZ5104 at 50 μmol/L inhibited metabolism

of CYP3A substrate by 24% and 23%, respectively. Osimertinib and AZ5104 at the highest concentration investigated did not clearly inhibit metabolism of the substrates of CYP1A2, CYP2C9, or CYP2C19. In addition, AZ7550 did not clearly inhibit metabolism of the substrates of CYP1A2, CYP2C9, CYP2C19, or CYP3A.

*: Phenacetin, diclofenac, S-mephenytoin, and midazolam, respectively, were used.

In the presence of osimertinib (0.0729 to 30 μmol/L), human liver microsomes were incubated with substrates* of UDP-glucuronosyltransferase (UGT) 1A1 and UGT2B7 to investigate the effects of osimertinib on metabolism of each UGT isoform substrate. Osimertinib at 9 and 30 μmol/L inhibited metabolism of UGT1A1 substrate by 19% and 42%, respectively. Osimertinib at the highest concentration investigated did not clearly inhibit the metabolism ofUGT2B7 substrate.

*: Estradiol and morphine were used.

The applicant suggested the possibility of pharmacokinetic interaction through inhibition of osimertinib against CYP3A in clinical settings on the basis of the above investigation results and in consideration that the C_{max} of osimertinib following multiple oral doses of osimertinib 80 mg QD to Japanese NSCLC patients was 0.78 μmol/L [see "4.(ii).B.(1) Differences in PK between Japanese and non-Japanese patients"].

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

Human hepatocytes were incubated with osimertinib (0.04-3.3 μmol/L) for 48 hours to investigate effects of osimertinib on induction of CYP isoforms (CYP1A, CYP2B6, and CYP3A). Osimertinib up to 3.3 μmol/L increased mRNA levels of CYP1A2 and CYP1A enzyme activity by 11 and 8.3 fold, respectively, compared with the group not incubated with osimertinib. In addition, osimertinib increased mRNA levels of CYP3A4 by 173 fold compared with the group not incubated with osimertinib, and increased CYP3A enzyme activity (up to 4.9 fold) in 2 of 3 hepatocyte lots investigated. The mRNA levels of CYP2B6 did not increase at the highest level of osimertinib concentration investigated.

On the basis of the above investigation results, the applicant explained that osimertinib possibly induces CYP3A4 and CYP1A2 in routine clinical use.

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

The applicant explained that the following investigation results demonstrated that osimertinib, AZ7550, and AZ5104 are substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

- In canine renal epithelial cell line MDCK expressing human P-gp (P-gp-expressing MDCK cell line), P-gp-mediated transport of osimertinib or AZ5104 (1 μmol/L) was investigated. Ratios of efflux permeability coefficient to influx permeability coefficient (efflux ratios) of osimertinib and AZ5104 in the presence of a P-gp inhibitor (valspodar, 1 μmol/L) were 1.01 and 0.875, respectively, which were lower than the respective ratios in the absence of the P-gp inhibitor (13.4 and 186, respectively). The efflux ratio of AZ7550 (10 and 30 μmol/L) in P-gp-expressing MDCK cell line was ≥2 fold that in P-gp-non-expressing MDCK cell line.

- In MDCK cell line expressing human BCRP (BCRP-expressing MDCK cell line), transport of osimertinib or AZ5104 (1 μmol/L) via BCRP was investigated. Their efflux ratios in the presence of a BCRP inhibitor (Ko143, 10 μmol/L) were 1.35 and 1.51, respectively, which were lower than the respective ratios in the absence of the BCRP inhibitor (5.40 and 7.06, respectively). The efflux ratio of AZ7550 (10 and 30 μmol/L) in BCRP-expressing MDCK cell line was ≥2 fold that in BCRP-non-expressing MDCK cell line.

- In human embryonic kidney cell line HEK293 expressing human organic anion transport polypeptide (OATP) 1B1 (OATP1B1-expressing HEK293 cell line), transport of osimertinib, AZ7550, or AZ5104 (1-30 μmol/L) via OATP1B1 was investigated. Maximum ratios of uptake rate in OATP1B1-expressing HEK293 cell line to that in OATP1B1-non-expressing HEK293 cell line (influx rate ratio) were 1.13, 1.13, and 1.24, respectively, in the investigated concentration ranges of osimertinib, AZ7550, and AZ5104.

- In HEK293 cell line expressing human OATP1B3 (OATP1B3-expressing HEK293 cell line), transport of osimertinib, AZ7550, or AZ5104 (1-30 μmol/L) via OATP1B3 was investigated. Influx rate ratios of osimertinib, AZ7550, and AZ5104 in OATP1B3-expressing HEK293 cell line were 1.11, 1.00, and 1.03, respectively, at the maximum concentration in the range investigated.

On the basis of the following investigation results, taking into account that C_{max} of osimertinib following multiple oral doses of osimertinib 80 mg QD to Japanese NSCLC patients was 0.78 μmol/L [see "4.(ii).B.(1) Differences in PK between Japanese and non-Japanese patients"], and assuming that plasma protein binding rate is 10%. the applicant explained that the pharmacokinetic interactions mediated by BCRP inhibition by osimertinib may occur in routine clinical use, although pharmacokinetic interactions mediated by inhibition of P-gp, OATP1B1, OAT1 or OAT3, MATE1 or MATE2-K, or OCT2 by osimertinib is unlikely to occur. In addition, based on results from a study on the impact of concomitant use of osimertinib with BCRP substrate (rosuvastatin) on the PK of the BCRP substrate (Study D5160C00019), the applicant explained that osimertinib increases the exposure to a drug acting as a substrate of BCRP in clinical settings [see "4.(ii).A.(4).4) Study on drug interaction with rosuvastatin].

- In canine renal epithelial cell line MDCK II expressing human P-gp the inhibitory effect of osimertinib (1-300 μmol/L) on P-gp-mediated transport of ^{3}H-digoxin (5 μmol/L) was investigated. Osimertinib did not markedly inhibit the P-gp-mediated transport at the highest concentration investigated.

- In MDCKII cell line expressing human BCRP, the inhibitory effect of osimertinib (0.0293-293 μmol/L) on BCRP-mediated transport of prazosin (1 μmol/L) was investigated. Osimertinib did not markedly inhibit the BCRP-mediated transport at the highest concentration investigated.

- Caco2 cell line expressing human BCRP was used to investigate the inhibitory effect of osimertinib (1-300 μmol/L) on BCRP-mediated transport of ^{3}H-rosuvastatin (1 μmol/L). Osimertinib inhibited the BCRP-mediated transport (IC_{50} value, 2.0 μmol/L).

- HEK293 cell line expressing OATP1B1 or OATP1B3 was used to investigate the inhibitory effect of osimertinib (0.3-100 μmol/L) on transport of a substrate* of the corresponding transporter via OATP1B1 or OATP1B3. Osimertinib inhibited the transport via OATP1B1 (IC_{50} value, 22 μmol/L), and also inhibited the transport via OATP1B3 (IC_{50} value, 52.5 μmol/L).

- HEK293 cell line expressing human OAT1 or OAT3 was used to investigate the inhibitory effect of osimertinib (0.3-100 μmol/L) on transport of a substrate* of the corresponding transporter via OAT1 or OAT3. Osimertinib at the highest concentration investigated did not significantly inhibit the transport via OAT1 or OAT3.

- HEK293 cell line expressing human MATE1 or MATE2-K, was used to investigate the inhibitory effect of osimertinib (0.3-100 μmol/L) on transport of a substrate* of the corresponding transporter via MATE1 or MATE2-K. Osimertinib inhibited the transport via MATE1 (IC_{50} value, 4.63 μmol/L), and also inhibited the transport via MATE2-K (IC_{50} value, 23.0 μmol/L).

- HEK293 cell line expressing human OCT2, was used to investigate the inhibitory effect of osimertinib (0.3-100 μmol/L) on transport of ^{14}C-metformin (10 μmol/L) via OCT2. Osimertinib inhibited the transport via OCT2 (IC_{50} value, 7.98 μmol/L).

  *: The substrates of transporters were ^{3}H-labeled estradiol-17β-glucuronide (0.02 μmol/L) and atorvastatin (0.15 μmol/L) for OATP1B1 and OATP1B3; *p*-aminohippurate (10 μmol/L) and furosemide (5 μmol/L) for OAT1 and OAT3; and metformin (50 μmol/L) and 4-(4-(diethylamino)styryl)-*N*-methylpyridinium iodide) (1 μmol/L) for MATE1 and MATE2-K.

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

Based on the submitted data and the following review, PMDA has concluded that the applicant's discussions on absorption, distribution, metabolism, and excretion and pharmacokinetic interactions of osimertinib are acceptable.

3.(ii).B.(1) Tissue distribution

The results from a tissue distribution study in pigmented rats suggested high affinity of osimertinib or its metabolites to melanin [see "3.(ii).A.(2).1) Tissue distribution"]. Given this finding, PMDA asked about the safety of osimertinib in melanin-containing tissues.

The applicant's explanation:
Although the incidence of adverse events involving the skin, melanin-containing tissue, was high in the phase II part of the AURA study and the AURA2 study [see "4.(iii).B.(3).12) Skin disorder"], many of the events of skin disorder reported in the Japanese population whose tissues have more melanin than those in the non-Japanese population were at Grade ≤2; and no serious adverse events involving the eyes occurred [see "4.(iii).B.(3).14) Others"]. The affinity of osimertinib and its metabolites to melanin is therefore considered to raise no safety concerns.

PMDA accepted the applicant's explanation.

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

The *in vitro* study results suggested that osimertinib (a) inhibits CYP3A [see "3.(ii).A.(5).1) Enzyme inhibition"]; (b) induces CYP1A2 and CYP3A4 [see "3.(ii).A.(5).2) Enzyme induction"]; and (c) is a substrate of P-gp and BCRP [see "3.(ii).A.(5).3) Transporters"]. The applicant explained the pharmacokinetic interactions of osimertinib with CYP1A2 substrates as well as P-gp and BCRP inhibitors in routine clinical use as shown below. On the basis of the results from a study of effects of concomitant use of osimertinib with CYP3A substrate (simvastatin) on the PK of the CYP3A substrate (Study D5160C00014), the applicant explained that osimertinib does not markedly affect the PK of a drug metabolized by CYP3A in routine clinical use [see "4.(ii).A.(4).3) Study of drug interactions with simvastatin"].

- Because the CYP1A2 induction effect of osimertinib was weaker than its CYP3A4 induction effect [see "3.(ii).A.(5).2) Enzyme induction"]; and concomitant use of osimertinib with CYP3A substrate did not markedly affect the PK of the CYP3A substrate [see "4.(ii).A.(4).3) Study of drug interactions with simvastatin"], CYP1A2 induction of osimertinib is considered unlikely to cause pharmacokinetic interactions in routine clinical use. Also, in the phase II part of the AURA study and the AURA2 study, 33 of 411 patients concomitantly received a CYP1A2 substrate, but no clinical issues attributable to the pharmacokinetic interactions involving CYP1A2 occurred in these patients.
- Pharmacokinetic interactions of osimertinib with P-gp and BCRP inhibitors are considered unlikely to occur in routine clinical use for the following reasons: (a) The membrane permeability of osimertinib is high [see "3.(ii).A.(1).3) *In vitro* membrane permeability"], and the absorption rate of osimertinib in humans is suggested to be ≥81.9% [see "4.(ii).A.(3) Foreign phase I study"]; and (b) In the phase II part of the AURA study and the AURA2 study, no marked differences in exposure to or safety of osimertinib were observed between patients concomitantly receiving P-gp or BCRP inhibitor (39 of 411 and 6 of 411 patients, respectively) and other patients (not concomitantly receiving such inhibitor; 372 of 411 and 405 of 411 patients, respectively).

PMDA's view:
At the time of this review, clinical studies have not raised any clinically significant concerns attributable to the pharmacokinetic interactions of osimertinib with CYP1A2 substrates as well as P-gp and BCRP inhibitors. However, information on drug-metabolizing enzyme- or transporter-mediated pharmacokinetic interactions with osimertinib is considered important to ensure proper use of osimertinib. Therefore, PMDA considers it necessary to continue collecting the relevant information and provide the information appropriately to healthcare professionals in clinical settings when useful findings become available.

3.(iii) Summary of toxicology studies

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

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

Although no single-dose toxicity studies of osimertinib have been conducted, acute toxicity and approximate lethal dose were evaluated on the basis of the following studies.

3.(iii).A.(1).1) Micronucleus assay in rats
Osimertinib 0 (vehicle, 0.5% hydroxypropylmethylcellulose), 30, 150, or 300 mg/kg QD was administered orally to male Han Wistar rats (n = 7/group) for 2 days.

There were neither deaths nor changes in clinical signs.

On the basis of the above, the approximate lethal dose in this study was determined to be >300 mg/kg.

3.(iii).A.(1).2) Maximum tolerated oral dose toxicity study in rats (Reference data)
Osimertinib 100, 300, or 1000 mg/kg QD was administered orally to male Han Wistar rats (n = 1-3/group) for 2 days followed by 6 day observation period.

Decreased physical activity, irregular respiration, decreased respiratory rate, loose stool, and hunchback position occurred post-dose on Day 2 in the1000 mg/kg group, and 1 of 1 animal in this group was sacrificed moribund. Decreased body weight, increased water intake, loose stool, watery stool, and piloerection occurred in the 300 mg/kg/day group.

On the basis of the above, the approximate lethal dose and maximum tolerated dose (MTD) in this study were determined to be 300 to 1000 mg/kg and 300 mg/kg/day, respectively.

3.(iii).A.(1).3) Maximum tolerated oral dose toxicity study in dogs (Reference data)
Single oral doses of osimertinib 10, 30, 100, 200, and 400 mg/kg were sequentially administered ≥2 days apart to the same beagle dogs (n = 1/sex), and then oral doses of 100 mg/kg QD were administered for 5 days.

No deaths occurred, but findings included decreased food consumption and increased cholesterol at single doses of ≥10 mg/kg; vomiting at doses of ≥100 mg/kg; decreased body weight and decreased potassium at doses of ≥200 mg/kg; and decreased activity as well as decreases in red blood cell count, hematocrit, hemoglobin, and sodium at a dose of 400 mg/kg.

On the basis of the above, the approximate lethal dose in this study was determined to be >400 mg/kg.

3.(iii).A.(2) Repeat-dose toxicity
The applicant submitted 1- and 3-month repeated oral dose toxicity studies in rats and dogs as evaluation data. The applicant also submitted 7- and 14-day repeated oral dose toxicity studies in rats and 14-day repeated oral dose toxicity study in dogs as reference data. Histopathological findings in these studies mainly included atrophy, degeneration, and inflammation of the gastrointestinal epithelium, epidermal degeneration of the skin, decreased lymphocytes in the thymus, decreased cell density in the bone marrow, decreased glycogen in the liver, and changes (corneal epithelial atrophy etc.) in the cornea of the eye.

3.(iii).A.(2).1) One-month repeated oral dose toxicity study in rats
Osimertinib 0 (vehicle, 0.5% hydroxypropylmethylcellulose), 4, 10, 20 (females only), or 40 (males only) mg/kg QD was administered orally to Han Wistar rats (n = 10/sex/group) for 1 month followed by a 4-week recovery period.

Findings in males included corneal epithelial atrophy in the ≥4 mg/kg groups; decreases in hemoglobin and hematocrit, undescended sperm cells in the testis in the ≥10 mg/kg groups; and reduced body weight gain, decreased food consumption, piloerection, crust formation on the naso-oral part, increases in white blood cell count, neutrophil count, lymphocyte count, and monocyte count, decreases in triglyceride, cholesterol, total protein, albumin, and globulin, decreased weights of the thymus, liver, epididymis, and prostate, epithelium atrophy of the tongue, inflammatory cell infiltration in the skin and naso-oral part, hair follicle dysplasia, erosion, and ulcer on the epidermis, sinus erythrocytes and erythrophagocytosis in the mesenteric lymph node, and seminiferous tubule degeneration in the testis as well as decreased sperm count and cell debris in the epididymis in the 40 mg/kg group.

Findings in females included corneal epithelial atrophy in the ≥4 mg/kg groups; increases in neutrophil count and white blood cell count, epithelium atrophy in the tongue, thin epithelium, inflammatory cell infiltration, and epithelium degeneration in the uterus as well as corpus luteum degeneration and inflammatory cell infiltration in the ovary in the ≥10 mg/kg groups; and piloerection, decreases in total protein and albumin, inflammatory cell infiltration in the skin and naso-oral part, hair follicle dysplasia, erosion, and ulcer in the epidermis as well as sinus erythrocytes and erythrophagocytosis in the mesenteric lymph node in the ≥20 mg/kg group. The increases in neutrophil count and white blood cell count in the ≥10 mg/kg groups were considered to have little toxicological significance, because they fell within the historical range.

All of these findings at the end of the treatment period were reversible or tended to be reversible.

On the basis of the above, the no observed adverse effect level (NOAEL) in this study was determined to be <4 mg/kg/day.

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

Osimertinib 0 (vehicle, water at pH 3-3.5 adjusted with methanesulfonic acid), 1, 10, 20 (females only), or 40/20 (males only) mg/kg QD was administered orally to Han Wistar rats (n = 10/sex/group) for 3 months. In the 40/20 mg/kg group, administration was initiated at a dose of 40 mg/kg, but administration was interrupted from Day 56 to Day 61 due to aggravated clinical signs, and then resumed at a reduced dose of 20 mg/kg on Day 62. In this study, effects of osimertinib on male fertility were evaluated [see "3.(iii).A.(5).1) Fertility and early embryonic development"].

Findings in males included crust formation in the ≥1 mg/kg groups (except for the 10 mg/kg group); reduced body weight gain, corneal epithelial atrophy, epithelium atrophy in the tongue and esophagus, degeneration, regeneration, single cell necrosis and lymphocyte infiltration in the Harderian gland, foamy alveolar macrophage accumulation as well as undescended sperm cells in the ≥10 mg/kg groups; and dry fur, abnormal fur, peeling, increases in neutrophil count, monocyte count, basophil count, and white blood cell count, increases in fibrinogen and globulin, decreases in albumin and albumin/globulin (A/G) ratio, increases in urine specific gravity and total protein/creatine ratio by urinalysis, blood in the urine, decreased epididymis and prostate weights, epithelium atrophy and ulcer in the forestomach, follicular and perifollicular inflammation in the skin, erythrophagocytosis in the mesenteric lymph node as well as increased hematopoiesis in the spleen in the 40/20 mg/kg group.

Findings in females included reduced body weight gain, peeling and crust formation, increased N-acetyl-β-D-glucosaminidase/creatinine ratio by urinalysis, decreased uterus weight, corneal epithelial atrophy, epithelium atrophy in the tongue and esophagus, follicular and perifollicular inflammation in the skin, thin epithelium in the vagina and uterus, degeneration, regeneration, single cell necrosis, and lymphocyte infiltration in the Harderian gland, foamy alveolar macrophage accumulation as well as increased hematopoiesis in the spleen in the ≥10 mg/kg groups; and hunchback position, abnormal gait, abnormal fur, increases in neutrophil count, monocyte count, basophil count, and white blood cell count, increases in fibrinogen and globulin, deceases in albumin and A/G ratio, increases in urine specific gravity and total protein/creatine ratio by urinalysis, blood in the urine, epithelium atrophy and ulcer in the forestomach as well as erythrophagocytosis in the mesenteric lymph node in the 20 mg/kg group.

Crust observed in males in the 1 mg/kg group was considered unrelated to osimertinib, because it was transient, the incidence fell within the laboratory's historical range, and no histopathological findings were noted in the skin. All changes observed in urinalysis data of females and males were considered to be of little toxicological significance, because none of them were associated with histopathological changes.

Foamy alveolar macrophage accumulation was investigated by electron microscopy, yielding findings suggesting that early phospholipidosis and accumulation of lipofuscin or multivesicular bodies were noted in the cytoplasm of macrophages. Foamy alveolar macrophage accumulation was considered to be of little toxicological significance, because it was slight to mild in severity, and other inflammatory or degenerative changes associated with the above finding were not observed in the lung. On the basis of a report indicating that EGFR is processed through multivesicular bodies before degradation in the

lysosome (*Biochem Soc Trans.* 2009;37:173-177), the applicant explained the potential mechanism of development of foamy alveolar macrophage accumulation as follows: osimertinib is likely to inhibit degradation of EGFR in lysosomes, and thus multivesicular bodies are possibly accumulated in the cytoplasm of macrophages.

On the basis of the above, the NOAEL in this study was determined to be 1 mg/kg/day for both males and females. AUC_t (254 and 543 nmol·h/L in males and females, respectively) in the 1 mg/kg group was approximately 0.02 to 0.04 fold the clinical exposure.*

*: The arithmetic mean AUC_t of osimertinib was 14,980 nmol·h/L after multiple oral doses of osimertinib 80 mg/day in Japanese NSCLC patients in the phase II part of the AURA study.

3.(iii).A.(2).3) One-month repeated oral dose toxicity study in dogs

Osimertinib 0 (vehicle, 0.5% hydroxypropylmethylcellulose), 2, 6, or 20/12 mg/kg QD was administered orally to beagle dogs (n = 3-6/sex/group) for 1 month, and 3 animals each in both sexes in the 20/12 mg/kg group underwent a 4-week recovery period after 1 month administration. In the 20/12 mg/kg group, administration was initiated at a dose of 20 mg/kg, but interrupted from Day 8 to Day 10 due to occurrence of corneal epithelial ulcer and erosion, conjunctival redness, etc., and then resumed at a reduced dose of 12 mg/kg on Day 11.

Findings included decreased food consumption, reduced body weight gain, and decreased body weight, abnormal stool (loose, watery, reddish, and mucous stool), high cholesterol level, increased insulin, seminiferous tubule atrophy in the testis as well as round germ cells in the epididymis in the ≥2 mg/kg groups; vomiting, corneal epithelial atrophy, and epithelium atrophy in the tongue in the ≥6 mg/kg groups; and salivation, discoloration in the gingiva and tongue, ataxia, decreased activity, translucency, ulcer, and erosion in the cornea, conjunctival reddening and lacrimation, high fibrinogen level, low albumin level, mucosal atrophy in the duodenum, inflammatory cell infiltration in the ileum as well as epidermis atrophy in the skin in the 20/12 mg/kg group.

Although increase of insulin was possibly related to the effects of osimertinib on IGF1R and INSR [see "3.(i).A.(1).2) Inhibitory effect on kinases other than EGFR"], but was considered to be of no toxicological significance because it was transient, was not dose-dependent, and was not associated with changes in glucose level.

After a 4-week recovery period, all of these findings were reversible or tended to be reversible.

On the basis of the above, the NOAEL in this study was determined to be <2 mg/kg/day.

3.(iii).A.(2).4) Three-month repeated oral dose toxicity study in dogs

Osimertinib 0 (vehicle, water at pH 3-3.5 adjusted with methanesulfonic acid), 1, 3, or 10/6 mg/kg QD was administered orally to beagle dogs (n = 4/sex/group) for 3 months. In the 10/6 mg/kg group, administration was initiated at a dose of 10 mg/kg, but was given at a reduced dose of 6 mg/kg on Day 23 onward in all animals due to symptoms in eyes such as corneal epithelial ulcer and erosion, conjunctival reddening, eyelid closure, etc., and was interrupted in some animals for 1 to 8 days during the treatment period.

Findings included high cholesterol level in ≥1 mg/kg groups; conjunctival reddening and secretion in the ≥3 mg/kg groups; and translucency and opacity in the cornea, high fibrinogen level and neutrophil count, low albumin and calcium levels, corneal epithelial atrophy, seminiferous tubule atrophy in the testis as well as decreased sperm count in the epididymis in the 10/6 mg/kg group.

The findings of conjunctival reddening and secretion in the 3 mg/kg group were considered to be of little toxicological significance, because they were transient. All the changes in clinical chemistry values in the ≥1 mg/kg groups were considered to be of little toxicological significance, because they were slight in severity and not associated with histopathological changes.

On the basis of the above, the NOAEL in this study was determined to be 3 mg/kg/day. AUC_t (2210 nmol·h/L) in the 3 mg/kg group was approximately 0.15 fold the clinical exposure.*

*: The arithmetic mean AUC_t of osimertinib was 14,980 nmol·h/L after multiple oral doses of osimertinib 80 mg/day in Japanese NSCLC patients in the phase II part of the AURA study.

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

As genotoxicity studies, the applicant conducted a bacterial reverse mutation assay, chromosomal aberration assay in mouse lymphoma cells, and rat micronucleus assay, and none of them indicated genotoxicity. The exposure to osimertinib at the highest dose (300 mg/kg/day, MTD) in the rat micronucleus assay was estimated to be 34,400 nmol·h/L,[*1] which was approximately 2.3 fold the clinical exposure.[*2]

*1: Estimated from AUC_t at a dose of 300 mg/kg/day in the maximum tolerated oral dose toxicity study in rats.
*2: The arithmetic mean AUC_t of osimertinib was 14,980 nmol·h/L after multiple oral doses of 80 mg/day in Japanese NSCLC patients in the phase II part of the AURA study.

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

Since osimertinib is intended to treat advanced or recurrent NSCLC, no carcinogenicity test was conducted.

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

3.(iii).A.(5).1) Fertility and early embryonic development

Effects of osimertinib on male fertility were evaluated in the 3-month repeat-dose toxicity study in rats [see "3.(iii).A.(2).2) Three-month repeated oral dose toxicity study in rats"]. Osimertinib 0 (vehicle, water at pH 3-3.5 adjusted with methanesulfonic acid and sodium hydroxide), 4, 10, or 40/20 mg/kg QD was administered orally to male Han Wistar rats for 3 months, and during Week 10 and Week 11, these male rats were housed with untreated female Han Wistar rats at a ratio of 1:1. As a result, decrease in the number of live implantation and increased preimplantation loss were observed in mated untreated females in the 40/20 mg/kg group.

On the basis of the above, the NOAEL for male fertility was determined to be 10 mg/kg/day.

The applicant explained that male patients receiving osimertinib need to use a contraceptive, because osimertinib has potential adverse effects on male fertility on the basis of (a) the above investigation results; (b) the observed impact on the testis in repeat-dose toxicity studies in rats and dogs [see "3.(iii).A.(2) Repeat-dose toxicity"]; and (c) EGFR expression in the testis, and epidermal growth factor involvement in spermatogenesis regulation (*J Urol.* 2005;174:2089-2090, *Arch Androl.* 1998;40:133-146).

The applicant also explained that osimertinib potentially affects female fertility from the following aspects:

- In a repeat-dose toxicity study in rats [see "3.(iii).A.(2).1) One-month repeated oral dose toxicity study in rats"], histopathological changes were observed in the ovary, uterus, and vagina, and these findings were considered related to the inhibition of physiological functions of epidermal growth factor in regulating normal ovarian functions and growth stimulation of uterus inner membrane and adenosquamous cells (*Molec Cell Endocrinol.* 1986;44:99-108, *Acta Physiol Scand.* 1995;154:177-183, *Anticancer Res.* 2003;23:3639-3650, *Toxicol Pathol.* 2001;29:159-173).
- In a study to evaluate effects on fertility and early embryonic development to implantation in rats (osimertinib was administered for 14 days before mating, during mating, and until gestation day 8), number of live implantation decreased and the incidence of early embryonic deaths increased.

3.(iii).A.(5).2) Study of embryo-fetal and pre- and postnatal development

In this study, female rats were treated with osimertinib from gestation day 2 to lactation day 6 to investigate the effects on embryos and fetuses. This study consisted of 3 phases, of which Phase 1 and Phase 3 included histopathological examination on the maternal cornea and tongue. In this study, osimertinib was detected in the fetuses and offspring in the ≥20 mg/kg groups.

(a) Phase 1:

Osimertinib 0 (vehicle, water at pH 3-3.5 adjusted with methanesulfonic acid or sodium hydroxide) or 20 mg/kg QD was administered orally to pregnant Han Wistar rats (n = 6/group) from gestation day 2 to gestation day 20, and necropsy was performed on gestation day 20.

In maternal animals, reduced body weight gain and decreased food consumption, corneal epithelial atrophy, and glossal epithelial atrophy were observed in the 20 mg/kg group. In embryos and fetuses, decreased number of live fetuses and increased incidence of early embryonic deaths were observed in the 20 mg/kg group.

(b) Phase 2:
Osimertinib 0 (vehicle, water at pH 3-3.5 adjusted with methanesulfonic acid or sodium hydroxide), 1, 10, 20, or 30 mg/kg QD was administered orally to pregnant Han Wistar rats (n = 6/group) from gestation day 6 to gestation day 16, and necropsy was performed on gestation day 21.

In maternal animals, piloerection, salivation, loose stool, and reduced body weight gain and decreased food consumption were observed in the ≥20 mg/kg groups. In embryos and fetuses, decreased mean fetal weight was observed in the ≥20 mg/kg groups.

On the basis of the above, the NOAEL in this study was determined to be 10 mg/kg for both maternal animals and embryos and fetuses.

(c) Phase 3:
Osimertinib 0 (vehicle, water at pH 3-3.5 adjusted with methanesulfonic acid or sodium hydroxide), 1, or 30 mg/kg QD was administered orally to pregnant Han Wistar rats (n = 6/group) from gestation day 6 to lactation day 6, and necropsy was performed 7 to 9 days postpartum.

In 1 of 6 maternal animals in the 30 mg/kg group, aggravated clinical signs (emaciation, dyspnea, cold to the touch, partial eyelid closure, etc.) and decreased body weight were observed, and thus the animal was sacrificed moribund on gestation day 23. In other maternal animals in the 30 mg/kg group, changes in clinical signs such as piloerection and emaciation, reduced body weight gain and decreased food consumption as well as corneal epithelial atrophy and corneal edema associated with vacuolation in the corneal endothelium were observed. In all 5 animals in the 30 mg/kg group, decreased delivery index and live birth index as well as total litter loss in the embryos, fetuses, and offspring were observed. Moreover, since total litter loss rate in the vehicle group was as high as 50% (3 of 6 animals), the study was conducted again.

In the second study, osimertinib 0 (vehicle, water at pH 3-3.5 adjusted with methanesulfonic acid and sodium hydroxide), 1, or 20 mg/kg QD was administered orally to pregnant Han Wistar rats (n = 6/group) from gestation day 6 to lactation day 6, and necropsy was performed 7 to 9 days postpartum.

In 1 of 6 maternal animals in the 20 mg/kg group, aggravated clinical signs (irregular respiration and decreased activity) as well as reduced body weight and decreased food consumption were observed, and thus the animal was sacrificed moribund on lactation day 4. In the other maternal animals, reduced body weight gain and decreased food consumption, corneal epithelial atrophy, and epithelium atrophy and ulcer with tongue inflammation were observed in the 20 mg/kg group. In embryos, fetuses, and offspring in the 20 mg/kg group, increased frequency of total litter loss (2 of 6 animals) and low mean body weight of offspring were observed.

On the basis of the above, the NOAEL in this study was determined to be 1 mg/kg for any of maternal animals, embryos, fetuses, and offspring. AUC_t (1130 nmol·h/L)[*1] in the 1 mg/kg group was approximately 0.08 fold the clinical exposure.[*2]

*1: AUC_t in maternal animals on gestation day 16 in the 1 mg/kg group in Phase 2
*2: The arithmetic mean AUC_t of osimertinib was 14,980 nmol·h/L after multiple oral doses of osimertinib 80 mg/day in Japanese NSCLC patients in the phase II part of the AURA study.

The applicant therefore explained that women of childbearing potential should be advised to use an appropriate contraceptive, because osimertinib has potential adverse effects on embryonic and fetal development on the basis of the above investigation results and the following published literature.

- Epidermal growth factor plays an important role in placental implantation as well as embryonic growth and differentiation. In EGFR-knockout mice, growth retardation, epithelium development

disorder as well as pre-implantation and postnatal deaths are induced (*Nature.* 1995;376:337-341, *Science.* 1995;269:230-238).

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

3.(iii).A.(6).1) Phototoxicity study

Mouse-fibroblast cells Balb/c were treated with osimertinib at 0.0476 to 150 μg/mL with or without UVA irradiation, and were assessed for cytotoxicity to evaluate phototoxicity of osimertinib. The Photo Irritation Factor (IC_{50} without UVA irradiation/IC_{50} with UVA irradiation) was 1.2, which was smaller than 2, the criterion for negative results. Osimertinib was determined to be non-phototoxic.

3.(iii).A.(6).2) Toxicity studies of a metabolite

A 1-month repeat-dose toxicity study of AZ5104, an osimertinib metabolite, in rats (0, 5, 10, or 15 mg/kg) was conducted. Findings other than those in the repeat-dose toxicity study of osimertinib in rats included increased frequency of granular horizontal band in the cornea, inflammatory cell infiltration in the adrenal gland, degeneration and necrosis in the adrenal cortex as well as single cell necrosis in the pancreas. The relationship between change in the cornea and AZ5104 was considered unknown, because the change was not dose-dependent and slight in severity. The findings in the adrenal gland and pancreas were considered potentially related to aggravated clinical signs. In the AZ5104 (15 mg/kg) group, in which findings in adrenal gland and pancreas were found, AUC_t (4060 nmol·h/L) was approximately 2.5 fold the clinical exposure* to this metabolite. All of these findings resolved or were reversible after a 1-month recovery period.

*: The arithmetic mean AUC_t of AZ5104 was 1619 nmol·h/L after multiple oral doses of AZ5104 in Japanese NSCLC patients in the phase II part of the AURA study.

3.(iii).A.(6).3) Safety evaluation of impurities

The drug substance contains impurities ([redacted], [redacted], [redacted], and [redacted]) at levels exceeding the qualification threshold defined in "Guideline for Impurities in New Drug Substances" (PMSB/ELD Notification No. 1216001 dated December 16, 2002). The applicant explained the safety of (a) the relevant 4 impurities and (b) mutagenic or potentially mutagenic impurities* as follows:

*: [redacted]

(a) In the 3-month repeat-dose toxicity study of osimertinib in rats [see "3.(iii).A.(2).2) Three-month repeated oral dose toxicity study in rats"], the estimated amounts of these impurities at the MTD exceeded the corresponding amounts in clinical studies, thus the general toxicity of these relevant impurities is considered confirmed. For genotoxicity, the risk of these relevant impurities to develop toxicity is considered low in patients treated with osimertinib, because the maximum intake of these impurities is <1 mg/day in clinical studies; and *in silico* analysis using DEREK (2014 1.0), Leadscope (3.0.25) etc., did not suggest genotoxicity risk.

(b) All of 9 mutagenic or potentially mutagenic impurities are removed in the manufacturing process and their concentrations in the drug substance are adequately low.

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

Based on the submitted data and the following review, PMDA concluded that non-clinical toxicity evaluation does not raise issues related to clinical use of osimertinib, except for its use in pregnant or possibly pregnant women.

3.(iii).B.(1) Effects on the cornea

Epidermal growth factor has been reported to be a factor stimulating cell division in the corneal epithelium (*Eye* 1994;8:170-183, *Mol Biol Reports.* 1996;23:47-58); and findings in the cornea were noted in repeat-dose toxicity studies of osimertinib in rats and dogs [see "3.(iii).A.(2) Repeat-dose toxicity"]. Concerning these matters, PMDA asked the applicant to explain the effects of osimertinib on the cornea in routine clinical use.

The applicant's response:

The findings in the cornea in the above toxicity studies are considered attributable to decreased production of corneal epithelial cells caused by the EGFR inhibitory effect of osimertinib. In the AURA2 study and in the phase II part of the AURA study, 2 events of corneal disorder were reported [for eye disorders including changes in the cornea in clinical studies, see "4.(iii).B.(3).14) Others"]. However, considering that these 2 events were non-ulcerative, and that keratitis and ulcerative keratitis in patients treated with EGFR-TKIs other than osimertinib have been scarcely reported (*Cancer Nursing.* 2007;30:S10-6, *Cancer Treat Rev.* 2014;40:197-203), osimertinib impacts on the cornea are considered unlikely to occur in routine clinical use.

In addition, epithelium atrophy and translucency in the cornea observed in the repeat-dose toxicity studies in rats and dogs were found to be reversible. On the other hand, opacity in the cornea observed in the 3-month repeat-dose toxicity study in dogs has not been investigated for reversibility. In a 6-month repeat-dose toxicity study of gefitinib, an EGFR-TKI, in dogs, opacity in the cornea was observed as well, and did not completely resolve even after a 12-week recovery period (*Anticancer Res.* 2003;23:3639-3650). On the basis of this report, opacity in the cornea after administration of osimertinib may not resolve completely.

PMDA's view:
The findings in the cornea noted in the toxicity studies are potentially related to pharmacological action of osimertinib, and its clinical use is considered to have a corresponding risk. PMDA therefore concluded that the findings in the cornea noted in the repeated-dose toxicity studies in rats and dogs should be included in the package insert etc., to provide appropriate cautions to healthcare professionals in clinical settings.

3.(iii).B.(2) Use of osimertinib in pregnant or possibly pregnant women
PMDA asked the applicant to explain the reason why osimertinib was not contraindicated for pregnant or possibly pregnant women.

The applicant's response:
In the study of effects on embryo-fetal and pre- and postnatal development, toxicological effects on fetal survival rate and early post-natal survival rate were observed in animals treated with osimertinib [see "3.(iii).A.(5) Reproductive and developmental toxicity"], therefore, osimertinib is considered to have a risk against embryo-fetal development. However, osimertinib is designed to be a drug indicated for patients with advanced or recurrent NSCLC, and thus in consideration of cases where expected therapeutic benefits outweigh the possible risk against embryo-fetal development associated with osimertinib, it was not contraindicated for pregnant women or for women who may possibly be pregnant. The package insert etc., will include the findings noted in the study for effects on embryo-fetal and pre- and postnatal development to provide cautions to healthcare professionals in clinical settings.

PMDA's view:
PMDA concluded that osimertinib should be contraindicated in pregnant women or in women who may possibly be pregnant, because in the study for effects on embryo-fetal development, decreased survival rate of fetuses and offspring was observed at exposure comparable to the clinical exposure [see "3.(iii).A.(5).2) Study for effects on embryo-fetal and pre- and postnatal development"], and studies for effects on embryo-fetal development have not been conducted in animals other than rats. Consequently, evaluation on teratogenicity is considered insufficient.

4. Clinical data

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

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

Oral dosage forms of osimertinib include capsules, liquid, tablets for phase I studies (phase I tablets), and film-coated tablets, and those formulations were used to investigate the pharmacokinetics (PK) etc., (the table below). The difference between the formulations of film-coated tablets 40 mg and 80 mg corresponds to "Level [redacted]" as defined in "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64 dated February 14, 2000, partially revised by PFSB/ELD Notification No. 0229-10 dated February 29, 2012). The bioequivalence between these

formulations was confirmed by the dissolution test. The to-be-marketed formulations are manufactured in the same process as those of film-coated tablets 40 mg and 80 mg used in clinical studies.

Formulations used in clinical studies

Formulation	Study
Capsules (20 and 40 mg)	Phase I part of a global phase I/II study (Study D5160C00001 [AURA study]), foreign phase I study (Study D5160C00005)
Liquid	Foreign phase I studies (Studies D5160C00005 and D5160C00011)
Phase I tablets (20 and 80 mg)	Phase I part of a global phase I/II study (Study D5160C00001 [AURA study]), foreign phase I study (Study D5160C00005)
Film-coated tablets (40 and 80 mg)	Phase II part of a global phase I/II study (Study D5160C00001 [AURA study]), global phase II study (Study D5160C00002 [AURA2 study]), foreign phase I studies (Studies D5160C00009, D5160C00010, D5160C00012, D5160C00013, D5160C00014, and D5160C00019)

4.(i).A.(1) Analytical methods

"Cobas EGFR Test Kit" (Roche Diagnostics K.K.) was used to identify EGFR T790M mutation, an EGFR mutation substituting a threonine (T) with a methionine (M) at position 790 of EGFR, in clinical studies. With this kit, real-time polymerase chain reaction (PCR) was performed. Also, a marketing application was filed for "Cobas EGFR Mutation Test Kit, Version 2.0" (Roche Diagnostics K.K.), an improved product of "Cobas EGFR Mutation Test Kit," on October 30, 2015 as an *in vitro* diagnostic product that helps decide whether to prescribe osimertinib or not.

4.(i).A.(2) Assay

Concentrations of osimertinib and its major metabolites, AZ5104 (desmethyl) and AZ7550 (desmethyl), in human plasma and urine samples were determined by LC-MS/MS. The lower limit of quantitation was 0.052, 0.052, and 0.050 nmol/L in plasma and 1.04, 1.04, and 1.00 nmol/L in urine, respectively.

4.(i).A.(3) Foreign phase I study (5.3.1.1.1, Study D5160C00009 [November 2014 – ongoing (data cut-off on March 23, 2015)])

A two-treatment, two-period crossover study was conducted to investigate food effect in 38 patients with unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after treatment with an EGFR-TKI (34 patients included in the PK analysis).

Patients received a single oral dose of osimertinib 80 mg under fasted conditions (osimertinib was administered after overnight fasting and then the fasted state was continued for another 4 hours) or 30 minutes after a high-fat diet (fat accounted for approximately 50% of approximately 800-1000 kcal in total), and underwent a 9-day washout period between Period 1 and Period 2.

As a result, the median t_{max} of osimertinib administered under fasted conditions was comparable to that of osimertinib administered after a high-fat diet. The geometric mean ratios [90% confidence interval (CI)] of C_{max} and AUC_{72h} of osimertinib administered after a high-fat diet to the respective parameters of osimertinib administered under the fasted conditions were 0.93 [0.81, 1.06] and 1.06 [0.95, 1.19], and 90% CI of the geometric mean ratios fell within a range from 0.80 to 1.25.

4.(i).A.(4) Foreign phase I study (5.3.1.2.1, Study D5160C00005 [October 2013 to June 2014])

A three-period, open-label study was conducted to investigate relative bioavailability (BA) of osimertinib in 16 healthy adult subjects.

Subjects received single oral doses of osimertinib 20 mg in the forms of capsule, liquid, and phase I tablet in this order under fasted conditions (osimertinib was administered after overnight fasting and then the fasted state was continued for another 4 hours), and underwent ≥21-day washout period between administration.

As a result, the geometric mean ratio [90% CI] of C_{max} and AUC_{inf} of osimertinib administered in phase I tablet form to the respective parameters of osimertinib administered in capsule form was 1.00 [0.87, 1.14] and 1.05 [0.93, 1.18]. Also, the geometric mean ratio [90% CI] of C_{max} and AUC_{inf} of osimertinib administered in liquid to the respective parameters of osimertinib administered in capsule form was 0.96

[0.84, 1.10] and 0.98 [0.87, 1.10], and the relative BAs of phase I tablet and liquid forms were comparable to that of capsule form.

4.(i).A.(5) Foreign phase I study (5.3.3.3.1, Study D5160C00010 [September 2014 to January 2015])

A two-period, open-label study was conducted to investigate effects of a proton pump inhibitor (omeprazole) on the PK of osimertinib in 68 healthy adult subjects (57 subjects included in the PK analysis).

Subjects orally received omeprazole 40 mg QD from Day 1 to Day 5 and a single dose of osimertinib 80 mg on Day 5, then underwent ≥21-day washout period and finally orally received a single dose of osimertinib 80 mg.

Results showed that the median t_{max} of osimertinib administered alone was comparable to that of osimertinib administered in combination with omeprazole. In addition, the geometric mean ratio [90% CI] of C_{max} and AUC_{inf} of osimertinib administered in combination with omeprazole to the respective parameters of osimertinib administered alone was 1.02 [0.95, 1.09] and 1.07 [1.00, 1.13], and C_{max} or AUC_{inf} of osimertinib did not depend clearly on whether it was administered alone or in combination with omeprazole.

4.(ii) Summary of clinical pharmacology studies

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

The PK of osimertinib was investigated in healthy adult subjects and NSCLC patients who received osimertinib alone or in combination with itraconazole, rifampicin, simvastatin, or rosuvastatin.

4.(ii).A.(1) Global phase I/II study (5.3.5.1.1-1, 5.3.5.1.2-1, Study D5160C00001 [AURA study] [March 2013 – ongoing (data cut-off on May 1, 2015)])

An open-label study was conducted to investigate the PK etc., of osimertinib in 403 patients with unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC (382 patients included in the PK analysis) (phase I part).

During the dose-escalation period, patients received a single oral dose of osimertinib 20, 40, 80, 160, or 240 mg, underwent a washout period of approximately 7 days, and then received multiple oral doses at the same dose level QD. During the dose-expansion period, patients orally received multiple doses of osimertinib 20, 40, 80, 160, or 240 mg QD. During these periods, plasma concentrations of osimertinib and its metabolites (AZ5104 and AZ7550) were determined.

PK parameters of osimertinib are shown in the table below. In the dose range investigated, C_{max} and AUC of osimertinib increased almost dose-proportionally. Multiple doses of osimertinib resulted in its accumulation, and the accumulation factor was 3.2 for capsules and 3.4 for phase I tablets. On Day 22 of multiple doses of osimertinib (capsules) 80 mg, AUC_t of AZ5104 and AZ7550 were 10.4% and 9.8% of that of osimertinib, respectively.

PK parameters of osimertinib

Dose (mg)	Time point	n	C_{max} (nmol/L)	t_{max}[*3] (h)	AUC_{72h} (nmol·h/L)	AUC[*4] (nmol·h/L)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
20[*1]	After single-dose administration	6	48.0 ± 41.9	7.1 (6.0, 24.0)	2176 ± 2324	-	-	-	-
	Day 22 of multiple-dose administration	7	129 ± 89.2	8.0 (4.0, 24.0)	-	2371 ± 1626	-	24.0 ± 13.5	-
40[*1]	After single-dose administration	6	86.5 ± 60.6	7.0 (3.0, 23.9)	2855 ± 1261	-	-	-	-
	Day 22 of multiple-dose administration[*4]	45	336 ± 155	6.0 (2.0, 12.0)	-	6155 ± 2690	-	15.5 ± 6.8	-
80[*1]	After single-dose administration	6	165 ± 128	7.0 (2.9, 24.1)	6093 ± 4267	-	-	-	-
	Day 22 of multiple-dose administration[*5]	115	710 ± 391	4.1 (1.0, 12.0)	-	13,490 ± 7263	-	15.0 ± 7.1	-
80[*2]	After single-dose administration	11	247 ± 174	6.0 (2.1, 23.8)	8840 ± 5727	12,170[*6] ± 7340	48.6[*6] ± 6.5	16.9[*6] ± 7.9	1216[*6] ± 604
	Day 22 of multiple-dose administration	35	680 ± 298	6.0 (2.0, 12.0)	-	13,040 ± 5685	-	14.2 ± 5.8	-
160[*1]	After single-dose administration	5	484 ± 261	8.0 (4.0, 12.0)	17,980 ± 10,610	26,370[*7] ± 11,860	50.3[*7] ± 4.2	13.9[*7] ± 6.2	1028[*7] ± 493
	Day 22 of multiple-dose administration[*5]	113	1429 ± 769	4.2 (1.1, 12.1)	-	27,300 ± 14,850	-	15.4 ± 8.9	-
240[*1]	After single-dose administration	7	553 ± 343	5.9 (4.0, 12.0)	20,140 ± 13,080	34,820[*8] ± 19,830	47.3[*8] ± 9.5	20.1[*8] ± 15.2	1274[*9] ± 741
	Day 22 of multiple-dose administration[*5]	18	1604 ± 612	6.0 (2.1, 8.0)	-	30,520 ± 11,610	-	18.5 ± 8.3	-

Arithmetic mean ± SD; -, Not calculated; *1, Capsules; *2, Phase I tablets; *3, Median (range); *4, AUC_{inf} for single-dose administration, and AUC_t for Day 22 of multiple-dose administration; *5, Pooled results from the dose-escalation period and the dose-expansion period; *6, n = 9; *7, n = 3; *8, n = 6

An open-label study was conducted to investigate the PK etc., of osimertinib in 201 patients with unresectable, advanced or recurrent EGFR T790M mutation-positive NSCLC that progressed after EGFR-TKI therapy (191 patients included in the PK analysis) (phase II part).

Patients orally received osimertinib 80 mg QD, and plasma concentrations of osimertinib and its metabolites (AZ5104 and AZ7550) were determined.

PK parameters of osimertinib are shown in the table below. The pre-dose geometric mean concentrations on Day 15 and Day 22 of osimertinib, AZ5104, and AZ7550 were as follows: 428 and 438 nmol/L; 46.8 and 48.4 nmol/L; and 37.4 and 41.6 nmol/L, respectively. The applicant therefore explained that the PK of osimertinib and AZ5104 possibly reached a steady state on Day 15, but the PK of AZ7550 did not. On Day 22 of multiple-dose administration of osimertinib (film-coated tablets) 80 mg, AUC_t of AZ5104 and AZ7550 were 10.6% and 9.9% of that of osimertinib, respectively.

PK parameters of osimertinib

Time point	Analyte	C_{max} (nmol/L)	t_{max}* (h)	AUC_t (nmol·h/L)	CL/F (L/h/kg)
Day 22	Osimertinib	694 ± 333	6.0 (1.0, 24.0)	13,240 ± 6441	14.7 ± 6.51
	AZ5104	71.4 ± 43.5	6.0 (0, 23.9)	1424 ± 886	-
	AZ7550	58.3 ± 25.1	6.1 (0, 23.3)	1095 ± 323	-

Arithmetic mean ± SD; n = 183; -, Not calculated; *, Median (range)

4.(ii).A.(2) Global phase II study (5.3.5.1.3-1, Study D5160C00002 [AURA2 study] [April 2014 – ongoing (data cut-off on May 1, 2015)])

An open-label study was conducted to investigate the PK, etc. of osimertinib in 210 patients with unresectable, advanced or recurrent EGFR T790M mutation-positive NSCLC that progressed after EGFR-TKI therapy (195 patients included in the PK analysis).

Patients orally received osimertinib 80 mg QD, and plasma concentrations of osimertinib and its metabolites (AZ5104 and AZ7550) were determined.

PK parameters of osimertinib are shown in the table below. The mean pre-dose concentrations on Day 22 and Day 43 of osimertinib, AZ5104, and AZ7550 were as follows, respectively: 459 and 407 nmol/L; 56.2 and 47.2 nmol/L; and 47.5 and 45.2 nmol/L. The applicant therefore explained that the PK of osimertinib, AZ5104, and AZ7550 possibly reached a steady state on Day 22.

PK parameters of osimertinib

Time point	n	Analyte	C_{max} (nmol/L)	t_{max}*1 (h)	AUC*2 (nmol·h/L)	CL/F (L/h/kg)
Day 1	178	Osimertinib	233 ± 149	5.9 (2.0, 8.6)	1208 ± 881	-
		AZ5104	8.16 ± 5.55	7.8 (3.9, 8.7)	39.6 ± 29.9	-
		AZ7550	4.30 ± 2.76	7.9 (3.9, 8.7)	20.2 ± 14.2	-
Day 43	192	Osimertinib	580 ± 259	5.9 (1.0, 23.4)	11,040 ± 4736	17.1 ± 7.23
		AZ5104	57.9 ± 32.4	6.0 (0, 24.0)	1174 ± 649	-
		AZ7550	57.1 ± 26.2	6.1 (0, 24.0)	1185 ± 538	-

Arithmetic mean ± SD; -, Not calculated; *1, Median (range); *2, AUC_{8h} for Day 1, and AUC_t for Day 43

In some patients in Study D5160C00001 (AURA study) and Study D5160C00002 (AURA2 study), plasma concentration profiles of osimertinib had multiple peaks. Taking account that the t_{max} of osimertinib was approximately 6 hours, the applicant explained that this finding was considered attributable to slow absorption of osimertinib over the entire gastrointestinal tract.

4.(ii).A.(3) Foreign phase I study (5.3.3.1.1, Study D5160C00011 [May to August 2014])

An open-label study was conducted to investigate mass balance of osimertinib in 8 healthy adult subjects. Subjects received a single oral dose of ^{14}C-labeled osimertinib 20 mg in a liquid form under fasted conditions, and blood and plasma concentrations of radioactivity as well as plasma concentrations of osimertinib and its metabolites (AZ5104 and AZ7550) were determined.

The geometric mean ratio of AUC_{inf} of radioactivity in blood to that in plasma was 0.917, indicating that distribution of osimertinib and its metabolites in blood was comparable to that in plasma. AUC_{inf} of osimertinib, AZ5104, and AZ7550 in plasma were 0.83%, 0.08%, and 0.07%, respectively, of that of radioactivity in plasma. The urinary and fecal excretion rates of radioactivity (percentage of the radioactivity excreted) up to 84 days post-dose were 14.2% and 67.8%, respectively, and the urinary excretion rates of osimertinib, AZ5104, and AZ7550 were 0.82%, 0.42% and 0.46%, respectively. The applicant explained that these data demonstrate that osimertinib or its metabolites are mainly excreted in feces.

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

4.(ii).A.(4).1) Study of drug interactions with itraconazole (5.3.3.4.1, Study D5160C00012 [November 2014 – ongoing (data cut-off on April 3, 2015)])

An open-label study was conducted to investigate effects of itraconazole (a cytochrome P450 [CYP] 3A inhibitor) on the PK of osimertinib in 39 patients with unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after EGFR-TKI therapy (36 patients included in the PK analysis).

Patients received single oral doses of osimertinib 80 mg on Day 1 and Day 10 and multiple oral doses of itraconazole 200 mg twice daily (BID) from Day 6 to Day 18, and the PK of osimertinib was analyzed.

The geometric mean ratios [90% CI] of C_{max} and AUC_t of osimertinib administered in combination with itraconazole (Day 10) to the respective parameters of osimertinib administered alone (Day 1) were 0.80 [0.73, 0.87] and 1.24 [1.15, 1.35]. The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of the 2 major metabolites when osimertinib was administered in combination with itraconazole (Day 10) to the respective parameters of the metabolites when osimertinib was administered alone (Day 1) were 0.76 [0.64, 0.90] and 1.08 [0.94, 1.24] for AZ5104, and 0.44 [0.40, 0.49] and 0.49 [0.44, 0.55] for AZ7550.

On the basis of the above, the applicant explained that concomitant use with a CYP3A inhibitor had no marked effects on the exposure to osimertinib.

4.(ii).A.(4).2) Study of drug interactions with rifampicin (5.3.3.4.2, Study D5160C00013 [December 2014 – ongoing (data cut-off on July 9, 2015)])

An open-label study was conducted to investigate effects of rifampicin (a CYP3A inducer) on the PK of osimertinib in 41 patients with unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after EGFR-TKI therapy (41 patients included in the PK analysis).

Patients received multiple oral doses of osimertinib 80 mg QD for 77 days (from Day 1 to Day 77) and multiple oral doses of rifampicin 600 mg QD from Day 29 to Day 49, and the PK of osimertinib was analyzed.

The geometric mean ratios [90% CI] of C_{max} and AUC_t of osimertinib administered in combination with rifampicin (Day 49) to the respective parameters of osimertinib administered alone (Day 28) were 0.27 [0.24, 0.30] and 0.22 [0.20, 0.24]. The geometric mean ratios [90% CI] of C_{max} and AUC_t of the 2 major metabolites when osimertinib was administered in combination with rifampicin (Day 49) to the respective parameters of the metabolites when osimertinib was administered alone (Day 28) were 0.22 [0.19, 0.25] and 0.19 [0.17, 0.21] for AZ5104 and 1.39 [1.28, 1.52] and 1.30 [1.19, 1.41] for AZ7550.

The above finding suggested that the PK of osimertinib is affected when osimertinib is administered in combination with a CYP3A inducer. The applicant therefore explained that caution against combination administration of osimertinib and a CYP3A inducer should be provided.

4.(ii).A.(4).3) Study of drug interactions with simvastatin (5.3.3.4.3, Study D5160C00014 [December 2014 – ongoing (data cut-off on April 30, 2015)])

An open-label study was conducted to investigate effects of osimertinib on the PK of simvastatin (a CYP3A substrate) in 52 patients with unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after EGFR-TKI therapy (49 patients included in the PK analysis).

Patients received multiple oral doses of osimertinib 80 mg QD from Day 3 to Day 32 and single oral doses of simvastatin 40 mg on Day 1 and Day 31, and the PK of simvastatin was analyzed.

The geometric mean ratios [90% CI] of C_{max} and AUC_t of simvastatin administered in combination with osimertinib (Day 31) to the respective parameters of simvastatin administered alone (Day 1) were 0.77 [0.63, 0.94] and 0.91 [0.77, 1.08].

On the basis of the above, the applicant explained that concomitant use of osimertinib with a CYP3A substrate was considered unlikely to have clinically significant effects on the PK of a CYP3A substrate.

4.(ii).A.(4).4) Study of drug interactions with rosuvastatin (5.3.3.4.4, Study D5160C00019 [March 2015 – ongoing (data cut-off on July 11, 2015)])

An open-label study was conducted to investigate effects of osimertinib on the PK of rosuvastatin (a substrate of breast cancer resistance protein [BCRP]) in 44 patients with unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after EGFR-TKI therapy (44 patients included in the PK analysis).

Patients received multiple oral doses of osimertinib 80 mg QD from Day 4 to Day 34 and single oral doses of rosuvastatin 20 mg on Day 1 and Day 32, and the PK of rosuvastatin was analyzed.

The geometric mean ratios [90% CI] of C_{max} and AUC_t of rosuvastatin administered in combination of osimertinib (Day 32) to the respective parameters of rosuvastatin administered alone (Day 1) were 1.72 [1.46, 2.03] and 1.35 [1.15, 1.57].

The above finding suggested that concomitant use with osimertinib increased the exposure to BCRP substrate. The applicant therefore explained that caution against concomitant use of osimertinib with a BCRP substrate should be provided.

4.(ii).A.(5) Investigation of relationship between exposure and changes in QT/QTc interval

A linear mixed-effects model-based analysis was performed on data from the AURA2 study to investigate the relationship between plasma concentrations of osimertinib and baseline changes of QT interval correcting influence from the heart rate by Fridericia formula (QTcF). As a result, QTcF tended to increase with an increasing concentration of osimertinib. The estimated mean change in QTcF at C_{max} in the treatment with osimertinib 80 mg QD and the upper limit of 90% CI were 14.2 and 15.8 msec, respectively. Meanwhile, the change in QTcF in the AURA2 study (mean [90% CI]) was 14.5 [14.0, 15.0] msec. On the basis of the above, the applicant explained that osimertinib potentially prolongs QT interval.

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

A non-linear mixed-effects model (software used, [redacted])–based population pharmacokinetic (PPK) analysis was performed on the PK data of osimertinib obtained from the AURA and AURA2 studies, and Study D5160C00005 (24,028 time points in 780 subjects), where the PK of osimertinib was described by a model comprising a 1-compartment model with first-order absorption process and a 1-compartment model of AZ5104.

In this analysis, effects of covariates listed in the table below were investigated on the relative BA (F), CL/F, and distribution volume (V/F).

Covariates investigated

PK parameter	Covariate
F	Dose, dosage form, diet condition, and presence or absence of NSCLC
CL/F of osimertinib	Dose, diet condition, body weight, age, sex, race, with or without smoking habit, ALT, bilirubin, creatinine clearance, presence or absence of NSCLC
CL/F of AZ5104	Body weight, age, sex, race, ALT, AST, creatinine clearance, presence or absence of NSCLC
V/F of osimertinib and AZ5104	Body weight, serum albumin

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase

As a result, body weight was identified as a significant covariate on CL/F and V/F of osimertinib and CL/F of AZ5104. Presence or absence of NSCLC and race were also identified as significant covariates on CL/F of osimertinib and AZ5104, respectively. The applicant's explanation of the effects of those significant covariates on the PK of osimertinib or its metabolite, on the basis of the above results:

- The exposure to osimertinib in subjects whose weight was at 5- and 95-percentile points (43 and 90 kg, respectively) in the body weight distribution of the analysis set was estimated to be 30% higher and 20% lower, respectively, than the median weight of the analysis set (62 kg). In clinical studies, however, no clear differences in efficacy or safety were found among body weight categories of the patients (<43 kg; ≥43 kg and <53kg; ≥53 kg and <62 kg; ≥62 kg and <73 kg; ≥73 kg and <90 kg; and ≥90 kg). In view of this finding, such differences in exposure are considered unlikely to raise clinically significant issues.
- The exposure to osimertinib in NSCLC patients was estimated to be lower than that in healthy adult subjects. Such a difference was considered potentially attributable to effects from cancer-related inflammation on the expression of drug metabolizing enzymes and transporters (*Clin Pharmacol Ther.* 2015;98:76-86).
- The exposure to AZ5104 in the Japanese and Chinese population, etc., was estimated to be 10% to 23% lower than that in the Caucasian population. Although the reason for the differences in exposure to AZ5104 among races remains unknown, such differences are considered unlikely to raise clinically significant issues, because the exposure to AZ5104 is approximately 10% of that to osimertinib [see "4.(ii).A.(1) Global phase I/II study"].

4.(ii).A.(7) Effects of renal impairment on the PK of osimertinib

The applicant's explanation of low likelihood of effects of renal impairment on the PK of osimertinib:

- Study D5160C00011 showed that the urinary excretion rates of osimertinib and its metabolites (percentage of the radioactivity excreted) were 14.2% [see "4.(ii).A.(3) Foreign phase I study"], indicating that the contribution of renal excretion to osimertinib elimination is limited.

- The PPK analysis of osimertinib included 265 patients with normal renal function and 330, 149, and 3 patients with mild, moderate, and severe renal impairment, respectively,* in whom mean CL/F of osimertinib was estimated to be 16.7, 15.8, 13.7, and 15.4 L/h, respectively. The PK of osimertinib was not significantly different among patients with different renal impairment status [see "4.(ii).A.(6) Population pharmacokinetic analysis"].
- The incidence of adverse events in the phase II part of the AURA study and the AURA2 study did not differ significantly between patients with mild to moderate renal impairment* and patients with normal renal functions.
  *: Creatinine clearance (CrCL) in patients with normal renal function, and with mild, moderate, and severe renal impairment was as follows, respectively: ≥90 mL/min; ≥60 mL/min and <90 mL/min; ≥30 mL/min and <60 mL/min; and ≥15 mL/min and <30 mL/min.

4.(ii).A.(8) Relationship between exposure to osimertinib and efficacy and safety

Data obtained from the AURA study and the AURA2 study were investigated for the relationship of AUC_{τ} of osimertinib or AZ5104 at a steady state (AUC_{SS}) and the efficacy and safety. Individual AUC_{SS} values used in this investigation were estimated by PPK analysis [see "4.(ii).A.(6) Population pharmacokinetic analysis"].

4.(ii).A.(8).1) Relationship between exposure and efficacy

The relationship of AUC_{SS} of osimertinib or AZ5104 and the response rate in the phase II part of the AURA study and the AURA2 study was analyzed with a logistic regression model. The investigation revealed no clear relationship of exposure to osimertinib or AZ5104 and the response rate.

4.(ii).A.(8).2) Relationship between exposure and safety

The relationship of AUC_{SS} of osimertinib or AZ5104 and rash or diarrhoea, adverse events commonly reported by patients receiving EGFR-TKIs, in the AURA study and the AURA2 study was analyzed with a logistic regression model (*Drug Saf.* 2004;27:1081-1092, *Front Oncol.* 2014;4:1-6). The incidence of rash and diarrhoea tended to increase with increasing exposure to osimertinib or AZ5104.

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

4.(ii).B.(1) Differences in PK between Japanese and non-Japanese patients

The applicant's explanation that no clear differences were observed in the PK of osimertinib between Japanese and non-Japanese patients:

- PK parameters of osimertinib on Day 22 of multiple oral doses of osimertinib 80 mg QD in film-coated tablet form in the phase II part of the AURA study were compared among races (the table below). Individual values of C_{max} and AUC_t in Japanese patients (387-1670 nmol/L and 7680-35,300 nmol·h/L, respectively) mostly fell within the range of individual values of corresponding exposure parameters in non-Japanese Asians (244-1820 nmol/L and 4080-36,300 nmol·h/L, respectively) and in non-Asians (260-2440 nmol/L and 4740-42,500 nmol·h/L, respectively). Similar results were obtained in PK parameter values among races following (a) multiple oral doses of osimertinib 80 mg QD in film-coated tablet form in the AURA2 study and (b) multiple doses of osimertinib 80 and 160 mg QD in capsule form in the phase I part of the AURA study.

PK parameters of osimertinib and its metabolites (AZ5104, AZ7550) on Day 22 of multiple-dose administration

Race	n	Analyte	C_{max} (nmol/L)	t_{max}* (h)	AUC_t (nmol·h/L)
Japanese	32	Osimertinib	782 ± 333	6.0 (2.0, 11.1)	14,980 ± 6809
		AZ5104	80.4 ± 46.8	6.0 (0, 23.9)	1619 ± 972
		AZ7550	60.8 ± 17.1	8.0 (0, 12.0)	1260 ± 379
Non-Japanese Asian	75	Osimertinib	653 ± 283	6.0 (1.9, 24.0)	12,510 ± 5717
		AZ5104	68.0 ± 45.3	6.0 (0, 23.8)	1367 ± 909
		AZ7550	53.2 ± 25.4	7.8 (0, 23.1)	1094 ± 528
Non-Asian	76	Osimertinib	698 ± 374	6.0 (1.0, 22.6)	13,220 ± 6888
		AZ5104	70.9 ± 40.1	6.0 (0, 23.3)	1398 ± 825
		AZ7550	62.3 ± 27.0	6.0 (0, 23.3)	1265 ± 552

Arithmetic mean ± SD; *, Median (range)

- In the PPK analysis, race was not identified as a significant covariate on PK parameters of osimertinib. Although exposure to AZ5104 was presumed to differ among races, such difference was considered unlikely to raise clinically significant issues [see "4.(ii).A.(6) Population pharmacokinetic analysis"].

PMDA accepted the applicant's explanation.

4.(ii).B.(2) Use of osimertinib in patients with hepatic impairment

There are no clinical data available on the PK of osimertinib in patients with hepatic impairment.

The applicant's explanation on the use of osimertinib in patients with hepatic impairment:
In view of the following points, mild hepatic impairment is considered to have no effects on the PK of osimertinib. The PK of osimertinib and its metabolites, however, are potentially affected by hepatic impairment, because CYP3A4 is mainly involved in metabolism of osimertinib [see "3.(ii).A.(3) Metabolism"]; and osimertinib and its metabolites are mainly excreted in feces [see "4.(ii).A.(3) Foreign phase I study"]. In addition, since the experience with osimertinib therapy in patients with moderate and severe hepatic impairment is limited, caution is needed when administering osimertinib in those patients. Furthermore, a foreign clinical study (Study D5160C00008) is currently ongoing to investigate effects of hepatic impairment on the PK of osimertinib, and the results are to be obtained in [redacted] 20[redacted].

- In the PPK analysis, none of the liver function test values (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and total bilirubin) were identified as significant covariates on the PK of osimertinib [see "4.(ii).A.(6) Population pharmacokinetics analysis"].
- In the phase II part of the AURA study and the AURA2 study, CL/F values in 265 patients with normal hepatic function, 44 patients with mild hepatic impairment, and 1 patient with moderate hepatic impairment* (geometric mean, except for the patient with moderate impairment [individual value]) were 22.8, 18.2, and 22.6 L/h, respectively, suggesting that mild hepatic impairment is unlikely to affect the PK of osimertinib.
- Between the patients with mild hepatic impairment* and patients with normal hepatic functions, no marked difference was noted in the incidence of adverse events in the AURA2 study and the phase II part of the AURA study.
  *: Classified according to US National Cancer Institute Organ Dysfunction Working Group classification

PMDA's view:
PMDA accepted the applicant's explanation. For Study D5160C00008, results have to be provided appropriately to healthcare professionals in clinical settings as soon as they become available.

4.(iii) Summary of clinical efficacy and safety

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

The applicant submitted efficacy and safety evaluation data in the form of 3 study results: 1 global phase I/II study; 1 global phase II study; and 1 foreign phase I study. In addition, the applicant submitted reference data from 7 foreign phase I studies.

List of clinical studies for the efficacy and safety

Data category	Location	Study	Phase	Population	No. of enrollment	Dosage regimen	Major endpoint
Evaluation data	Global	D5160C00001 (AURA)	I/II	Phase I part: Unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC Phase II part: Unresectable, advanced or recurrent EGFR T790M mutation positive NSCLC that progressed after EGFR-TKI therapy	(a) 44 (b) 359 (c) 201	Phase I part: (a) Dose-escalation period; Multiple oral doses of osimertinib 20, 40, 80, 160, or 240 mg QD (b) Dose-expansion period; Multiple oral doses of osimertinib 20, 40, 80, 160, or 240 mg QD Phase II part: (c) Multiple oral doses of osimertinib 80 mg QD	PK Safety Efficacy

Data category	Location	Study	Phase	Population	No. of enrollment	Dosage regimen	Major endpoint
		D5160C00002 (AURA2)	II	Unresectable, advanced or recurrent EGFR T790M mutation positive NSCLC that progressed after EGFR-TKI therapy	210	Multiple oral doses of osimertinib 80 mg QD	Efficacy Safety PK
	Foreign	D5160C00009	I	Unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after EGFR-TKI therapy	38	A single oral dose of osimertinib 80 mg in the fasted state or after a high-fat diet	PK Safety Tolerability
Reference data	Foreign	D5160C00005	I	Healthy adult subjects	32 (a) 16 (b) 16	(a) Part A: A single oral dose of osimertinib (capsules, liquid, or tablets) 20 mg in the fasted state (b) Part B: A single oral dose of osimertinib (tablets) 20 mg in the fasted state or after a high-fat diet	BA
		D5160C00010	I	Healthy adult subjects	68	Multiple oral doses of omeprazole 40 mg QD from Day 1 to Day 5, and a single oral dose of osimertinib 80 mg (tablets) on Day 5, followed by a ≥21-day washout period and then a single oral dose of osimertinib 80 mg	PK
		D5160C00011	I	Healthy adult subjects	8	A single oral dose of ^{14}C-labeled osimertinib 20 mg	PK
		D5160C00012	I	Unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after EGFR-TKI therapy	39	Single oral doses of osimertinib 80 mg (tablets) on Day 1 and Day 10, and multiple oral doses of itraconazole 200 mg BID from Day 6 to Day 18	PK Safety Tolerability
		D5160C00013	I	Unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after EGFR-TKI therapy	41	Multiple oral doses of osimertinib 80 mg QD, and oral doses of rifampicin 600 mg QD from Day 29 to Day 49	PK Safety Tolerability
		D5160C00014	I	Unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after EGFR-TKI therapy	52	Single oral doses of simvastatin 40 mg on Day 1 and Day 31, and multiple oral doses of osimertinib 80 mg QD from Day 3	PK Safety Tolerability
		D5160C00019	I	Unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after EGFR-TKI therapy	44	Single oral doses of rosuvastatin 20 mg on Day 1 and Day 32, and multiple oral doses of osimertinib 80 mg QD from Day 4	PK Safety Tolerability

Individual clinical studies are summarized below.

The major non-fatal adverse events observed in clinical studies are described in "4.(iv) Adverse events etc., observed in clinical studies" and study data on the PK are described in "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and in "4.(ii) Summary of clinical pharmacology studies."

Evaluation data

(1) Clinical pharmacology study

The applicant submitted data from a clinical pharmacology study in patients with advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after EGFR-TKI therapy [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical

pharmacology studies"]. No deaths occurred during the osimertinib treatment period in the following 1 study.

Foreign phase I study (5.3.1.1.1, Study D5160C00009 [November 2014 – ongoing (data cut-off on March 23, 2015)])

(2) Global studies

1) Global phase I/II study (5.3.5.1.1-1, 5.3.5.1.2-1; Study D5160C00001 [AURA study] [March 2013 – ongoing (data cut-off on May 1, 2015)])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of osimertinib in patients with unresectable, advanced or recurrent EGFR activating mutation-positive* NSCLC (target sample size; approximately 36 patients in the dose-escalation period of the phase I part, approximately 162 patients in the dose-expansion period of the phase I part, and approximately 175 patients in the phase II part) at 35 medical institutions including 16 in Japan.

*: The dose-escalation period of the phase I part included patients with NSCLC progressed after EGFR-TKI therapy; dose-expansion period included patients with NSCLC progressed after EGFR-TKI therapy and EGFR-TKI therapy-naïve NSCLC patients with EGFR activating mutation (mutations in EGFR gene related to responsiveness to EGFR-TKIs such as a deletion in exon 19; L858R mutation [substitution of arginine (R) for leucine (L) at position 858 in exon 21 of EGFR gene]; and L861Q mutation [substitution of glutamine [Q] for L at position 861 in exon 21]) - positive. The phase II part included patients with EGFR T790M mutation-positive NSCLC that progressed after EGFR-TKI therapy.

During the dose-escalation period of the phase I part, patients received a single oral dose of osimertinib 20, 40, 80, 160, or 240 mg, underwent a washout period of approximately 7 days, and then received multiple oral doses at the same dose level QD. During the dose-expansion period, patients orally received osimertinib 20, 40, 80, 160, or 240 mg QD. In the phase II part, patients continued multiple oral doses of osimertinib 80 mg QD until disease progression or discontinuation of treatment.

In the phase I part, 402 patients enrolled in the study and treated with osimertinib (43 in the dose-escalation period and 359 in the dose-expansion period) were included in the safety analysis.

In the phase II part, 201 patients enrolled in the study and treated with osimertinib were included in the full analysis set (FAS) and in the safety analysis set. Of the patients in the FAS, 199 in whom lesion imaged at baseline was later diagnostically measurable on central review were defined as the response analysis set and the efficacy analysis set.

The RECIST ver1.1-based response rate by the central review in the response analysis set, the primary efficacy endpoint in the phase II part, are shown in the table below.

Best overall response and response rate (response analysis set, RECIST Ver.1.1, central review)

Best overall response	Number of patients (%)
	N = 199
Complete response (CR)	0
Partial response (PR)	122 (61.3)
Stable disease (SD)	58 (29.1)
Progressive disease (PD)	19 (9.5)
Response (CR + PR)	122
(Response rate [95% CI] %)	(61.3 [54.2, 68.1])

Forty-three of 402 patients (10.7%) in the phase I part died during the osimertinib treatment period or within 28 days after the end of osimertinib treatment. The causes included disease progression in 29 patients; pneumonia in 4; pneumonia and disease progression in 2; and lung infection and disease progression, respiratory failure and pneumonia, respiratory tract infection bacterial, septic shock, suicide attempt, dyspnoea, pulseless electrical activity, and renal failure in 1 each. Of these, a causal relationship to osimertinib could not be ruled out for pneumonia in 1 patient. In the phase II part, 28 of 201 patients (13.9%) died during the osimertinib treatment period or within 28 days post-treatment. The causes included disease progression in 20 patients; interstitial lung disease (ILD) and disease progression in 2; cerebrovascular accident, cerebral haemorrhage/disease progression, acute respiratory failure/disease progression, pneumonia/disease progression, pneumonitis/respiratory failure/disease progression, and

cardiac failure congestive/liver disorder/urinary tract infection bacterial in 1 each. Of these, a causal relationship to osimertinib could not be ruled out for ILD in 2 patients and pneumonitis in 1 patient.

2) Global phase II study (5.3.5.1.3-1, Study D5160C00002 [AURA2 study] [April 2014 – ongoing (data cut-off on May 1, 2015)])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of osimertinib in patients with unresectable, advanced or recurrent EGFR T790M mutation-positive NSCLC that progressed after EGFR-TKI therapy (target sample size, approximately 175 subjects) at 44 medical institutions including 14 in Japan.

Patients received multiple oral doses of osimertinib 80 mg QD until disease progression or discontinuation of treatment.

A total of 210 patients enrolled in the study and treated with osimertinib were included in the FAS and the safety analysis set. Of the patients in the FAS, 199 in whom lesion imaged at baseline was later diagnostically measurable on central review were defined as the response analysis set and efficacy analysis set.

The RECIST ver1.1-based response rate by the central review in the response analysis set, the primary efficacy endpoint in this study, are shown in the table below.

Best overall response and response rate (response analysis set, RECIST Ver.1.1, central review)

Best overall response	Number of patients (%)
	N = 199
Complete response (CR)	2 (1.0)
Partial response (PR)	139 (69.8)
Stable disease (SD)	41 (20.6)
Progressive disease (PD)	15 (7.5)
Not evaluable (NE)	2 (1.0)
Response (CR + PR) (Response rate [95% CI] %)	141 (70.9 [64.0, 77.1])

Twenty-four of 210 patients (11.4%) died during the osimertinib treatment period or within 28 days after the end of osimertinib treatment. The causes included disease progression in 19 patients; and pneumonia/disease progression, pneumonia, ILD, pneumonia aspiration/disease progression, and failure to thrive in 1 patient each. Of these, a causal relationship to osimertinib could not be ruled out for ILD in 1 patient.

Reference data

Clinical pharmacology study

The applicant submitted data from the following 7 clinical pharmacology studies in healthy adult subjects and patients with advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after EGFR-TKI therapy [see "4.(i) Summary of biopharmaceutic studies and associated analytical methods" and "4.(ii) Summary of clinical pharmacology studies"]. Two patients died during the osimertinib treatment period in Study D5160C00019. The cause was disease progression in both patients, and their causal relationship to osimertinib was ruled out.

1) Foreign phase I study (5.3.1.2.1, Study D5160C00005 [October 2013 to June 2014])
2) Foreign phase I study (5.3.3.1.1, Study D5160C00011 [May to August 2014])
3) Foreign phase I study (5.3.3.3.1, Study D5160C00010 [September 2014 to January 2015])
4) Foreign phase I study (5.3.3.4.1, Study D5160C00012 [November 2014 – ongoing (data cut-off on April 3, 2015)])
5) Foreign phase I study (5.3.3.4.2, Study D5160C00013 [December 2014 – ongoing (data cut-off on July 9, 2015)])
6) Foreign phase I study (5.3.3.4.3, Study D5160C00014 [December 2014 – ongoing (data cut-off on April 30, 2015)])
7) Foreign phase I study (5.3.3.4.4, Study D5160C00019 [March 2015 – ongoing (data cut-off on July 11, 2015)])

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

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

PMDA considered that the most important clinical studies for evaluating the efficacy and safety of osimertinib in the submitted data were the phase II part of the AURA study and the AURA2 study, which evaluated the efficacy and safety of osimertinib in patients with unresectable, advanced or recurrent EGFR T790M mutation-positive NSCLC that progressed after EGFR-TKI therapy, and determined to evaluate focusing on these studies.

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

On the basis of the following review, PMDA has concluded that the efficacy of osimertinib is demonstrated to a certain extent in patients with unresectable, advanced or recurrent EGFR T790M mutation-positive NSCLC that progressed after EGFR-TKI therapy.

4.(iii).B.(2).1) Efficacy endpoint and evaluation results

The applicant's explanation on the efficacy of osimertinib in patients with unresectable, advanced or recurrent EGFR T790M mutation-positive NSCLC:

Clinical practice guidelines in and out of Japan recommend treatment with EGFR-TKIs for unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC on the basis of biological properties of the cancer (Japan Lung Cancer Society. *Guidelines for Diagnosis and Management of Lung Cancer by EBM*. 2014 ed. Kanehara & Co., Ltd. 2014; US National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology: Lung Cancer. v.3*. 2016 [NCCN guideline (v.3.2016)]). It is, however, known that conventional EGFR-TKIs are not permanently effective, and subsequent development of resistance to these inhibitors result in recurrence of the disease. The mechanism of development of the resistance has been reported to be attributable to EGFR T790M mutation (*Clin Cancer Res.* 2013;19:2240-2247, etc.). Osimertinib is an EGFR-TKI that has inhibited growth of EGFR T790M mutation-positive cancer [see "3.(i).A.(1) Primary pharmacodynamics"]. Therefore, osimertinib is expected to be effective in patients with unresectable, advanced or recurrent EGFR T790M mutation-positive NSCLC.

In addition to the above findings, the phase II part of the AURA study and the AURA2 study presented the response rate [95% CI] (%), the primary endpoint, of 61.3 [54.2, 68.1] and 70.9 [64.0, 77.1], respectively. The response rates from these studies are considered clinically significant in view of the following points.

- Since patients with unresectable, advanced or recurrent NSCLC are commonly complicated with symptoms such as dyspnoea, cough, and chest pain, reducing tumor in size and achieving response are reported important in alleviating these clinical symptoms (*JAMA.* 2003;290:2149-2158).
- In patients with unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC, the response rate to the second-line therapy with conventional antineoplastic drugs after EGFR-TKI therapy was reported to be 20% to 30% (*Int J Cancer.* 2010;126:247-255, *Cancer Biol Med.* 2012;9:38-43, etc.). Median PFS and overall survival (OS) of the second-line therapy were reported to be 3 to 6 months and 1 to 2 years, respectively (*Int J Cancer.* 2010;126:247-255, *Cancer Biol Med.* 2012;9:38-43, etc.).

Additionally, the median progression-free survival (PFS) [95% CI] on the basis of the central review of the phase II part of the AURA study and the AURA2 study (data cut-off on May 1, 2015) are not reached [8.1, not reached] (event incidence, 39.8%) and 8.6 months [8.3, 9.7] (event incidence, 37.6%), respectively, although the results are immature.

PMDA's view:

The true endpoint in NSCLC patients is OS, but the relationship between the response rate and OS remains unknown. PMDA therefore considers it difficult at present to evaluate survival benefit of osimertinib in patients with EGFR T790M mutation-positive NSCLC that progressed after EGFR-TKI therapy. However, taking into account the characteristics of the disease to be treated with and the mechanism of action of osimertinib [see "3.(i).B. Mechanism of action and efficacy of osimertinib against EGFR T790M mutation-positive NSCLC"], and on the basis of response rate from the phase II part of the AURA study and the AURA2 study, PMDA has concluded that osimertinib has demonstrated

a certain degree of efficacy in patients with EGFR T790M mutation-positive NSCLC that progressed after EGFR-TKI therapy.

4.(iii).B.(2).2) Efficacy in Japanese patients

The response rate in the Japanese patient population in the phase II part of the AURA study and the AURA2 study are shown in the table below.

Best overall response and response rate in Japanese patient population (response analysis set, RECIST Ver.1.1, central review)

Best overall response	Number of patients (%)			
	Phase II part of the AURA study		The AURA2 study	
	Japanese patient population N = 34	Overall population N = 199	Japanese patient population N = 42	Overall population N = 199
Complete response (CR)	0	0	0	2 (1.0)
Partial response (PR)	20 (58.8)	122 (61.3)	28 (66.7)	139 (69.8)
Stable disease (SD)	12 (35.3)	58 (29.1)	11 (26.2)	41 (20.6)
Progressive disease (PD)	2 (5.9)	19 (9.5)	3 (7.1)	15 (7.5)
Not evaluable (NE)	0	0	0	2 (1.0)
Response (CR + PR) (Response rate [95% CI] %)	20 (58.8 [40.7, 75.4])	122 (61.3 [54.2, 68.1])	28 (66.7 [50.5, 80.4])	141 (70.9 [64.0, 77.1])

PMDA's view:

In the phase II part of the AURA study and the AURA2 study, the response rate in the Japanese patient population was comparable to that in the overall population. PMDA has therefore concluded that the efficacy of osimertinib can be expected in Japanese patients as well.

4.(iii).B.(3) Safety [for adverse events, see "4.(iv) Adverse events etc., observed in clinical studies"]

As a result of the following review, PMDA has concluded that adverse events requiring special attention during osimertinib treatment included ILD-like events, QT interval prolonged, haematotoxicity, liver disorder, cardiac disorder (excluding QT interval prolonged), thromboembolism, and infection.

Although attention should be paid to the above adverse events as well as gastrointestinal disorder, skin disorder, nail disorder, and corneal disorder during osimertinib treatment, PMDA has concluded that osimertinib is tolerable if physicians with sufficient knowledge and experience in cancer chemotherapy (i) take appropriate measures including monitoring and managing adverse events, and interrupting and discontinuing treatment and (ii) perform above measures strictly for serious adverse events such as ILD. Safety information on osimertinib, however, is limited, and thus the information should be continuously collected after the market launch and new safety information should be appropriately provided to healthcare professionals in clinical settings as soon as it becomes available [see "4.(iii).B.(6) Post-marketing investigations" and "4.(iii).B.(7) Post-marketing risk minimization activities"].

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

The applicant's explanation on the safety profile of osimertinib:

In the phase II part of the AURA study and the AURA2 study, the same dosage form (tablets) and dosage regimen were used in the same target populations, and the safety profiles were not markedly different between these studies. The safety of osimertinib was therefore investigated on the basis of the data pooled from these 2 studies (pooled phase II study data).

The safety overview and adverse events with an incidence of ≥10% in pooled phase II study data are shown in the table below.

Safety overview (pooled phase II study data, data cut-off on May 1, 2015)

	Number of patients (%)
	N = 411
All adverse events	401 (97.6)
Grade ≥3 adverse events	121 (29.4)
Adverse events leading to death	13 (3.2)
Serious adverse events (including death)	83 (20.2)
Adverse events leading to treatment discontinuation	23 (5.6)
Adverse events leading to dose reduction	18 (4.4)
Adverse events leading to treatment interruption	77 (18.7)

Adverse events with an incidence of ≥10%
(pooled phase II study data, data cut-off on May 1, 2015)

Preferred term (MedDRA/J ver18.0)	Number of patients (%) N = 411	
	All Grades	Grade ≥3
All adverse events	401 (97.6)	121 (29.4)
Diarrhoea	174 (42.3)	4 (1.0)
Rash	98 (23.8)	0
Dry skin	95 (23.1)	0
Paronychia	72 (17.5)	0
Nausea	69 (16.8)	2 (0.5)
Decreased appetite	65 (15.8)	3 (0.7)
Constipation	62 (15.1)	1 (0.2)
Cough	57 (13.9)	1 (0.2)
Fatigue	57 (13.9)	2 (0.5)
Pruritus	57 (13.9)	0
Back pain	52 (12.7)	3 (0.7)
Stomatitis	49 (11.9)	0
Platelet count decreased	47 (11.4)	2 (0.5)
Headache	42 (10.2)	1 (0.2)

Grade ≥3 adverse events with an incidence of ≥1% in pooled phase II study data included pneumonia in 11 of 411 patients (2.7%); pulmonary embolism in 9 of 411 patients (2.2%); dyspnoea and neutrophil count decreased in 7 of 411 patients (1.7%) each; anaemia in 6 of 411 patients (1.5%); ALT increased and electrocardiogram QT prolonged in 5 of 411 patients (1.2%) each; diarrhoea, hyponatraemia, pneumonitis, and thrombocytopenia in 4 of 411 patients (1.0%) each. Serious adverse events with an incidence of ≥1% included pneumonia and pulmonary embolism in 11 of 411 patients (2.7%) each; and ILD and pneumonitis in 4 of 411 patients (1.0%) each. Adverse events leading to treatment discontinuation with an incidence of ≥1% included ILD and pneumonitis in 5 of 411 patients (1.2%) each.

PMDA's view:
PMDA considers that attention should be paid in the treatment with osimertinib to all Grades adverse events with high incidences, Grade ≥3 adverse events, serious adverse events, and adverse events leading to treatment discontinuation identified in the pooled phase II study data. Although information on the incidence of these events should be provided appropriately to healthcare professionals in clinical settings, PMDA has concluded that osimertinib is tolerable if appropriate measures such as monitoring and management of adverse events, and dose adjustment of osimertinib are taken by physicians with sufficient knowledge and experience in cancer chemotherapy, and post-marketing safety actions are appropriately taken [see"4.(iii).B.(7) Post-marketing risk minimization activities"]. Since the experience with osimertinib therapy in Japanese patients is limited, and the relevant safety information of osimertinib has not been sufficiently collected, PMDA considers it necessary to collect post-marketing safety information 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's explanation on differences in safety of osimertinib between Japanese and non-Japanese patients on the basis of pooled phase II study data:
Overview of safety in the Japanese patient population and the non-Japanese patient population and adverse events with an incidence of ≥10% in either of these populations are shown in the table below.

Safety overview (pooled phase II study data, data cut-off on May 1, 2015)

	Number of patients (%)	
	Japanese patient population N = 80	Non-Japanese patient population N = 331
All adverse events	77 (96.3)	324 (97.9)
Grade ≥3 adverse events	31 (38.8)	90 (27.2)
Adverse events leading to death	2 (2.5)	11 (3.3)
Serious adverse events (including death)	15 (18.8)	68 (20.5)
Adverse events leading to treatment discontinuation	7 (8.8)	16 (4.8)
Adverse events leading to dose reduction	9 (11.3)	9 (2.7)
Adverse events leading to treatment interruption	24 (30.0)	53 (16.0)

Adverse events with an incidence of ≥10% in either Japanese or non-Japanese patient population (pooled phase II study data, data cut-off on May 1, 2015)

Preferred term (MedDRA/J ver18.0)	Number of patients (%)			
	Japanese patient population N = 80		Non-Japanese patient population N = 331	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	77 (96.3)	31 (38.8)	324 (97.9)	90 (27.2)
Diarrhoea	33 (41.3)	2 (2.5)	141 (42.6)	2 (0.6)
Paronychia	27 (33.8)	0	45 (13.6)	0
Rash	23 (28.8)	0	75 (22.7)	0
White blood cell count decreased	21 (26.3)	3 (3.8)	10 (3.0)	0
Dry skin	20 (25.0)	0	75 (22.7)	0
Platelet count decreased	20 (25.0)	1 (1.3)	27 (8.2)	1 (0.3)
Stomatitis	19 (23.8)	0	30 (9.1)	0
Nasopharyngitis	15 (18.8)	0	20 (6.0)	0
Dermatitis acneiform	12 (15.0)	0	16 (4.8)	0
Nausea	12 (15.0)	1 (1.3)	57 (17.2)	1 (0.3)
Neutrophil count decreased	12 (15.0)	4 (5.0)	13 (3.9)	3 (0.9)
Anaemia	11 (13.8)	3 (3.8)	29 (8.8)	3 (0.9)
Pyrexia	11 (13.8)	0	11 (3.3)	0
Constipation	10 (12.5)	0	52 (15.7)	1 (0.3)
ALT increased	9 (11.3)	2 (2.5)	18 (5.4)	3 (0.9)
AST increased	9 (11.3)	1 (1.3)	17 (5.1)	0
Fatigue	8 (10.0)	1 (1.3)	49 (14.8)	1 (0.3)
Rash maculo-papular	8 (10.0)	1 (1.3)	15 (4.5)	0
Decreased appetite	8 (10.0)	1 (1.3)	57 (17.2)	2 (0.6)
Headache	6 (7.5)	0	36 (10.9)	1 (0.3)
Pruritus	6 (7.5)	0	51 (15.4)	0
Back pain	4 (5.0)	0	48 (14.5)	3 (0.9)
Cough	3 (3.8)	0	54 (16.3)	1 (0.3)

Adverse events for which the incidence was ≥10% higher in the Japanese patient population than in the non-Japanese patient population included paronychia, white blood cell count decreased, platelet count decreased, stomatitis, nasopharyngitis, dermatitis acneiform, neutrophil count decreased, and pyrexia. Grade ≥3 adverse events for which the incidence was ≥2% higher in the Japanese patient population than in the non-Japanese patient population included white blood cell count decreased, neutrophil count decreased, anaemia, and ILD. Serious adverse events that occurred in more than 1 patient of the Japanese patient population at an incidence ≥1% higher than that in the non-Japanese patient population included ILD (3 of 80 Japanese patients [3.8%], 1 of 331 non-Japanese patients [0.3%]), and adverse events leading to treatment discontinuation at an incidence ≥1% higher than that in the non-Japanese patient population included ILD (3 of 80 Japanese patients [3.8%], 2 of 331 non-Japanese patients [0.6%]).

PMDA's view:
Although the pooled phase II study data presented adverse events with an incidence higher in the Japanese patient population than in the non-Japanese patient population, including paronychia, white blood cell count decreased, and platelet count decreased, many of these events were Grade ≤2. PMDA has therefore concluded that osimertinib can be tolerable in Japanese patients if appropriate measures

such as monitoring and management of adverse events, and dose adjustment of osimertinib are taken by physicians with sufficient knowledge and experience in cancer chemotherapy. Compared with the non-Japanese patient population, however, the Japanese patient population tended to experience serious ILD and ILD leading to treatment discontinuation more frequently, some of which were fatal. PMDA has therefore concluded that attention should be paid to ILD.

In the following sections, major events in the pooled phase II study data were evaluated in consideration of events listed as those requiring attention in the "Clinically Significant Adverse Reactions" section in the package inserts of conventional EGFR-TKIs: gefitinib, erlotinib hydrochloride, and afatinib maleate.

4.(iii).B.(3).3) ILD-like events

The applicant's explanation on ILD-like events in patients receiving osimertinib regarding (a) the incidence and characteristics of ILD-like events in clinical studies, (b) risk factors of ILD in patients receiving osimertinib, and (c) post-marketing safety measures:

(a) Incidence and characteristics of ILD-like events in clinical studies:

As ILD-like events, events classified into the following MedDRA preferred terms (PTs) were tabulated: "Interstitial lung disease," "pneumonitis," "acute interstitial pneumonitis," "alveolitis," "diffuse alveolar damage," "idiopathic pulmonary fibrosis," "lung disorder," "pulmonary toxicity," "pulmonary fibrosis," "organising pneumonia," "acute lung injury," and "acute respiratory distress syndrome".

In the pooled phase II study data (data cut-off on May 1, 2015), all Grade ILD-like events occurred in 12 of 411 patients (2.9%; ILD in 6, pneumonitis in 5, and organising pneumonia in 1), and Grade ≥3 ILD-like events occurred in 7 of 411 patients (1.7%; pneumonitis in 4 and ILD in 3). Serious ILD-like events occurred in 8 of 411 patients (1.9%; ILD in 4 and pneumonitis in 4), of whom 4 patients (ILD in 3 and pneumonitis in 1) died. In the Japanese patient population, all Grade ILD-like events occurred in 6 of 80 patients (7.5%), and Grade ≥3 ILD-like events occurred in 3 of 80 patients (3.8%). Serious ILD-like events occurred in 4 of 80 patients (5.0%), of whom 2 died.

In addition, detailed analysis on ILD-like events was performed, in view of their importance, on the pooled data from clinical studies with osimertinib (including unlocked safety data)* (clinical development program data) (data cut-off on June 1, 2015).

*: Data in 1221 patients treated with osimertinib in the AURA study, the AURA2 study, Study D5160C00009, Study D5160C00012, Study D5160C00013, and Study D5160C00014 as well as studies in patients with lung cancer: Study D5160C00008, Study D5160C00003, and Study D5160C00006

In the clinical development program data, ILD-like events occurred in 29 of 1151 patients (2.5%) during osimertinib monotherapy. Serious ILD-like events occurred in 18 of 1151 patients (1.6%), including 4 fatal events. Details of patients with ILD-like events are shown in the table below. In a clinical study (Study D5160C00006) in which osimertinib was administered in combination with antibody targeting Programmed death-ligand 1, ILD-like events occurred in 6 of 70 patients (8.6%) (data cut-off on June 1, 2015).

List of patients who developed ILD-like events while receiving osimertinib (clinical development program data)

Age	Sex	Dose of osimertinib	Race*[1]	Adverse events	CTCAE Grade	Seriousness	Date of onset (Day)	Causal relationship to osimertinib	Action on osimertinib	Outcome
Phase I part of the AURA study										
6	Male	80mg	Japanese	ILD	2	Non-serious	84	Related	Treatment discontinuation	Recovered
6	Female	80mg	Japanese	ILD	3	Serious	42	Related	Treatment discontinuation	Improved
6	Male	80mg	Japanese	Pneumonitis	2	Serious	63	Related	Treatment discontinuation	Recovered
7	Female	80mg	Japanese	Pneumonitis	2	Serious	14	Related	Treatment discontinuation	Recovered
6	Male	80mg	Japanese	Pneumonitis	3	Serious	50	Related	Treatment discontinuation	Not recovered
6	Male	80mg	Japanese	Pneumonitis	1	Non-serious	85	Related	Treatment discontinuation	Not recovered
4	Female	80mg	Japanese	Pneumonitis	3	Serious	131	Related	Treatment discontinuation	Improved
8	Female	80mg	Japanese	Pneumonitis	3	Serious	22	Related	Treatment discontinuation	Improved
6	Female	160mg	Japanese	Pneumonitis	1	Non-serious	43	Related	Treatment discontinuation	Recovered
6	Female	80mg	Asian	Pneumonitis	3	Serious	54	Related	Treatment discontinuation	Improved
5	Female	160mg	Asian	Pneumonitis	3	Non-serious	85	Related	Treatment discontinuation	Recovered
7	Male	80mg	Non-Asian	Pneumonitis	2	Non-serious	19	Related	Treatment discontinuation	Improved
4	Female	80mg	Non-Asian	Pneumonitis	1	Non-serious	43	Related	None	Recovered
6	Female	160mg	Non-Asian	ILD	4	Serious	40	Related	Treatment discontinuation	Recovered
7	Female	160mg	Non-Asian	Pneumonitis	3	Serious	27	Related	Treatment discontinuation	Recovered
8	Male	160mg	Non-Asian	Pneumonitis	2	Non-serious	42	Related	Treatment discontinuation	Recovered
Phase II part of the AURA study										
5	Female	80mg	Japanese	ILD	5	Serious	230	Related	Treatment discontinuation	Died
6	Female	80mg	Japanese	ILD	5	Serious	47	Related	Treatment discontinuation	Died
6	Male	80mg	Japanese	ILD	1	Non-serious	85	Related	Treatment discontinuation	Recovered
6	Female	80mg	Japanese	Organising pneumonia	1	Non-serious	206	Not-related	Treatment interruption	Recovered
6	Female	80mg	Asian	ILD	1	Non-serious	163	Related	Treatment discontinuation	Recovered
6	Female	80mg	Non-Asian	Pneumonitis	3	Serious	40	Related	Treatment discontinuation	Recovered
6	Male	80mg	Non-Asian	Pneumonitis	3	Serious	148	Related	Treatment discontinuation	Not recovered
6	Male	80mg	Non-Asian	Pneumonitis	5	Serious	219	Related	Treatment discontinuation	Died
The AURA2 study										
8	Female	80mg	Japanese	Pneumonitis	3	Serious	17	Related	Treatment discontinuation	Recovered
3	Male	80mg	Japanese	ILD	1	Serious	79	Related	Treatment discontinuation	Improved
6	Female	80mg	Asian	Pneumonitis	1	Non-serious	83	Related	Treatment discontinuation	Recovered
6	Female	80mg	Non-Asian	ILD	5	Serious	59	Related	Treatment discontinuation	Died
Study D5160C00003										
7	Female	80mg	Japanese	Pneumonitis	1	Non-serious	39	Related	Treatment discontinuation	Recovered
Study D5160C00012										
4	Female	80mg	Asian	Organising pneumonia	2	Serious	15	Related	Treatment discontinuation	Improved

*1, "Asian" excludes Japanese. *2, ILD was not yet diagnosed on June 1, 2015 (data cut-off date), but was later definitively diagnosed.

On the basis of the follow-up survey (up to October 1, 2015) in 30 patients of the above table, ILD-like events associated with osimertinib are characterized as follows:

- The median period (range) from the start of osimertinib treatment to onset of ILD-like event was 52 days (14-230 days), and most of the events occurred within 85 days (approximately 12 weeks) after the start of treatment.
- Of 30 patients with ILD-like events in the above table, 15 were asymptomatic. The events were found out by diagnostic imaging to be performed regularly in the study.
- CT images of ILD-like events associated with osimertinib monotherapy were characterized by abnormal findings such as bilateral diffuse ground glass opacity and infiltrative shadow.
- Of 30 patients who experienced ILD-like events associated with osimertinib monotherapy, 21 were treated with steroids, and 14 of these (66.7%) recovered or improved. Of those treated with steroids, 16 received antibiotics concomitantly.
- The incidence of ILD was higher in Japanese patients than in non-Japanese patients.

(b) Risk factors of ILD in patients receiving osimertinib:
On the basis of published literature on risk factors of ILD in NSCLC patients (*Clin Chest Med.* 2004;25:479-519, *Am J Respir Crit Care Med.* 2008;177:1348-1357, *Ann Intern Med.* 1997;127:356-364), potential risk factors* were identified. Then, on pooled data from the AURA study and the AURA2 study, the relationship of the identified potential risk factors and ILD-like events was analyzed in the overall population (766 patients) and the Japanese patient population (119 patients).

*: Identified potential risk factors included performance status, age, sex, ethnic group, body surface area, body weight, smoking history, treatment line, history of radiation therapy on the lungs, history of chemotherapy, history of lung surgery, cardiac disease, diabetes mellitus, respiratory disease, hypoalbuminaemia, time from the first diagnosis, pleural effusion retention, and pericardial effusion

The lower limit of confidence interval was >1 only for the odds ratio of the incidence of ILD-like events between categories in ethnic group (Japanese vs non-Asian, odds ratio [95% CI] of 2.94 [1.16, 7.42]) among the risk factors in overall population. Since no adjustments were made to this analysis, other factors are possibly involved as confounding factors. A report on a different antineoplastic drug (*Japan Medical Association Journal.* 2007;50:405-411) also showed that the incidence of ILD was higher in Japanese patients than in non-Asian patients. Thus the applicant considers that the incidence of ILD-like events is possibly higher in Japanese patients than in non-Asian patients. The analysis in the Japanese patient population did not indicate a clear difference in the incidence of ILD-like events between categories of any risk factors.

(c) Post-marketing safety measures:
Safety measures on ILD-like events in the phase II part of the AURA study and the AURA2 study are as follows:

- Patients with a history of ILD and those complicated with active ILD were excluded from the study.
- ILD-like events were monitored by vital sign measurement, physical examination, and interview every 3 weeks, as well as chest CT scan every 6 weeks. Moreover, to enable earlier detection of ILD-like events in Japanese patients in view of the higher incidence in them, they were monitored more thoroughly, starting in the middle of studies, by adding the following: chest X-ray examination on Weeks 1, 2, 3, and 4; imaging examination (chest X-ray or CT scan) on Weeks 6, 9, and 12; and percutaneous oxygen saturation (SpO_2) measurement at every regular visit.
- If a symptom suggestive of ILD (dyspnoea, cough, etc.) developed or aggravated, or ILD was suspected from imaging, osimertinib should be interrupted and appropriate treatment and detailed examination should be done. If ILD was diagnosed, osimertinib should be discontinued, and ii) if ILD was ruled out, resumption of osimertinib should be considered following consultation with the sponsor.

On the basis of the above, to ensure early detection of ILD-like events as well as subsequent prompt diagnosis and treatment, a caution statement for the ILD-like events will be included in the Warning section of the package insert, and the following measures will be taken for post-marketing safety.

- A guide for proper use of osimertinib for healthcare professionals as well as materials and a caution leaflet for patients providing information necessary for early detection of ILD-like events are prepared to warn those involved in use of osimertinib. Conditions of use for osimertinib

(requirements for medical institutions and physicians, and request for cooperation from pharmacies and wholesalers to ensure the safety measures) should be established to ensure that the caution statement is thoroughly applied in the clinical settings.

- Healthcare professionals are thoroughly informed that they shall instruct patients to visit a medical institution immediately when they have symptoms suggestive of an ILD-like event.

Furthermore, the applicant plans an all-case survey to identify adverse drug reactions in routine clinical use [see "4.(iii).B.(6) Post-marketing investigations"], and to provide new information about ILD-like events to healthcare professionals in clinical settings as soon as such information becomes available.

PMDA's view:
In the pooled phase II study data, the incidence of ILD-like events was 7.5% (6 of 80 patients) in the Japanese patient population, which was higher than 1.8% (6 of 331 patients) in the non-Japanese patient population, and also some Japanese patients died. In addition, the incidence of ILD-like events tended to be higher in Japanese patients with NSCLC receiving osimertinib than in patients receiving approved EGFR-TKIs,* although it is difficult to compare accurately because the patient characteristics are different in those 2 populations. In the phase II part of the AURA study and the AURA2 study, eligible patients were carefully selected, potential symptoms were closely monitored through regular observation and imaging examination to ensure early detection of ILD-like events and prompt action, and in the case of developing the concerned event, osimertinib was interrupted first, and then, followed by a diagnosis and a treatment. In view of the above, strict safety measures against ILD-like events are considered necessary.

*: The incidence in untreated and treated patients were 1.8% (2 of 114 patients) and 5.7% (14 of 244 patients), respectively, for gefitinib (counted as ILD) (see "Review Report, Iressa Tablets 250, dated November 16, 2011"); 5.8% (6 of 103 patients) and 4.9% (6 of 123 patients), respectively, for erlotinib hydrochloride (see "Review Report, Tarceva Tablets 25 mg, 100 mg, and 150 mg, dated May 7, 2013"); and 7.4% (4 of 54 patients) and 4.8% (3 of 62 patients), respectively, for afatinib maleate (see "Review Report, Giotrif Tablets 20 mg, 30 mg, 40 mg, and 50 mg, dated September 19, 2013).

On the basis of the above, PMDA considers that the following points should be included in the package insert etc., to advise healthcare professionals in clinical settings appropriately. Furthermore, a post-marketing all-case survey should be conducted to identify ILD-like events and risk factors of ILD should be further investigated, and then new information should be provided to medical practices appropriately when such information becomes available [see "4.(iii).B.(6) Post-marketing investigations"].

- Monitoring of symptoms by regular observation and imaging examination, as specified in clinical studies.
- Rules for dose adjustment according to the ILD-like events, as specified in clinical studies.
- The incidence of and risk factors for the relevant events in clinical studies
- Appropriateness of osimertinib treatment should be judged carefully on the basis of pre-treatment chest CT scan and interview to confirm complications or history of ILD-like events.
- Appropriate measures should be taken if the relevant event occurs.
- Thorough cautions and information should be provided to patients.

4.(iii).B.(3).4) QT interval prolonged

The applicant's explanation on QT interval prolonged in patients receiving osimertinib:
Patients who showed the following conditions were excluded from the phase II part of the AURA study and the AURA2 study: QTcF exceeding 470 msec; electrocardiography revealing clinically significant abnormalities; and possessing factors increasing a risk of QT interval prolonged or arrhythmia (congenital long QT interval syndrome, concomitant use of drugs known to prolong QT interval, etc.). QT interval was also monitored regularly, and if QTcF exceeded 500 msec, or was prolonged by >60 msec from baseline, osimertinib was interrupted.

As QT-interval-prolonged-related events, events classified into the following MedDRA PTs were tabulated: "Torsade de pointes," "ventricular tachycardia," "electrocardiogram QT interval abnormal," "long QT syndrome congenital," "long QT syndrome," "electrocardiogram QT prolonged." Also the

following preferred terms related to other QT interval prolonged were tabulated: “Generalised tonic-clonic seizure,” “partial seizures,” “seizure,” “sudden death,” “syncope,” “ventricular fibrillation,” and “ventricular flutter.”

In the pooled phase II study data, QT-interval-prolonged-related events occurred in 18 of 411 patients (4.4%; electrocardiogram QT prolonged in 17 and syncope in 1), and of them, 5 patients experienced a Grade 3 event (all of them were electrocardiogram QT prolonged). Among QT-interval-prolonged-related events, neither serious ones nor those leading to treatment discontinuation occurred. QT-interval-prolonged-related events leading to dose reduction or treatment interruption occurred in 3 of 441 patients (0.7%) and 8 of 411 patients (1.9%), respectively. The median time to the first onset (range) to the first onset of electrocardiogram QT prolonged was 86.0 days (1-169 days).

Changes in QTcF associated with osimertinib administration in the pooled phase II study data are shown in the table below.

Changes in QTcF associated with osimertinib administration (pooled phase II study data)

	Number of patients (%)
	N = 411
Maximum	
>480msec	16 (3.9)
>500msec	1 (0.2)
>550msec	0
Increase from baseline (maximum)	
>30msec	170 (41.4)
>60msec	11 (2.7)
>100msec	1 (0.2)
Mean increase from baseline (maximum) [90% CI] (msec)	
	28.4 [27.17, 29.58]

In the clinical studies of osimertinib other than the phase II part of the AURA study and the AURA2 study,* serious QT-interval-prolonged-related events occurred in 3 patients (partial seizures, seizure, and syncope in 1 each), but their causal relationship to osimertinib was ruled out.

*: Phase I part of the AURA study, Study D5160C00009, Study D5160C00012, Study D5160C00013, Study D5160C00014, and Study D5160C00019 (hereinafter collectively referred to as other clinical studies of osimertinib)

PMDA’s view:
Since osimertinib has been shown to prolong QT interval, and Grade 3 QT interval prolonged occurred in patients receiving osimertinib, attention should be paid to QT interval prolonged during osimertinib treatment. Cautions for QT interval prolonged should be provided to healthcare professionals in medical settings appropriately through the package insert and relevant materials including information on the incidence of the related events in clinical studies. Moreover, information that patients with a risk of QT interval prolonged were excluded from the clinical studies should be provided through the relevant materials. Furthermore, cautions for QT interval prolonged and arrhythmia should also be appropriately provided to healthcare professionals through the package insert and relevant materials so that electrolyte test and electrocardiography are periodically performed during osimertinib treatment, and appropriate actions such as treatment interruption of osimertinib are taken if these events occur.

4.(iii).B.(3).5) Haematotoxicity

The applicant’s explanation on haematotoxicity associated with osimertinib:
As suspected haematotoxic events, events classified into haematotoxicity-related PTs under MedDRA system organ classes (SOCs) of “blood and lymphatic system disorders” and “investigations” were tabulated.

The incidence of haematotoxic events identified in the pooled phase II study data are shown in the table below.

Haematotoxicity events with an incidence of ≥1% (pooled phase II study data)

Preferred term (MedDRA/J ver18.0)	Number of patients (%) N = 411	
	All Grades	Grade ≥3
All adverse events	126 (30.7)	26 (6.3)
Platelet count decreased	47 (11.4)	2 (0.5)
Anaemia	40 (9.7)	6 (1.5)
White blood cell count decreased	31 (7.5)	3 (0.7)
Neutrophil count decreased	25 (6.1)	7 (1.7)
Thrombocytopenia	22 (5.4)	4 (1.0)
Neutropenia	17 (4.1)	2 (0.5)
Leukopenia	12 (2.9)	3 (0.7)
Lymphopenia	5 (1.2)	1 (0.2)

No fatal haematotoxicity events occurred in the pooled phase II study data. Serious haematotoxicity events occurred in 6 of 411 patients (1.5%; anaemia in 3, thrombocytopenia in 2, and disseminated intravascular coagulation, neutrophil count decreased, and platelet count decreased in 1 each [some experienced multiple events]). For any of these events except for anaemia in 2 patients, a causal relationship to osimertinib could not be ruled out. The haematotoxicity events leading to treatment discontinuation, dose reduction, or treatment interruption occurred in 1 of 411 patients (0.2%), 4 of 411 (1.0%), and 16 of 411 (3.9%), respectively. The median time to the first onset (range) of a haematotoxicity event was 22 days (1-253 days).

In the Japanese patient population in the pooled phase II study data, all Grades haematotoxicity events occurred in 44 of 80 patients (55.0%), and Grade ≥3 haematotoxicity events occurred in 11 of 80 patients (13.8%). Serious haematotoxicity events occurred in 2 of 80 patients (2.5%; anaemia, neutrophil count decreased, platelet count decreased, and disseminated intravascular coagulation in 1 each [some experienced with multiple events]). For any of the events, a causal relationship to osimertinib could not be ruled out. The haematotoxicity events leading to treatment discontinuation, dose reduction, or treatment interruption occurred in 1 of 80 patients (1.3%), 2 of 80 (2.5%), and 6 of 80 (7.5%), respectively.

In the other clinical studies of osimertinib, serious haematotoxicity events occurred in 2 patients (pancytopenia and anaemia in 1 each), and for both events, a causal relationship to osimertinib was ruled out.

PMDA's view:
Because in clinical studies, serious haematotoxicity events for which a causal relationship to osimertinib could not be ruled out occurred in patients receiving osimertinib; and in the pooled phase II study data, the incidence of haematotoxicity events tended to be higher in the Japanese patient population than in the non-Japanese patient population, attention should be paid to haematotoxicity events during osimertinib treatment. Accordingly, information on the incidence of haematotoxicity events in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert and relevant materials. In addition, cautions for such events should also be appropriately provided to healthcare professionals through the package insert and relevant materials so that regular blood tests are performed to have patients carefully monitored during osimertinib treatment, and that appropriate actions are taken if these events occur.

4.(iii).B.(3).6) Liver disorders

The applicant's explanation on liver disorders associated with osimertinib:
As suspected liver disorders, events classified into liver disorder-related PTs under MedDRA SOC of "hepatobiliary disorders" or liver disorder-related PTs under "investigations" were tabulated as liver disorders.

The incidence of liver disorders identified in the pooled phase II study data are shown in the table below.

Liver disorders (pooled phase II study data)

Preferred term (MedDRA/J ver18.0)	Number of patients (%) N = 411	
	All Grades	Grade ≥3
All adverse events	46 (11.2)	8 (1.9)
ALT increased	27 (6.6)	5 (1.2)
AST increased	26 (6.3)	1 (0.2)
Blood bilirubin increased	6 (1.5)	1 (0.2)
Hyperbilirubinaemia	3 (0.7)	0
Hepatic function abnormal	2 (0.5)	1 (0.2)
Cholecystitis	1 (0.2)	0
Cholelithiasis	1 (0.2)	0
Drug-induced liver injury	1 (0.2)	1 (0.2)
Hepatomegaly	1 (0.2)	0
Jaundice	1 (0.2)	1 (0.2)
Liver disorder	1 (0.2)	1 (0.2)
Transaminases increased	1 (0.2)	0

In the pooled phase II study data, serious liver disorders occurred in 4 of 411 patients (1.0%; hepatic function abnormal, blood bilirubin increased and jaundice, liver disorder, and drug-induced liver injury in 1 each), and 1 of 411 patients (0.2%; liver disorder) died. Of serious liver disorders, a causal relationship to osimertinib could not be ruled out for hepatic function abnormal and drug-induced liver injury in 1 patient each. Liver disorders leading to treatment discontinuation or interruption occurred in 1 of 411 patients (0.2%) and 6 of 411 (1.5%), respectively. No liver disorders led to dose reduction.

In other clinical studies of osimertinib, serious liver disorders occurred in 4 patients (ALT increased/AST increased/blood bilirubin increased, cholangitis, cholecystitis, and hepatic enzyme increased in 1 each [some experienced multiple events]). Of these, a causal relationship to osimertinib could not be ruled out for the events in 1 patient (ALT increased/AST increased/blood bilirubin increased; given osimertinib 20 mg in the phase I part of the AURA study).

In clinical studies of osimertinib, no liver disorders met Hy's law (defined under Guidance for industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009).

PMDA's view:
Because Grade ≥3 liver disorders, serious liver disorders, and liver disorders leading to treatment discontinuation occurred in patients receiving osimertinib, and liver disorders are events requiring attention in patients receiving conventional EGFR-TKIs (see "Review Report, Giotrif Tablets 20 mg, 30 mg, 40 mg, and 50 mg, dated September 19, 2013"), attention should be paid to liver disorders during osimertinib treatment. Accordingly, information on the incidence of liver disorders in clinical studies should be provided through the package insert and relevant materials to raise cautions. In addition, cautions for such events should be appropriately provided to healthcare professionals in clinical settings through the package insert and relevant materials so that liver function test values are regularly monitored during osimertinib treatment, and appropriate actions such as treatment interruption of osimertinib are taken if abnormal findings are observed.

4.(iii).B.(3).7) Cardiac disorders (excluding QT interval prolonged)
The applicant's explanation on cardiac disorders (excluding QT interval prolonged) (cardiac disorders) associated with osimertinib:
Because osimertinib and its metabolites were considered to possibly inhibit HER2, protocols for the phase II part of the AURA study and the AURA2 study included exclusion criteria for cardiac disorder and specified periodic monitoring of left ventricular ejection fraction (LVEF) by echocardiography or MUGA scan.

As suspected cardiac disorders, events classified into PTs under MedDRA SOC of "cardiac disorders" or included in Standardised MedDRA Queries (SMQs) of "cardiac failure" and "cardiomyopathy" were tabulated.

The incidence of cardiac disorders identified in the pooled phase II study data are shown in the table below.

Cardiac disorders (pooled phase II study data)

Preferred term (MedDRA/J ver18.0)	Number of patients (%) N = 411	
	All Grades	Grade ≥3
All adverse events	24 (5.8)	8 (1.9)
Palpitations	4 (1.0)	0
Sinus tachycardia	4 (1.0)	0
Tachycardia	4 (1.0)	1 (0.2)
Ejection fraction decreased	3 (0.7)	2 (0.5)
Supraventricular tachycardia	2 (0.5)	2 (0.5)
Cardiac failure congestive	1 (0.2)	1 (0.2)
Mitral valve prolapse	1 (0.2)	1 (0.2)
Systolic dysfunction	1 (0.2)	1 (0.2)
Tachyarrhythmia	1 (0.2)	1 (0.2)
Atrioventricular block	1 (0.2)	0
Diastolic dysfunction	1 (0.2)	0
Extrasystoles	1 (0.2)	0
Tricuspid valve incompetence	1 (0.2)	0
Ventricular extrasystoles	1 (0.2)	0
Pulmonary oedema	1 (0.2)	0

In the pooled phase II study data, serious cardiac disorders occurred in 3 of 411 patients (0.7%; supraventricular tachycardia in 2 and cardiac failure congestive in 1), and of these, 1 of 411 patients (0.2%; cardiac failure congestive) died. For any of the serious cardiac disorders, a causal relationship to osimertinib was ruled out. No adverse events led to treatment discontinuation or dose reduction. Cardiac disorders leading to treatment interruption occurred in 5 of 411 patients (1.2%).

In the phase II part of the AURA study and the AURA2 study, changes in LVEF over time are shown in the table below. In the pooled phase II study data, of 375 patients who underwent echocardiography after the start of treatment, 9 patients (2.4%) presented with LVEF decreased by ≥10% from baseline and absolute LVEF of <50%. Many of these patients were found to have complications or history of diseases related to cardiac disorder, or to be on concomitant drugs that potentially become a risk of cardiac disorder (the table below).

Changes in LVEF over time following osimertinib treatment (phase II part of the AURA study and the AURA2 study)

Phase II part of the AURA study				The AURA2 study			
Time point	Number of patients	Median	Change from baseline	Time point	Number of patients	Median	Change from baseline
Baseline	196	65.0%		Baseline	209	63.0%	
Week 12	176	64.0%	-1.0%	Week 12	190	62.5%	-0.5%
Week 21	159	64.0%	-1.0%	Week 24	162	63.0%	-1.0%
Week 27	88	63.5%	-1.5%	Week 36	60	63.0%	-1.0%

List of patients receiving osimertinib with LVEF decreased by ≥10% from baseline and absolute LVEF of <50% (phase II part of the AURA study and the AURA2 study)

Age	Sex	LVEF			Number of days with minimum LVEF (after the start of treatment)	History or complication of relevant diseases, or concomitant drugs	Outcome
		Baseline	Minimum	Maximum change (%)			
Phase II part of the AURA study							
6[redacted]	Female	73%	46%	-27%	169 days	History of hypertension	Improved after treatment interruption (Day 190), not aggravated after resumption of osimertinib
7[redacted]	Female	62%	46%	-16%	251 days	History of pulmonary fibrosis	Continued osimertinib
The AURA2 study							
7[redacted]	Female	65%	30%	-35%	169 days	History of hypertension	Improved following treatment interruption of osimertinib and treatment with diuretic (Day 184)
7[redacted]	Male	58%	44%	-14%	109 days	History of chronic obstructive pulmonary disease	Continued osimertinib
7[redacted]	Female	63%	30%	-33%	130 days	History of hypertension and chronic renal failure	Discontinued treatment of osimertinib due to disease progression (Day 130)
5[redacted]	Female	60%	46%	-14%	166 days	Oral COX-2 inhibitor	Continued osimertinib
7[redacted]	Female	55%	45%	-10%	84 days	History of coronary heart disease, oral COX-2 inhibitor	Improved during continued osimertinib treatment (Day 170).
7[redacted]	Male	67%	43%	-24%	81 days	None	Recovered during continued osimertinib treatment (Day 175).
8[redacted]	Female	35%	25%	-10%	254 days	History of atrial fibrillation, palpitations, sinus tachycardia, oedema, and diabetes mellitus	Unknown.

COX-2: Cyclo-oxgenase-2

In other clinical studies of osimertinib, serious cardiac disorders occurred in 7 patients (cardiac failure acute, stress cardiomyopathy, myocardial infarction, pulseless electrical activity, cardiac failure congestive, bundle branch block left, and atrial flutter in 1 each), and of them, 1 patient (pulseless electrical activity) died. Of serious cardiac disorders, a causal relationship to osimertinib could not be ruled out for cardiac failure acute in 1 patient (given osimertinib 160 mg in phase I part of the AURA study), cardiac failure congestive in 1 (Study D5160C00013), and bundle branch block left in 1 (Study D5160C00014).

PMDA's view:
Although only a limited number of patients experienced cardiac disorders other than serious QT interval prolonged in clinical studies for which a causal relationship to osimertinib could not be ruled out, attention should be paid to the development of cardiac disorders other than QT interval prolonged since LVEF was changed in some of the patients receiving osimertinib. Accordingly, information on the incidence of cardiac disorders other than QT interval prolonged in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert and relevant materials to raise cautions. Also, relevant information should be further collected and appropriately provided to healthcare professionals when new findings become available.

4.(iii).B.(3).8) Thromboembolism

The applicant's explanation on thromboembolism associated with osimertinib:
As suspected thromboembolic events, those included in the following SMQs were tabulated: "Embolic and thrombotic events, arterial," "embolic and thrombotic events, venous," "embolic and thrombotic events, vessel type unspecified and mixed arterial and venous," and "thrombophlebitis."

The incidence of thromboembolic events identified in the pooled phase II study data are shown in the table below.

Thromboembolism (pooled phase II study data)

Preferred term (MedDRA/J ver18.0)	Number of patients (%) N = 411	
	All Grades	Grade ≥3
All adverse events	39 (9.5)	14 (3.4)
Pulmonary embolism	17 (4.1)	9 (2.2)
Deep vein thrombosis	12 (2.9)	1 (0.2)
Cerebral infarction	3 (0.7)	2 (0.5)
Cerebrovascular accident	3 (0.7)	2 (0.5)
Embolic cerebral infarction	1 (0.2)	1 (0.2)
Embolic stroke	1 (0.2)	1 (0.2)
Splenic infarction	1 (0.2)	1 (0.2)
Jugular vein thrombosis	1 (0.2)	0
Pelvic venous thrombosis	1 (0.2)	0
Arterial thrombosis	1 (0.2)	0
Retinal vein occlusion	1 (0.2)	0
Thrombophlebitis	1 (0.2)	0
Thrombophlebitis superficial	1 (0.2)	0
Disseminated intravascular coagulation	1 (0.2)	0
Transient ischaemic attack	1 (0.2)	0

In the pooled phase II study data, serious thromboembolic events occurred in 17 of 411 patients (4.1%; pulmonary embolism in 11, cerebral infarction, cerebrovascular accident, and deep vein thrombosis in 2 each, embolic stroke, disseminated intravascular coagulation, and transient ischaemic attack in 1 each [some experienced multiple events]), and of them, 1 patient (cerebrovascular accident) died. Of serious thromboembolism, a causal relationship to osimertinib could not be ruled out for cerebral infarction, pulmonary embolism, and disseminated intravascular coagulation in 1 patient each. Thromboembolism leading to treatment discontinuation and interruption occurred in 6 of 411 patients (1.5%; cerebrovascular accident and pulmonary embolism in 2 each, cerebral infarction and embolic cerebral infarction in 1 each) and 3 of 411 patients (0.7%; pulmonary embolism in 2 and disseminated intravascular coagulation in 1), respectively. No thromboembolic events led to dose reduction.

In other clinical studies of osimertinib, serious thromboembolic events occurred in 21 patients (pulmonary embolism in 12, thrombophlebitis and ischaemic stroke in 2, stress cardiomyopathy, myocardial infarction, deep vein thrombosis, embolic stroke, cerebrovascular accident, pulmonary artery thrombosis, peripheral artery thrombosis, and embolism in 1 each [some experienced multiple events]). Of these, a causal relationship to osimertinib could not be ruled out for pulmonary embolism in 2 patients (one given osimertinib 20 mg, the other 80 mg in the phase I part of the AURA study) and pulmonary artery thrombosis in 1 patient (given osimertinib 40 mg in the phase I part of the AURA study).

The applicant's further explanation on thromboembolic events in patients receiving osimertinib:
The incidence of thromboembolism is known to be high in cancer patients (*Crit Rev Oncol Hematol.* 2004;50:187-196). Thromboembolism is frequently comorbid particularly in NSCLC patients, and the incidence has been reported to be 3.0% to 13.8% (*Multidisciplinary Respir Med.* 2015;10:28), which is comparable to that in the study data. Accordingly, thromboembolism in the pooled phase II study data should not be considered definitely attributable to osimertinib.

PMDA's view:
Thromboembolism found in the clinical studies is considered possibly attributable to a history of diseases related to thromboembolism. On the other hand, serious thromboembolism occurred for which a causal relationship to osimertinib could not be ruled out. In view of this, attention should be paid to the development of thromboembolism. Accordingly, information on the incidence of thromboembolism in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert and relevant materials to raise cautions. Also, relevant information should be further collected and appropriately provided to healthcare professionals when new findings become available.

4.(iii).B.(3).9) Infection

The applicant's explanation of infections associated with osimertinib:

As suspected infection events, events classified into PTs under MedDRA SOC of "infections and infestations" were tabulated.

Infection events identified in the pooled phase II study data are shown in the table below.

Infection events with an incidence of ≥1% (pooled phase II study data)

Preferred term (MedDRA/J ver18.0)	Number of patients (%) N = 411	
	All Grades	Grade ≥3
All adverse events	212 (51.6)	24 (5.8)
Paronychia	72 (17.5)	0
Nasopharyngitis	35 (8.5)	0
Upper respiratory tract infection	30 (7.3)	1 (0.2)
Urinary tract infection	24 (5.8)	1 (0.2)
Pneumonia	16 (3.9)	11 (2.7)
Conjunctivitis	12 (2.9)	0
Bronchitis	8 (1.9)	0
Pharyngitis	8 (1.9)	0
Influenza	8 (1.9)	2 (0.5)
Cystitis	7 (1.7)	1 (0.2)
Viral upper respiratory tract infection	7 (1.7)	0
Sinusitis	6 (1.5)	0
Urinary tract infection bacterial	6 (1.5)	2 (0.5)
Rash pustular	6 (1.5)	0
Herpes zoster	5 (1.2)	0
Gastroenteritis	4 (1.0)	1 (0.2)
Lung infection	4 (1.0)	1 (0.2)
Folliculitis	4 (1.0)	0

In the pooled phase II study data, serious infections occurred in 25 of 411 patients (6.1%; pneumonia in 11, influenza in 3, urinary tract infection in 2, appendicitis, bronchopneumonia, gastroenteritis, lung infection, pharyngeal abscess, salmonella sepsis, sepsis, upper respiratory tract infection, viral infection, and urinary tract infection bacterial in 1 each [some experienced multiple events]). Of those, 4 of 411 patients (1.0%; pneumonia in 3 and urinary tract infection bacterial in 1) died. Of serious infections, a causal relationship to osimertinib could not be ruled out for influenza and lung infection in 1 patient each. Infection events leading to treatment discontinuation, dose reduction, or treatment interruption occurred in 1 of 411 patients (0.2%), 1 of 411 (0.2%), and 18 of 411 (4.4%), respectively.

In other clinical studies of osimertinib, serious infections occurred in 37 patients (pneumonia in 14, lung infection in 2, lower respiratory tract infection, Streptococcal bacteraemia, post procedural infection, erysipelas, abscess, urinary tract infection bacterial, bronchitis, device related infection, pyelonephritis acute, sepsis, septic shock, bacterial sepsis, upper respiratory tract infection, pneumonia pneumococcal, viraemia, bacteraemia, mediastinitis, respiratory tract infection bacterial, Klebsiella infection, cellulitis, respiratory syncytial virus infection, lobar pneumonia, and infectious pleural effusion in 1 each [some experienced multiple events]). Of them, 10 patients (pneumonia in 7, septic shock, lung infection, and respiratory tract infection bacterial in 1 each) died. A causal relationship to osimertinib could not be ruled out for the following: pneumonia in 1 patient (given osimertinib 20 mg in the phase I part of the AURA study) of fatal infections; or lobar pneumonia in 1 patient (given osimertinib 80 mg in Study D5160C000012) of non-fatal serious infections.

Most of serious infections in clinical studies were lung infections such as pneumonia. Even in patients with lung cancer not receiving chemotherapy, lung infection has been reported to occur at the incidence of approximately 2% to 5% (*Lancet Oncol.* 2015:13;528-538, *N Engl J Med.* 2005;353:123-132, *Lancet.* 2005;366:1527-1537, etc.), which is comparable to that in the pooled analysis. In view of the above findings, lung infections should not be considered definitely attributable to osimertinib.

PMDA's view:

Although, in the clinical studies, there were only limited number of serious infection events for which a causal relationship to osimertinib could not be ruled out, attention should be paid to the developments of infection events, since fatal infections occurred for which a causal relationship to osimertinib could

not be ruled out, and blood count decreased, a potential risk of infection, occurred after osimertinib treatment. Consequently, information on the incidence of infection in clinical studies should be appropriately provided to healthcare professionals in clinical setting through the package insert and relevant materials to raise cautions. Also, relevant information should be collected and appropriately provided to healthcare professionals when new findings become available.

4.(iii).B.(3).10) Diarrhoea

The applicant's explanation on diarrhoea associated with osimertinib:

In the phase II part of the AURA study and the AURA2 study, physicians were advised to take appropriate actions such as symptomatic therapy (use of antidiarrheal drugs etc.) and treatment interruption of osimertinib.

In the pooled phase II study data, diarrhoea occurred in 174 of 411 patients (42.3%), and 4 of 411 patients (1.0%) experienced Grade 3 diarrhoea. No fatal diarrhoea occurred. Serious diarrhoea occurred in 1 of 411 patients (0.2%), and its causal relationship to osimertinib could not be ruled out. Diarrhoea leading to treatment discontinuation and interruption occurred in 1 of 411 patients (0.2%) and 4 of 411 (1.0%), respectively. No diarrhoea led to dose reduction. The median time to the first onset of diarrhoea (range) in the pooled phase II study data was 18 days (1-251 days), and median total duration of all diarrhoea episodes (263 episodes; not limited to the first episodes) (range) was 81 days (1-310 days). In 95 of all 263 episodes (36.1%) of diarrhoea, patients were treated with antidiarrheal drugs. Of these, 61 episodes resolved, and 34 episodes did not. During diarrhoea episodes, electrolyte abnormality, dehydration, and renal impairment were observed in 6, 2, and 1 patients, respectively.

In other clinical studies of osimertinib, serious diarrhoea occurred in 7 patients; of these, a causal relationship to osimertinib could not be ruled out for the events in 4 patients (one given osimertinib 20 mg, another 80 mg, and remaining 2 given osimertinib 160 mg in the phase I part of the AURA study).

PMDA's view:

In the pooled phase II study data, grades of diarrhoea were mostly ≤2, but their incidence was high. In view of this, PMDA considers it necessary to provide cautions appropriately to healthcare professionals in clinical settings through the package insert and relevant materials, including the incidence of diarrhoea associated with osimertinib as well as the need to take appropriate measures in response to diarrhoea onset during osimertinib treatment.

4.(iii).B.(3).11) Gastrointestinal disorders (excluding diarrhoea)

The applicant's explanation on gastrointestinal disorders associated with osimertinib:

As suspected gastrointestinal disorders, PTs included in a MedDRA system organ class (SOC) of "gastrointestinal disorders" (except for diarrhoea); PTs of "gastroenteritis"; and a PT of "gastroenteritis clostridial" included in a MedDRA SOC of "infections and infestations"; and a PT of "gastroenteritis radiation" included in a MedDRA SOC of "injury, poisoning and procedural complications" were tabulated.

The incidence of gastrointestinal disorders identified in the pooled phase II study data are shown in the table below.

Gastrointestinal disorders with an incidence of ≥1% (pooled phase II study data)

Preferred term (MedDRA/J ver18.0)	Number of patients (%) N = 411	
	All Grades	Grade ≥3
All adverse events	223 (54.3)	8 (1.9)
Nausea	69 (16.8)	2 (0.5)
Constipation	62 (15.1)	1 (0.2)
Stomatitis	49 (11.9)	0
Vomiting	39 (9.5)	2 (0.5)
Abdominal pain upper	23 (5.6)	1 (0.2)
Abdominal pain	20 (4.9)	0
Dry mouth	20 (4.9)	0
Dyspepsia	10 (2.4)	0
Dysphagia	10 (2.4)	0
Gastrooesophageal reflux disease	10 (2.4)	0
Mouth ulceration	8 (1.9)	0
Abdominal distension	7 (1.7)	0
Gastritis	5 (1.2)	1 (0.2)
Abdominal discomfort	4 (1.0)	0
Haemorrhoids	4 (1.0)	0

In the pooled phase II study data, serious gastrointestinal disorder occurred in 7 of 411 patients (1.7%; constipation, inguinal hernia, nausea, vomiting, abdominal pain, gastritis, small intestinal obstruction, and gastroenteritis in 1 each [some experienced multiple events]). For any event, a causal relationship to osimertinib was ruled out. Gastrointestinal disorder leading to treatment discontinuation, dose reduction, or treatment interruption occurred in 1 of 411 patients (0.2%), 2 of 411 (0.5%) and 7 of 411 (1.7%), respectively. The median time to the first onset of a gastrointestinal disorder event (range) was 43 days (1-277 days).

In other clinical studies of osimertinib, serious gastrointestinal disorder occurred in 16 patients (nausea in 5, vomiting in 3, dysphagia in 2, and pancreatitis, food poisoning, intestinal obstruction, abdominal pain upper, haematemesis, small intestine ulcer, ileus, oesophageal stenosis, and oesophagitis in 1 each [some experienced multiple events]). Of these, a causal relationship to osimertinib could not be ruled out for the events in 4 patients (vomiting in 2 [one given osimertinib 20 mg, the other 160 mg], nausea in 1 [given osimertinib 20 mg], and intestinal obstruction in 1 [given osimertinib 160 mg], all in the phase I part of the AURA study).

PMDA's view:
Although only a limited number of patients experienced serious gastrointestinal disorder in the clinical studies, information about the incidence of major gastrointestinal disorder should be appropriately provided to healthcare professionals through the package insert to raise cautions, since, nausea, vomiting, and stomatitis are adverse events requiring careful attention during the use of conventional EGFR-TKIs, and the incidence of overall gastrointestinal disorder was high in patients receiving osimertinib.

4.(iii).B.(3).12) Skin disorder
The applicant's explanation on skin disorder associated with osimertinib:
In the phase II part of the AURA study and the AURA2 study, healthcare professionals were advised to recommend use of moisturizing cream to prevent skin disorder, and, in case of onset, take appropriate measures such as symptomatic therapy (use of external preparations) and treatment interruption of osimertinib.

As suspected skin disorders, PTs relevant to skin disorders but not involving nails* included in a MedDRA SOC of "skin and subcutaneous tissue disorders" and a MedDRA PT of "xerosis" were tabulated.

*: PTs included in a MedDRA high level term of "nail and nail bed conditions (excluding infections and infestations)" and PTs of "nail infection," "paronychia," and "nail bed infection"

The incidence of skin disorder identified in the pooled phase II study data are shown in the table below.

Skin disorder with an incidence of ≥1% (pooled phase II study data)

Preferred term (MedDRA/J ver18.0)	Number of patients (%) N = 411	
	All Grades	Grade ≥3
All adverse events	262 (63.7)	3 (0.7)
Rash	98 (23.8)	0
Dry skin	95 (23.1)	0
Pruritus	57 (13.9)	0
Dermatitis acneiform	28 (6.8)	0
Skin fissures	24 (5.8)	0
Rash maculo-papular	23 (5.6)	1 (0.2)
Alopecia	14 (3.4)	0
Erythema	11 (2.7)	1 (0.2)
Xerosis	10 (2.4)	0
Acne	9 (2.2)	0
Skin exfoliation	6 (1.5)	0
Rash pustular	6 (1.5)	0
Palmar-plantar erythrodysaesthesia syndrome	5 (1.2)	0
Folliculitis	4 (1.0)	0
Rash papular	4 (1.0)	0
Urticaria	4 (1.0)	0
Night sweats	4 (1.0)	0

No serious skin disorder was found in the pooled phase II study data. Skin disorder leading to treatment discontinuation, dose reduction, or treatment interruption occurred in 1 of 411 patients (0.2%), 1 of 411 (0.2%), and 2 of 411 (0.2%), respectively.

In the Japanese patient population in the pooled phase II study data, skin disorder (all grades) occurred in 56 of 80 patients (70.0%): Grade ≥3 skin disorder in 2 of 80 (2.5%); and skin disorder leading to treatment interruption, dose reduction, or treatment discontinuation in 2 of 80 (2.5%), 1 of 80 (1.3%), and 1 of 80 (1.3%), respectively.

In addition, in other clinical studies of osimertinib, serious skin disorder occurred in 1 patient (skin toxicity, osimertinib 80 mg in the phase I part of the AURA study), and its causal relationship to osimertinib could not be ruled out.

PMDA's view:
Skin disorder identified in the pooled phase II study data was mostly Grade 1-2, but the incidence of skin disorder was high. Consequently, healthcare professionals in clinical settings should be appropriately advised of the incidence of skin disorder associated with osimertinib and that appropriate measures should be taken in response to its onset during osimertinib treatment through the package insert and relevant materials.

4.(iii).B.(3).13) Nail disorder
The applicant's explanation on nail disorder associated with osimertinib:
In the phase II part of the AURA study and the AURA2 study, healthcare professionals were advised to recommend use of moisturizing cream to prevent nail disorder, and, in case of onset, take appropriate measures such as symptomatic therapy (use of external preparations) and treatment interruption of osimertinib.

As suspected nail disorders, PTs included in a MedDRA high level term of "nail and nail bed conditions (excluding infections and infestations)" and PTs of "nail infection," "paronychia," and "nail bed infection" were tabulated.

The incidence of nail disorder identified in the pooled phase II study data are shown in the table below.

Nail disorder with an incidence of ≥1% (pooled phase II study data)

Preferred term (MedDRA/J ver18.0)	Number of patients (%) N = 411	
	All Grades	Grade ≥3
All adverse events	107 (26.0)	0
Paronychia	72 (17.5)	0
Nail disorder	13 (3.2)	0
Onychoclasis	11 (2.7)	0
Nail discolouration	5 (1.2)	0
Nail ridging	5 (1.2)	0

In the pooled phase II study data, neither serious nail disorder nor nail disorder leading to treatment interruption or discontinuation occurred. Nail disorder leading to dose reduction occurred in 1 of 411 patients (0.2%).

In other clinical studies of osimertinib, no serious nail disorder occurred.

PMDA's view:
Nail disorder identified in the pooled phase II study data was mostly Grade 1-2, but the incidence of nail disorder was high. Consequently healthcare professionals in clinical settings should be appropriately advised of the incidences of nail disorder associated with osimertinib and that appropriate measures should be taken in response to its onset during osimertinib treatment through the package insert and relevant materials.

4.(iii).B.(3).14) Others
The applicant's explanation on corneal disorder, of which risk during clinical use of osimertinib was indicated by non-clinical study data [see "3.(iii).B.(1) Effects on the cornea"]:
As suspected eye disorder including corneal disorder, PTs included in a MedDRA SOC of "eye disorders" were tabulated.

The incidence of eye disorder identified in the pooled phase II study data are shown in the table below.

Eye disorder with an incidence of ≥1% (pooled phase II study data)

Preferred term (MedDRA/J ver18.0)	Number of patients (%) N = 411	
	All Grades	Grade ≥3
All adverse events	74 (18.0)	1 (0.2)
Dry eye	23 (5.6)	0
Vision blurred	12 (2.9)	0
Cataract	6 (1.5)	1 (0.2)
Blepharitis	4 (1.0)	0
Eye irritation	4 (1.0)	0
Eye pain	4 (1.0)	0
Lacrimation increased	4 (1.0)	0
Vitreous floaters	4 (1.0)	0

In the pooled phase II study data, neither serious eye disorders nor eye disorders leading to treatment discontinuation occurred. Eye disorder leading to dose reduction or treatment interruption occurred in 1 of 411 patients (0.2%) each.

In other clinical studies of osimertinib, serious eye disorder occurred in 1 patient (corneal erosion, osimertinib 80 mg in the phase I part of the AURA study), and its causal relationship to osimertinib was ruled out.

PMDA's view:
In the pooled phase II study data, most eye disorders associated with osimertinib were Grade 1-2. To date, no eye disorders of particular safety concern have occurred. In the non-clinical studies of osimertinib, however, corneal findings were observed, and their reversibility remains unknown [see "3.(iii).B.(1) Effects on the cornea"], and corneal disorder is known as an adverse event requiring attention during use of conventional EGFR-TKIs. In view of these, attention should be paid to corneal disorder in routine clinical use of osimertinib. Accordingly, information about the incidence of corneal

disorder in clinical studies should be appropriately provided to healthcare professionals in clinical settings through the package insert and relevant materials to raise cautions. Also, relevant information should be further collected and appropriately provided to healthcare professionals when new findings become available.

4.(iii).B.(4) Clinical positioning and indication

The proposed indication of osimertinib was "unresectable advanced or recurrent EGFR T790M mutation-positive non-small cell lung cancer that progressed during or after EGFR tyrosine kinase inhibitor treatment." The Precautions for Indications section included the following contents:

- The efficacy and safety of osimertinib are not yet established in EGFR-TKI-naïve patients with unresectable or recurrent NSCLC.

- Osimertinib should be used only in patients confirmed to be EGFR T790M mutation-positive. Approved *in vitro* diagnostics should be used to test for EGFR T790M mutation.

- Physicians should be thoroughly versed in the content of the "Clinical Studies" section, particularly concerning the previous medication in patients, and fully understand the efficacy and safety of osimertinib before selecting patients eligible for treatment.

- The efficacy and safety of osimertinib in adjuvant therapy are not yet established.

On the basis of the review of "4.(iii).B.(2) Efficacy" and "4.(iii).B.(3) Safety" as well as the following considerations described in this section, PMDA has concluded that the indication of osimertinib should be "inoperable or recurrent EGFR T790M mutation-positive non-small cell lung cancer resistant to EGFR tyrosine kinase inhibitors," and that the Precautions for Indications section should include the following statements.

- Osimertinib should be used only in patients confirmed to be EGFR T790M mutation-positive through tests performed by a thoroughly experienced pathologist or testing laboratory. Approved *in vitro* diagnostics should be used for the test.

- Physicians should be thoroughly versed in the content of the "Clinical Studies" section, fully understand the efficacy and safety of osimertinib, and carefully consider other treatment options before selecting patients eligible for osimertinib therapy.

- The efficacy and safety of osimertinib in adjuvant chemotherapy are not yet established.

4.(iii).B.(4).1) The target patient population, and indication of osimertinib

The treatment with osimertinib in patients with inoperable or recurrent EGFR T790M mutation positive NSCLC resistant to EGFR-TKIs is described in clinical practice guidelines and leading clinical oncology textbooks in and out of Japan as shown below. Meanwhile, no description on osimertinib was currently found in Japan Lung Cancer Society. *Guidelines for Diagnosis and Management of Lung Cancer by EBM*. 2014 ed.: Kanehara & Co., Ltd.; 2014 or *New Clinical Oncology.* 4th rev ed.: Nankodo; 2015.

[Clinical practice guidelines]

- US NCCN guideline (v.3.2016): Osimertinib is recommended for patients with advanced or recurrent EGFR activating mutation-positive NSCLC who has progressed after EGFR-TKI therapy and confirmed EGFR T790M mutation-positive (Category 2A).

- US National Cancer Institute Physician Data Query (NCI-PDQ) (dated December 15, 2015): Osimertinib is recommended for patients with EGFR T790M mutation-positive cancer who has progressed after EGFR-TKI therapy.

[Textbooks]
DeVita, Hellman, and Rosenberg's Cancer. *Principle & Practice of Oncology* 10th ed. USA. : Lippincott Williams & Wilkins; 2014:
Development of EGFR-TKIs such as osimertinib against EGFR activating mutation-positive NSCLC resistant to the conventional EGFR-TKIs has been ongoing, and clinical studies have presented results indicating their potential usefulness.

The applicant's explanation on the target patient population of osimertinib:
The phase II part of the AURA study and the AURA2 study revealed clinical usefulness of osimertinib in patients with unresectable, advanced or recurrent EGFR T790M mutation-positive NSCLC that progressed after EGFR-TKI therapy. In view of this, osimertinib can be positioned as one of the treatment options in these patients. To specify the target patient population of osimertinib, the Indication and Precautions for Indications sections were proposed as described above.

Currently, as a confirmatory study in the target patient population proposed in this new drug application, a global phase III study (Study D5160C00003 [AURA3 study]),* is ongoing.

*: A randomized, open-label study to compare the efficacy and safety of osimertinib between its monotherapy and combination therapy with platinum antineoplastic drug and pemetrexed sodium hydrate in patients with advanced or recurrent EGFR T790M mutation-positive NSCLC that progressed after the first-line treatment with EGFR-TKIs (target sample size, 410 subjects) (enrollment is to be completed in [redacted] 20[redacted], and the primary analysis results are to be available in [redacted] 20[redacted])

PMDA's view:
PMDA accepted the applicant's explanation and concluded that it is appropriate to indicate osimertinib for "inoperable or recurrent EGFR T790M mutation-positive non-small cell lung cancer resistant to EGFR tyrosine kinase inhibitors."

In this application, the efficacy of osimertinib is evaluated mainly on the basis of the response rate, and no information on the survival benefit is available. Therefore, it is necessary to carefully consider other treatment options. PMDA concluded that it is appropriate to include the following caution statement in the Precautions for Indications section.

- Physicians should be thoroughly versed in the content of the "Clinical Studies" section, fully understand the efficacy and safety of osimertinib, and carefully consider other treatment options before selecting patients eligible for osimertinib therapy.

4.(iii).B.(4).2) EGFR T790M mutation test
The applicant's explanation on EGFR T790M test:
In the phase II part of the AURA study and the AURA2 study, patients who were confirmed EGFR T790M mutation-positive by "Cobas EGFR Test Kit" (Roche Diagnostics K.K.) were included [see "4.(i).A.(1) Analytical methods"]. Subsequently, comparability of "Cobas EGFR Test Kit" to "Cobas EGFR Mutation Test Kit, Version 2.0" (Roche Diagnostics K.K.), an improved product of "Cobas EGFR Test Kit" and "Cobas EGFR Mutation Test Kit," was investigated in specimens from patients enrolled in the phase II part of the AURA study and the AURA2 study. The positive, negative, and overall concordance rates were 96.6%, 96.3%, and 96.5%, respectively.

On the basis of the above investigation results, the patient population confirmed to be EGFR T790M mutation-positive by "Cobas EGFR Mutation Test Kit, Version 2.0" is generally considered identical to that confirmed so by "Cobas EGFR Test Kit." PMDA has therefore concluded that it is appropriate to select patients by "Cobas EGFR Mutation Test Kit, Version 2.0," for which marketing application submitted by Roche Diagnostics K.K. is presently under review, with the following caution statement included in the Precautions for Indications section.

- Osimertinib should be used only in patients confirmed to be EGFR T790M mutation-positive through tests performed by a thoroughly experienced pathologists or testing laboratory. Approved *in vitro* diagnostics should be used for EGFR T790M mutation testing.

PMDA accepted the applicant's explanation.

4.(iii).B.(4).3) Efficacy and safety in adjuvant chemotherapy

The applicant's explanation:

Clinical study data on the efficacy and safety of osimertinib in the post-operative adjuvant chemotherapy are not yet obtained. Relevant information will be alerted in the Precautions for Indications section.

PMDA accepted the applicant's explanation.

4.(iii).B.(5) Dosage and administration

The proposed dosage and administration of osimertinib was "The usual adult dosage is 80 mg of osimertinib administered orally once daily." Moreover, the "Precautions for Dosage and Administration" section includes the following:

- Criteria for treatment interruption, dose reduction, and treatment discontinuation of osimertinib when an adverse event occurs.

- The efficacy and safety of osimertinib used in combination with other antineoplastic drugs are not yet established.

On the basis of the following review results, PMDA has concluded that it is appropriate to modify the description in the dosage and administration section of osimertinib as "The usual adult dosage is 80 mg of osimertinib administered orally once daily. The dose may be reduced, as appropriate, according to the patient's condition." It is also appropriate to include the above statement proposed by the applicant in the Precautions for Dosage and Administration as a caution.

4.(iii).B.(5).1) Dosage and administration of osimertinib

The applicant's rationale for the proposed dosage and administration of osimertinib:

The phase I part of the AURA study was conducted to investigate the maximum tolerated dose of osimertinib in patients with unresectable, advanced or recurrent EGFR activating mutation-positive NSCLC that progressed after EGFR-TKI therapy, and on the basis of the following study results on the safety and efficacy, the recommended dose of osimertinib was determined to be 80 mg.

- In the dose-escalation period, the daily dose of osimertinib was increased to 240 mg, but no dose limiting toxicity was identified. In the dose-expansion period, on the other hand, the incidence of adverse events leading to dose reduction tended to be higher at osimertinib 160 mg and 240 mg than that at osimertinib 80 mg.
- With regard to the efficacy, the response rates at osimertinib 160 mg and 240 mg were comparable to that at osimertinib 80 mg.

Consequently, the phase II part of the AURA study and the AURA2 study were conducted with multiple oral doses of osimertinib 80 mg QD, and they revealed clinical usefulness of osimertinib in patients with inoperable, or recurrent EGFR T790M mutation-positive NSCLC resistant to EGFR-TKIs. Therefore, the same dosage and administration as those applied to the phase II part of the AURA study and the AURA2 study were proposed.

PMDA accepted the applicant's rationale.

4.(iii).B.(5).2) Criteria for treatment interruption, dose reduction, and treatment discontinuation

The applicant's explanation on criteria for treatment interruption, dose reduction, treatment discontinuation, and resumption of treatment of osimertinib:

In the phase II part of the AURA study and the AURA2 study, specific criteria for treatment interruption, dose reduction, and treatment discontinuation were applied, and tolerability of osimertinib was confirmed accordingly. Consequently, the following criteria were specified in the Precautions for Dosage and Administration section on the basis of the criteria for treatment interruption and dose reduction in those 2 clinical studies and occurrence of adverse events in clinical studies. The table below specifies the dose of osimertinib when treatment was resumed after adverse drug reaction categorized as "others" led to treatment interruption, and the protocols of the phase II part of the AURA study and the AURA2 study specified that the investigator was to choose between administering the same dose as

before and the reduced dose.

- If an adverse drug reaction occurs, treatment should be interrupted, discontinued or continued at a reduced dose according to the symptom, severity, etc., and in view of the following criteria.

Criteria for treatment interruption, dose reduction, and treatment discontinuation

Organ system	Adverse drug reaction	Treatment interruption, dose reduction, or treatment discontinuation	Dosage and administration when treatment resumed
Respiratory system	Interstitial lung disease or pneumonitis	Discontinue treatment	-
Cardiac system	QTc >500 msec at two or more measurements	Interrupt treatment until QTc returns to <481 msec. If baseline QTc ≥481 msec, interrupt treatment until the value returns to baseline level.	Reduce the dose to 40 mg QD
	QTc value prolonged accompanied by signs or symptoms of serious arrhythmia	Discontinue treatment	
Others	Grade ≥3 adverse drug reactions	Interrupt treatment (up to 3 weeks) until the signs and symptoms improve to Grade 0 to 2.	80 mg or 40 mg QD
		Discontinue treatment if the signs or symptoms do not improve to Grade 0 to 2 within up to 3-week interruption.	-

Grade is determined in accordance with Common Terminology Criteria for Adverse Events (CTCAE) ver.4.0.

PMDA's view:
The applicant's explanation is generally acceptable in view of the premise that osimertinib is to be used by physicians with sufficient knowledge and experience in cancer chemotherapy. Clinical studies, however, showed that osimertinib prolonged QT interval, and thus on the basis of the protocols of the phase II part of the AURA study and the AURA2 study, it is appropriate to specify the following criteria of osimertinib dose adjustment when QT interval prolonged occurs: Osimertinib should be interrupted when QTc value is found >500 msec. Consequently, PMDA has concluded that the Precautions for Dosage and Administration section should include the following:

- If an adverse drug reaction occurs, treatment should be interrupted, discontinued or continued at a reduced dose according to the symptom, severity, etc., and in view of the following criteria. In case of dose reduction, osimertinib 40 mg QD should be administered.

Criteria for treatment interruption, dose reduction, and treatment discontinuation

Adverse drug reaction	Severity	Measures
Interstitial lung disease or pneumonitis	-	Discontinue treatment.
QT interval prolonged	QTc >500 msec	Interrupt treatment until QTc returns to <481 msec or baseline level. When QTc returns to <481 msec or baseline level, resume treatment at a reduced dose. Discontinue treatment if the sign does not resolve within 3 weeks.
	QT interval prolonged accompanied by signs or symptoms of serious arrhythmia	Discontinue treatment.
Other adverse drug reactions	Grade ≥3	Interrupt treatment until signs and symptoms improve to Grade ≤2. Resume treatment, after improvement to Grade ≤2, at a reduced dose as necessary. If the signs or symptoms do not improve to Grade ≤2 within 3 weeks, discontinue treatment.

Grade is determined in accordance with Common Terminology Criteria for Adverse Events (CTCAE) ver.4.0.

4.(iii).B.(5).3) Combination with other antineoplastic drugs

The applicant's explanation:
Because the efficacy and safety data of osimertinib used in combination with other antineoplastic drugs have not been available, such use is not recommended. Cautions to this effect will be included in the Precautions for Dosage and Administration section.

PMDA accepted the applicant's explanation.

4.(iii).B.(6) Post-marketing investigations

The applicant's explanation on a post-marketing surveillance:

To investigate safety of osimertinib in routine clinical use, the applicant plans all-case post-marketing surveillance covering all patients treated with osimertinib (this Survey).

In this Survey, ILD is selected as a priority survey item, because its incidence was high in the pooled phase II study data, and this event is likely to result in a serious outcome if it occurs. QT interval prolonged is also selected, because non-clinical and clinical data on this event indicate that it is likely to become an important risk during clinical use of osimertinib, although no serious cases have yet been reported. Furthermore, Grade ≥3 diarrhoea, rash, dry skin, and paronychia are also selected as the priority survey items, because the incidence of these events were high regardless of their grades, and they, Grade ≥3 events are likely to become an important risk during clinical use of osimertinib.

The target sample size of this Survey has been set as 3000 patients to enable risk factor analysis for ILD due to the following reasons.

- (i) Currently available information of Japanese patients in clinical studies suggests that the incidence of ILD is unlikely to be <4% even in the low-risk subgroup of any risk factors potentially related to ILD. (ii) On the assumption that (a) the ratio of number of patients in the low-risk to high-risk subgroups for a risk factor is 3:1, (b) the incidence in the low-risk sub-group is 4% and (c) the odds ratio of the high-risk sub-group to the low-risk sub-group is 2.0, the sample size required to ensure 90% of statistical power, in a two-sided test with a significance level of 5%, is estimated to be 2200. (iii) However, the ratio of number of patients in the high-risk to the low-risk sub-groups is likely to differ depending on the risk factor to be investigated. In view of this matter, enrolling more patients than the above estimate seemed desirable, and thus the target sample size was set at 3000.

In this Survey, the follow-up period was set at 12 months in view of the following: (a) ILD, a priority survey item, lasted for 230 days at the most from the start of treatment in the Japanese patient population; (b) any of QT interval prolonged, a priority survey item, and events related to other priority survey items (diarrhoea, rash, dry skin, and paronychia of all Grades) developed <1 year after the start of treatment in the overall population.

PMDA's view:

Because safety information on osimertinib is limited in the data submitted for this application, it is necessary to conduct a post-marketing survey covering all patients treated with osimertinib over a specified period to collect safety information promptly without bias, and to provide the obtained safety information to healthcare professionals in clinical settings immediately. In addition, the review in "4.(iii).B.(3).3) ILD-like events" indicates that safety measures against a risk of ILD is especially important during osimertinib treatment. The applicant should not only collect information on the occurrence of ILD, but also analyze risk factors of ILD in this Survey to promptly provide information on the obtained results to healthcare professionals. Furthermore, interim analysis should be reported when certain amount of information is accumulated before the final results of this Survey become available. On the basis of these analyses, the applicant should consider to take appropriate actions such as revising pharmacovigilance plan and providing information to healthcare professionals in clinical settings.

The priority survey items in this Survey should include not only items specified by the applicant but also the following adverse events requiring attention during osimertinib treatment: haematotoxicity, liver disorder, cardiac disorder (except for QT interval prolonged), thromboembolism, infection, and corneal disorder.

The target sample size of this Survey planned by the applicant is acceptable, because of the importance of investigating ILD risk factors. The follow-up period in this Survey, however, should be re-examined in view of the occurrence of the events in clinical studies selected as priority survey items including additional ones.

4.(iii).B.(7) Post-marketing risk minimization activities

The applicant's explanation on post-marketing risk minimization activities:

ILD is an adverse event requiring special attention during osimertinib treatment and is to be listed as an

important identified risk in the draft risk management plan. In the pooled phase II study data, (a) the incidence was higher in the Japanese patient population than in the non-Japanese patient population; and (b) fatal events were noted. In order to ensure post-marketing safety in spite of concerns for possible ILD occurrence, the following are scheduled to be conducted as additional risk minimization activities: (i) conditions of osimertinib use will be established; (ii) requirements for medical institutions and physicians will be established to ensure osimertinib will be administered to patients eligible for osimertinib therapy under supervision of physicians with adequate knowledge and experience in cancer chemotherapy at a medical institution capable of handling emergencies associated with the treatment; (iii) the requirements will be explained to healthcare professionals in advance through materials such as guidelines for proper use; (iv) a pretreatment checklist for proper use will be prepared to help physicians to select eligible patients appropriately; and (v) pharmacies and wholesalers will be requested to cooperate to take safety measures.

PMDA's view:
In view of the incidence and seriousness of ILD in clinical studies, it is especially important to take measures to ensure osimertinib will be administered to eligible patients by physicians with adequate knowledge about the risk of osimertinib such as ILD and capable of risk management at medical institutions with sufficient resources to handle emergencies, and to ensure patients will be adequately informed of the safety and efficacy of osimertinib. Although the above additional risk minimization activities planned by the applicant are considered acceptable, whether or not to continue such activities should be considered at a specified time point such as data-lock point of periodic safety update reports on the basis of the latest information.

4.(iv) Adverse events etc., observed in clinical studies
Deaths reported in clinical study results submitted for safety evaluation were described in "4.(iii) Summary of clinical efficacy and safety." Major non-fatal adverse events were shown below.

4.(iv).(1) Global phase I/II study (Study D5160C00001 [AURA study])
4.(iv).(1).1) Phase I part
Adverse events occurred in all 31 patients in the capsule group in second-line or later therapy and all 12 patients in the tablet group in second-line or later therapy of the dose-escalation period as well as all 60 patients in the capsule group in first-line therapy, 268 of 271 patients (98.9%) in the capsule group in second-line or later therapy, and 25 of 28 patients (89.3%) in the tablet group in second-line or later therapy of the dose-expansion period. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 27 of 31 patients (87.1%) and all 12 as well as 59 of 60 (98.3%), 231 of 271 (85.2%), and 24 of 28 (85.7%) in the respective groups.

Serious adverse events occurred in 9 of 31 (29.0%) in the capsule group in second-line or later therapy and 4 of 12 (33.3%) in the tablet group in second-line or later therapy of the dose-escalation period as well as 14 of 60 (23.3%) in the capsule group in first line therapy, 78 of 271 (28.8%) in the capsule group in secondary-line or later therapy, and 4 of 28 (14.3%) in the tablet group in secondary-line or later therapy of the dose-expansion period. Serious adverse events reported by ≥5 patients in the phase I part included pneumonia in 13 (3.2%), pulmonary embolism in 12 (3.0%), diarrhoea and pneumonitis in 7 (1.7%) each, and nausea in 5 (1.2%). Of these, a causal relationship to the study drug could not be ruled out for pneumonitis in 7, diarrhoea in 4, pulmonary embolism and nausea in 2 each, and pneumonia in 1.

Adverse events leading to study drug discontinuation occurred in 2 of 31 (6.5%) in the capsule group in second-line or later therapy of the dose-escalation period as well as 5 of 60 (8.3%) in the first-line capsule group, 27 of 271 (10.0%) in the second-line capsule group, and 4 of 28 (14.3%) in the tablet group in second-line or later therapy of the dose-expansion period. Adverse events leading to study drug discontinuation reported by ≥3 patients in the phase I part include pneumonitis in 9 (2.2%) and pneumonia in 3 (0.7%). Of these, a causal relationship to the study drug could not be ruled out for pneumonitis in 9.

4.(iv).(1).2) Phase II part

Adverse events occurred in 198 of 201 patients (98.5%), and adverse events for which a causal relationship to the study drug could not be ruled out occurred in 183 of 201 patients (91.0%). Adverse events with an incidence of ≥10% are shown in the table below.

Adverse events with an incidence of ≥10%

System organ class Preferred term (MedDRA/J ver18.0)	Number of patients (%) Osimertinib group N = 201	
	All Grades	Grade ≥3
All adverse events	198 (98.5)	60 (29.9)
Infections and infestations		
Paronychia	40 (19.9)	0
Blood and lymphatic system disorders		
Anaemia	20 (10.0)	4 (2.0)
Metabolism and nutrition disorders		
Decreased appetite	36 (17.9)	2 (1.0)
Nervous system disorders		
Headache	22 (10.9)	0
Respiratory, thoracic and mediastinal disorders		
Cough	32 (15.9)	0
Gastrointestinal disorders		
Constipation	30 (14.9)	1 (0.5)
Diarrhoea	93 (46.3)	2 (1.0)
Nausea	35 (17.4)	2 (1.0)
Stomatitis	27 (13.4)	0
Vomiting	23 (11.4)	2 (1.0)
Skin and subcutaneous tissue disorders		
Dry skin	43 (21.4)	0
Pruritus	25 (12.4)	0
Rash	49 (24.4)	0
Musculoskeletal and connective tissue disorders		
Back pain	27 (13.4)	1 (0.5)
General disorders and administration site conditions		
Asthenia	20 (10.0)	3 (1.5)
Fatigue	25 (12.4)	2 (1.0)
Investigations		
Platelet count decreased	27 (13.4)	1 (0.5)

Serious adverse events occurred in 41 of 201 patients (20.4%). Serious adverse events reported by ≥3 patients were pneumonia in 7 patients (3.5%), and pulmonary embolism and pneumonitis in 3 patients (1.5%) each. Of these, a causal relationship to the study drug could not be ruled out for pneumonitis in 3 patients.

Adverse events leading to study drug discontinuation occurred in 12 of 201 patients (6.0%). Those reported by ≥3 patients were interstitial lung disease and pneumonitis in 3 patients (1.5%) each, and a causal relationship to the study drug could not be ruled out for any of them.

4.(iv).(2) Global phase II study (Study D5160C00002 [AURA2 study])

Adverse events occurred in 203 of 210 patients (96.7%), and those for which a causal relationship to the study drug could not be ruled out occurred in 172 of 210 patients (81.9%). Adverse events with an incidence of ≥10% are shown in the table below.

Adverse events with an incidence of ≥10%

System organ class Preferred term (MedDRA/J ver18.0)	Number of patients (%) Osimertinib group N = 210	
	All Grades	Grade ≥3
All adverse events	203 (96.7)	61 (29.0)
Infections and infestations		
Paronychia	32 (15.2)	0
Nasopharyngitis	21 (10.0)	0
Metabolism and nutrition disorders		
Decreased appetite	29 (13.8)	1 (0.5)
Respiratory, thoracic and mediastinal disorders		
Cough	25 (11.9)	1 (0.5)
Gastrointestinal disorders		
Constipation	32 (15.2)	0
Diarrhoea	81 (38.6)	2 (1.0)
Nausea	34 (16.2)	0
Stomatitis	22 (10.5)	0
Skin and subcutaneous tissue disorders		
Dry skin	52 (24.8)	0
Pruritus	32 (15.2)	0
Rash	49 (23.3)	0
Musculoskeletal and connective tissue disorders		
Back pain	25 (11.9)	2 (1.0)
General disorders and administration site conditions		
Fatigue	32 (15.2)	0

Serious adverse events occurred in 42 of 210 patients (20.0%). Those reported by ≥3 patients were pulmonary embolism in 8 patients (3.8%) and pneumonia in 4 patients (1.9%). Of these, a causal relationship to the study drug could not be ruled out for pulmonary embolism in 1 patient.

Adverse events leading to study drug discontinuation occurred in 11 of 210 patients (5.2%). No adverse events experienced by ≥3 patients led to study drug discontinuation.

4.(iv).(3) Foreign phase I study (Study D5160C00009)

Adverse events occurred in 22 of 38 patients (57.9%), and those for which a causal relationship to the study drug could not be ruled out occurred in 9 of 38 patients (23.7%).

A serious adverse event occurred in 1 of 38 patients (2.6%). The event was atrial flutter, and its causal relationship to the study drug was ruled out.

There were no adverse events leading to study drug discontinuation.

4.(iv).(4) Foreign phase I study (Study D5160C00005)

4.(iv).(4).1) Part A (study to assess relative BA)

Adverse events occurred in 10 of 16 subjects (62.5%), and a causal relationship to the study drug was ruled out for all of them.

There were no serious adverse events or adverse events leading to study drug discontinuation.

4.(iv).(4).2) Part B (study to assess food effect)

Adverse events occurred in 6 of 16 subjects (37.5%), and those for which a causal relationship to the study drug could not be ruled out occurred in 1 subject (6.3%).

No serious adverse events occurred.

An adverse event leading to study drug discontinuation occurred in 1 of 16 subjects (6.3%). The event was ALT, and its causal relationship to the study drug could not be ruled out.

4.(iv).(5) Foreign phase I study (Study D5160C00010)

4.(iv).(5).1) Period 1 (combination therapy with osimertinib and omeprazole)

Adverse events occurred in 24 of 68 subjects (35.3%), and those for which a causal relationship to the study drug could not be ruled out occurred in 2 of 68 subjects (2.9%).

Serious adverse events occurred in 3 of 68 subjects (4.4%). These events were transaminases increased in 2 subjects (2.9%), and cholelithiasis and blood creatine phosphokinase increased in 1 subject (1.5%) each, and their causal relationships to the study drug were ruled out.

Adverse events leading to study drug discontinuation occurred in 3 of 68 subjects (4.4%). These events were transaminases increased in 2 subjects (2.9%), and cholelithiasis and blood creatine phosphokinase increased in 1 subject (1.5%) each, and a causal relationship to the study drug was ruled out for all of them.

4.(iv).(5).2) Period 2 (osimertinib monotherapy)

Adverse events occurred in 10 of 47subjects (21.3%), and a causal relationship to the study drug was ruled out for all of them.

There were no serious adverse events or adverse events leading to study drug discontinuation.

4.(iv).(6) Foreign phase I study (Study D5160C00011)

Adverse events occurred in 7 of 8 subjects (87.5%), and those for which a causal relationship to the study drug could not be ruled out occurred in 1 of 8 subjects (12.5%).

There were no serious adverse events or adverse events leading to study drug discontinuation.

4.(iv).(7) Foreign phase I study (Study D5160C00012)

Adverse events occurred in 26 of 39 patients (66.7%), and those for which a causal relationship to the study drug could not be ruled out occurred in 6 of 39 patients (15.4%).

Serious adverse events occurred in 3 of 39 (7.7%). These events were respiratory syncytial virus infection, lobar pneumonia, and hepatic enzyme increased in 1 (2.6%) each. Of these, a causal relationship to the study drug could not be ruled out for lobar pneumonia in 1.

There were no adverse events leading to study drug discontinuation.

4.(iv).(8) Foreign phase I study (Study D5160C00013)

Adverse events occurred in 39 of 41 patients (95.1%), and those for which a causal relationship to the study drug could not be ruled out occurred in 33 of 41 patients (80.5%).

Serious adverse events occurred in 7 of 41 (17.1%). These events were hyperkalaemia, malaise, femur fracture, thrombophlebitis, influenza, muscular weakness, and cardiac failure congestive in 1 patient (2.4%) each. Of these, a causal relationship to the study drug could not be ruled out for cardiac failure congestive in 1 patient.

There were no adverse events leading to study drug discontinuation.

4.(iv).(9) Foreign phase I study (Study D5160C00014)

Adverse events occurred in 44 of 52 patients (84.6%), and those for which a causal relationship to the study drug could not be ruled out occurred in 28 of 52 patients (53.8%).

Serious adverse events occurred in 4 of 52 patients (7.7%). These events were myelodysplastic syndrome, thrombophlebitis, bundle branch block left, and infectious pleural effusion in 1 patient (1.9%) each. Of these, a causal relationship to the study drug could not be ruled out for bundle branch block left in 1 patient.

There were no adverse events leading to study drug discontinuation.

4.(iv).(10) Foreign phase I study (Study D5160C00019)
Adverse events occurred in 40 of 44 patients (90.9%), and those for which a causal relationship to the study drug could not be ruled out occurred in 22 of 44 patients (50.0%).

Serious adverse events occurred in 2 of 44 (4.5%). These events were pleural effusion and blood creatine phosphokinase increased in 1 patient (2.3%) each. Of these, a causal relationship to the study drug could not be ruled out for blood creatine phosphokinase increased in 1 patient.

An adverse event leading to study drug discontinuation occurred in 1 of 44 patients (2.3%). The event was dyspnoea in 1 patient (2.3%), and its causal relationship to the study drug was ruled out.

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 inspection and data integrity assessment

The assessment is ongoing. The results and PMDA's conclusion are to be reported in Review Report (2).

2. PMDA's conclusion on the results of GCP on-site inspection

The assessment is ongoing. The results and PMDA's conclusion are to be reported in Review Report (2).

IV. Overall Evaluation

Based on the submitted data, a certain extent of efficacy of osimertinib in the treatment of patients with inoperable or recurrent EGFR T790M mutation-positive NSNLC resistant to EGFR-TKIs has been demonstrated and its safety is acceptable in view of its observed benefits. The EGFR T790M mutation occurs within exon 20 of EGFR gene, resulting in an amino acid substitution from threonine (T) to methionine (M) at position 790 in EGFR. Osimertinib is a drug product containing a new active ingredient that inhibit growth of tumor with EGFR T790M mutation, which renders the cell resistant to EGFR-TKIs and thus have a clinical significance as a treatment option for inoperable or recurrent EGFR T790M mutation-positive NSNLC resistant to EGFR-TKIs. The safety, indication, post-marketing investigations, and risk minimization activities, etc., will be further discussed at the Expert Discussion.

This application may be approved if osimertinib is not considered to have particular problems based on comments from the Expert Discussion.

Review Report (2)

February 15, 2016

I. Product Submitted for Registration

[Brand name]	Tagrisso Tablets 40 mg Tagrisso Tablets 80 mg
[Non-proprietary name]	Osimertinib Mesilate
[Applicant]	AstraZeneca K.K.
[Date of application]	August 21, 2015

II. Content of the Review

The comments from the Expert Discussions and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are described in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

As a result of the review in "4.(iii).B.(2) Efficacy" of Review Report (1) and in view of the following points, PMDA concluded that efficacy of osimertinib mesilate (hereinafter referred to as osimertinib) is demonstrated to a certain extent in patients included in the phase II part of the AURA study and the AURA2 study on the basis of response rate in the phase II part of a global phase I/II study (Study D5160C00001 [AURA study]) and a global phase II study (Study D5160C00002 [AURA2 study]). The patients included in these studies had unresectable, advanced or recurrent NSCLC with EGFR T790M mutation which occurs within exon 20 of EGFR gene, resulting in an amino acid substitution at position 790 in EGFR from threonine (T) to methionine (M) and experienced progression after therapy with conventional EGFR-TKIs.

- EGFR T790M mutation is reported to be involved in the mechanism of development of resistance to EGFR-TKIs.

- Osimertinib is demonstrated to inhibit growth of EGFR T790M mutation-positive tumors.

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

(2) Safety

PMDA concluded in the review of "4.(iii).B.(3) Safety" of Review Report (1), that adverse events requiring special attention during osimertinib treatment are ILD-like events, QT interval prolonged, haematotoxicity, liver disorder, cardiac disorder (excluding QT interval prolonged), thromboembolism, and infection.

PMDA also concluded that osimertinib is tolerable provided that appropriate actions such as monitoring and management of adverse events, treatment interruption, and discontinuation are taken by physicians with sufficient knowledge and experience in cancer chemotherapy; and safety management is in place with strict monitoring, management, and treatment of serious adverse events such as ILD.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

(3) Clinical positioning and indication

PMDA concluded in the review of "4.(iii).B.(4) Clinical positioning and indication" of Review Report (1) that osimertinib can be positioned as one of the treatment options in patients included in the phase II part of the AURA study and the AURA2 study. PMDA therefore concluded that the appropriate indication of osimertinib should be "inoperable or recurrent EGFR T790M mutation-positive non-small cell lung cancer resistant to EGFR tyrosine kinase inhibitors." In this application, the efficacy of

osimertinib is mainly evaluated on the basis of response rate, but no information on the survival benefit is available. Therefore other treatment options should also be considered carefully. PMDA concluded that the following caution statement should be included in the Precautions for Indications section.

- Osimertinib should be used only in patients confirmed to be EGFR T790M mutation-positive through tests performed by a thoroughly experienced pathologist or testing laboratory. Approved *in vitro* diagnostics should be used for the test.

- Physicians should be thoroughly versed in the content of the "Clinical Studies" section, fully understand the efficacy and safety of osimertinib, and carefully consider other treatment options before selecting patients eligible for osimertinib therapy.

- The efficacy and safety of osimertinib in adjuvant chemotherapy are not yet established.

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

On the above basis, PMDA instructed the applicant to include the Indications and Precautions for Indication sections as described above, and the applicant agreed.

(4) Dosage and administration

As a result of its review in "4.(iii).B.(5) Dosage and administration" of Review Report (1) that it is appropriate to include the following statement in the Precautions for Dosage and Administration section, and specify dosage and administration of osimertinib as "The usual adult dosage is 80 mg of osimertinib administered orally once daily. The dose may be reduced, as appropriate, according to the patient's condition."

- The efficacy and safety of osimertinib used in combination with other antineoplastic drugs are not yet established.

- If an adverse drug reaction occurs, osimertinib treatment should be interrupted, discontinued or continued at a reduced dose according to the symptom, severity, etc., and in view of the following criteria. In case of dose reduction, osimertinib 40 mg should be administered once daily.

Criteria for treatment interruption, dose reduction, and treatment discontinuation

Adverse drug reaction	Severity	Measures
Interstitial lung disease or pneumonitis	-	Discontinue treatment.
QT interval prolonged	QTc >500 msec	Interrupt treatment until QTc returns to <481 msec or baseline level. When QTc returns to <481 msec or baseline level, resume treatment at a reduced dose. Discontinue treatment if the sign does not resolve within 3 weeks.
	QTc interval prolonged accompanied by signs or symptoms of serious arrhythmia	Discontinue treatment.
Other adverse drug reactions	Grade ≥3	Interrupt treatment until signs and symptoms improve to Grade ≤2. Resume treatment after improvement to Grade ≤2 at a reduced dose as necessary. If the signs or symptoms do not improve to Grade ≤2 within 3 weeks, discontinue treatment.

Grade is determined in accordance with Common Terminology Criteria for Adverse Events (CTCAE) ver.4.0.

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

PMDA instructed the applicant to revise the Dosage and Administration and Precautions for the Dosage and Administration sections accordingly, and the applicant agreed.

(5) Draft risk management plan

The applicant plans an all-case post-marketing surveillance covering all patients treated with osimertinib (this Survey) to investigate safety of osimertinib in routine use after market launch. Risk factors of ILD are to be analyzed in this Survey.

As a result of review in "4.(iii).B.(6) Post-marketing investigations" of Review Report (1), PMDA concluded that the applicant should conduct a survey covering all patients treated with osimertinib for a specified post-marketing period to collect safety information promptly without bias, and to immediately provide the obtained safety information to healthcare professionals in clinical settings since the available safety information for osimertinib is limited at present. The safety measures against risks of ILD is especially important during osimertinib treatment, and thus the applicant should not only collect information about ILD events, but also analyze risk factors of ILD in this Survey to provide the obtained results to healthcare professionals in clinical settings promptly.

In addition, PMDA has concluded on the implementation plan of this Survey as follow.

- The priority survey items in this Survey should include not only ILD, QT interval prolonged as well as Grade ≥3 diarrhoea, rash, dry skin, and paronychia, which have been specified by the applicant, but also haematotoxicity, liver disorder, cardiac disorder (excluding QT interval prolonged), thromboembolism, infection, and corneal disorder, which are adverse events requiring attention during osimertinib treatment.

- The target sample size of this Survey may be decided as the applicant proposed.

- The follow-up period in this Survey should be re-examined in view of the incidence of adverse events selected as the priority survey items including additional ones.

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

On the basis of the above discussion, PMDA instructed the applicant to re-examine this Survey plan.

The applicant responded as follows:
- Haematotoxicity, liver disorder, cardiac disorder (except for QT interval prolonged), thromboembolism, infection, and corneal disorder are added to the priority survey items. Rash and dry skin at Grade ≥3 are collectively classified as Grade ≥3 skin disorder.
- The follow-up period is to be set as12 months as initially planned, because events selected as the additional priority survey items also occurred approximately within 1 year after the start of the treatment.

PMDA's view:
PMDA accepted the applicant's response on this Survey plan.

On the basis of the above discussion, PMDA concluded that it is appropriate to specify the safety and efficacy specifications, and to implement additional pharmacovigilance activities and risk minimization activities in the present draft risk management plan as shown in the tables below.

Safety and efficacy specifications in draft risk management plan

Safety specifications		
Important identified risks	Important potential risks	Important missing information
• ILD • QT interval prolonged • Haematotoxicity • Liver disorder	• Cardiac disorders (excluding QT interval prolonged) • Thromboembolism • Infection • Corneal disorder	• Use in patients with hepatic impairment
Efficacy specifications		
• Efficacy in routine clinical use • Efficacy in patients with inoperable or recurrent EGFR T790M mutation-positive NSCLC resistant to EGFR-TKIs in the post-marketing clinical study of the global phase III study (Study D5160C00003 [AURA3 study])		

Outline of additional pharmacovigilance activities and additional risk minimization activities in draft risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Drug use-results survey • Post-marketing clinical study (the phase II part of the AURA study, the AURA2 study, and extension of the AURA3 study)	• Provide information obtained in the early post-marketing phase vigilance • Prepare and distribute materials for healthcare professionals • Prepare and supply materials for patients • Provide information through websites etc. • Set the conditions of drug use

Draft outline of drug use-results survey

Objective	To investigate the safety of osimertinib in routine clinical use as well as the incidence of ILD and its risk factors
Method	All-case survey using central registration system
Patients population	All patients treated with osimertinib
Follow-up period	12 months
Target sample size	3000 patients
Major survey items	Priority survey items: ILD, QT interval prolonged, haematotoxicity, liver disorder, cardiac disorder (excluding QT interval prolonged), thromboembolism, infection, corneal disorder, Grade ≥3 diarrhoea, Grade ≥3 skin disorder, and Grade ≥3 paronychia Other survey items: Characteristics of patients (sex, age, reason for using osimertinib, lesion site, tissue type, Performance Status, medical history or complication, etc.), use status of osimertinib, concomitant drugs and therapies, adverse events (including changes in laboratory values), etc.

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 inspection and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the new drug application. PMDA thus 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 Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics for the data submitted in the new drug application (5.3.5.1.1-1, 5.3.5.1.2-1, 5.3.5.1.3-1). PMDA concluded that the clinical studies were generally conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted application documents. The following was noted in some of the participating medical institutions although it did not significantly affect the overall evaluation of the study. It was notified to the head of the pertinent medical institutions for improvement.

Matters to be improved
Medical institutions
- Protocol deviation (incompliance with the provisions for pre-medication washout)

IV. Overall Evaluation

On the basis of the submitted data, PMDA concluded that the product may be approved after modifying the indication and dosage and administration as shown below with the following conditions for approval, provided that appropriate cautions are included in the package insert, and information for proper use of osimertinib is provided appropriately after the market launch; and the proper use of osimertinib is ensured under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy at medical institutions capable of handling emergencies associated with the treatment. Since osimertinib contains a new active ingredient, the re-examination period is 8 years. Both drug substance and the drug product are classified as powerful drugs, and the drug product is not classified

as a biological product or a specified biological product.

[Indication] Inoperable or recurrent EGFR T790M mutation-positive non-small cell lung cancer resistant to EGFR tyrosine kinase inhibitors

[Dosage and administration] The usual adult dosage is 80 mg of osimertinib administered orally once daily. The dose may be reduced, as appropriate, according to the patient's condition.

[Conditions for approval] The applicant is required to:

1. Develop and appropriately implement a risk management plan;

2. Conduct a drug use-results survey covering all patients treated with the product after market launch until data from a certain number of patients have been accumulated, to identify the characteristics of the patients treated with the product and to promptly collect safety and efficacy data so that necessary measures are taken to ensure proper use of the product, since an extremely limited number of patients participated in the clinical studies conducted in Japan; and

3. Take necessary measures before market launch to ensure that the product is used only under the supervision of physicians well versed in the diagnosis of lung cancer and chemotherapy at a medical institution capable of handling the risks associated with treatment in cooperation with a pharmacy with a supervising pharmacist.

[Warnings]

1. Osimertinib should be administered only to patients considered eligible for treatment with osimertinib according to the package insert, under supervision of physicians with adequate knowledge and experience in cancer chemotherapy at medical institutions with adequate facilities for the treatment of emergencies. Patients or their family members should be fully informed of the efficacy, risks of osimertinib (especially, early symptoms of interstitial lung disease, precautions during use, occurrence of fatal cases, etc.), and available therapies for non-small cell lung cancer. Informed consent should be obtained before starting treatment.

2. There are reports on patients who experienced interstitial lung disease after administration of osimertinib, resulting in death. Patients should be monitored carefully for early symptoms of the disease (dyspnoea, cough, and pyrexia, etc.) and by regular chest imaging examination through the whole treatment period. If any abnormality is observed, osimertinib should be discontinued, and appropriate measures should be taken. Especially, in the initial treatment phase, patients should be hospitalized or supervised under equivalent conditions to be carefully monitored for serious adverse reactions such as interstitial lung disease.

3. Careful judgment for the use of osimertinib should be made before the start of osimertinib treatment; patients should go through a chest CT scan and interview to confirm the absence of complication or history of interstitial lung disease.

[Contraindications]

1. Patients with a history of hypersensitivity to any component of osimertinib

2. Pregnant or possibly pregnant women

[Precautions for Indications]

1. Osimertinib should be used only in patients confirmed to be EGFR T790M mutation-positive through tests performed by a thoroughly experienced pathologist or testing laboratory. Approved *in vitro* diagnostics should be used for the test.

2. Physicians should be thoroughly versed in the content of the "Clinical Studies" section, and fully understand the efficacy and safety of osimertinib, and carefully consider other treatment options before selecting patients eligible for osimertinib therapy.

3. The efficacy and safety of osimertinib in adjuvant chemotherapy are not yet established.

[Precautions for Dosage and Administration]

1. The efficacy and safety of osimertinib used in combination with the other antineoplastic drugs are not yet established.

2. If an adverse drug reaction occurs, osimertinib treatment should be interrupted, discontinued or continued at a reduced dose according to the symptom, severity, etc., and in view of the following criteria. In case of dose reduction, osimertinib 40 mg should be administered once daily.

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