Report on the Deliberation Results

September 4, 2018

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

Brand Name	Lorbrena Tablets 25 mg Lorbrena Tablets 100 mg
Non-proprietary Name	Lorlatinib (JAN*)
Applicant	Pfizer Japan Inc.
Date of Application	January 30, 2018

Results of Deliberation

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

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

Conditions of Approval

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

2. Because of limited Japanese clinical study data, the applicant is required to conduct a post-marketing use-results survey covering all Japanese patients treated with the product. The survey must be continued until data of a certain number of patients are gathered so as to understand the characteristics of patients receiving the treatment and to collect safety and efficacy data promptly. Based on data collected, necessary measures must be taken to ensure the proper use of the product.

3. The applicant is required to take necessary measures, prior to its launch, to ensure that the product is prescribed by physicians with sufficient experience in the diagnosis and chemotherapy of lung cancer and that the product is available only at medical institutions and pharmacies with adequate capability to manage and explain the risks, etc. associated with the product.

**Japanese Accepted Name (modified INN)*

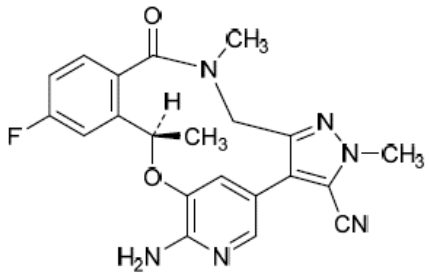
Review Report

August 17, 2018
Pharmaceuticals and Medical Devices Agency

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

Brand Name	Lorbrena Tablets 25 mg Lorbrena Tablets 100 mg
Non-proprietary Name	Lorlatinib
Applicant	Pfizer Japan Inc.
Date of Application	January 30, 2018
Dosage Form/Strength	Tablets, each containing 25 mg or 100 mg of Lorlatinib.
Application Classification	Prescription drug (1) Drug with a new active ingredient

Chemical Structure



Molecular formula:	$C_{21}H_{19}FN_6O_2$
Molecular weight:	406.41
Chemical name:	(10*R*)-7-Amino-12-fluoro-2,10,16-trimethyl-15-oxo-10,15,16,17-tetrahydro-2*H*-4,8-methenopyrazolo[4,3-*h*][2,5,11]benzoxadiazacyclotetradecine-3-carbonitrile

Items Warranting Special Mention

Designated as a drug covered by conditional early approval system (PSEHB/PED Notification No. 0608-2, dated June 8, 2018 by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with anaplastic lymphoma kinase (*ALK)* fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitor(s), and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The occurrence of central nervous system disorder and safety in combination with a cytochrome P450 (CYP) 3A inducer need to be further investigated via post-marketing surveillance.

Indication

ALK fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitor(s)

Dosage and Administration

The usual adult dosage is 100 mg of lorlatinib administered orally once daily. The dose may be adjusted according to the patient's condition.

Conditions of Approval

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

2. Because of limited Japanese clinical study data, the applicant is required to conduct a post-marketing use-results survey covering all Japanese patients treated with the product. The survey must be continued until data of a certain number of patients are gathered so as to understand the characteristics of patients receiving the treatment and to collect safety and efficacy data promptly. Based on data collected, necessary measures must be taken to ensure the proper use of the product.

3. The applicant is required to take necessary measures, prior to its launch, to ensure the product is prescribed by physicians with sufficient experience in the diagnosis and chemotherapy of lung cancer and that the product is available only at medical institutions and pharmacies with adequate capability to manage and explain the risks, etc. associated with the product.

Attachment

Review Report (1)

July 11, 2018

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

Product Submitted for Approval

Brand Name	Lorviqua Tablets 25 mg Lorviqua Tablets 100 mg
Non-proprietary Name	Lorlatinib
Applicant	Pfizer Japan Inc.
Date of Application	January 30, 2018
Dosage Form/Strength	Tablets, each containing 25 mg or 100 mg of Lorlatinib.
Proposed Indication(s)	*ALK* fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitor(s)

Proposed Dosage and Administration

The usual adult dosage is 100 mg of lorlatinib administered orally once daily. The dose may be adjusted according to the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Overview of the product submitted for approval

In non-small cell lung cancer (NSCLC), anaplastic lymphoma kinase (*ALK*) gene rearrangement induces the production of fusion protein such as echinoderm microtubule-associated protein-like 4 (EML4)-ALK (EML4-ALK), which contributes to the growth and survival of cancer cells and tumorigenic transformation of normal cells (*Nature.* 2007;448:561-6). It is reported that 3% to 5% of patients with NSCLC have *ALK* fusion gene (Guidance for *ALK* Gene Testing in Lung Cancer Patients, Version 2.1 [edited by Biomarker Committee, The Japan Lung Cancer Society]).

Lorlatinib is a tyrosine kinase inhibitor discovered by US-based Pfizer Inc. Lorlatinib is expected to inhibit tumor growth by inhibiting ALK phosphorylation in *ALK* fusion gene-positive tumor with resistance to conventional anaplastic lymphoma kinase-tyrosine kinase inhibitors (ALK-TKIs)[1)] with G1202R mutation (glycine at position 1202 is replaced by arginine), etc.

1.2 Development history, etc.

A global phase I/II study (Study 1001) was initiated by Pfizer Inc. (US) in January 2014 involving Japan, in patients with *ALK* fusion gene-positive advanced and/or recurrent NSCLC, etc. In Japan, patient enrollment in Study 1001 started in November 2015.

A marketing application was filed with the results of Study 1001 as the pivotal study in [redacted] 20[redacted] in the US and [redacted] 20[redacted] in EU and is currently under review. As of May 2018, lorlatinib has not been approved in any country or region.

In Japan, a marketing application for lorlatinib was submitted in January 2018 with the results of Study 1001 as the pivotal data.

Lorlatinib is qualified for the conditional early approval system (PSEHB/PED Notification No. 0608-2, June 8, 2018). Originally, the proposed brand name was “Lorviqua Tablets 25 mg, Lorviqua Tablets 100 mg,” and was later changed to “Lorbrena Tablets 25 mg, Lorbrena Tablets 100 mg” at the request of the applicant.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder. The general properties of the drug substance, including description, solubility, acid dissociation constant, distribution coefficient, hygroscopicity, melting point, and optical rotation were determined. The drug substance is present in 29 crystalline forms, including anhydride, hydrates, and solvates. However, it has been confirmed that the commercial-scale production under critical process parameter (CPP) control allows only Crystal Form 7 (anhydride) to be formed and that Crystal Form 7 (anhydride) does not change in stability studies.

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1) In Japan, crizotinib, alectinib, and ceritinib are approved for the indication of *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC.

The chemical structure of the drug substance was elucidated by ultraviolet/visible spectrum (UV/VIS), infrared absorption spectrum (IR), nuclear magnetic resonance spectrum (NMR) (^{1}H- and ^{13}C-NMR), mass spectrometry, and single crystal X-ray diffractometry.

2.1.2 Manufacturing process

The drug substance is synthesized from the starting materials of [redacted],[2] [redacted],[3] and [redacted].[4]

A quality control strategy was developed by a quality-by-design (QbD) approach, and the following processes were used (Table 1):

- Identification of critical quality attributes (CQAs)
- (a) Identification of CPPs affecting the CQAs and (b) determination of proven acceptable range (PAR) of manufacturing process parameters, based on the quality risk assessment and on the experimental design.

Table 1. Outline of the control strategy for the drug substance

CQA	Control method
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	Manufacturing process, [redacted]
[redacted]	Manufacturing process, [redacted]
[redacted]	Manufacturing process, [redacted]
[redacted]	Manufacturing process, [redacted]
[redacted]	Manufacturing process, [redacted]
[redacted]	[redacted]
[redacted]	[redacted]

The purification process of [redacted] of [redacted][5] and the synthesizing process of the drug substance were defined as critical steps, and [redacted] of [redacted][5] were controlled as critical intermediates.

2.1.3 Control of drug substance

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

2.1.4 Stability of drug substance

Table 2 shows stability studies conducted on the drug substance. A photostability testing showed that the drug substance is not photostable.

2) [redacted]
3) [redacted]
4) [redacted]
5) [redacted]

Table 2. Stability studies of drug substance

Test	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 pilot-scale batches	25°C	60% RH	Low-density polyethylene bag (double-layered) + high-density polyethylene drum	18 months
Accelerated testing		40°C	75% RH		6 months

Based on the above, a retest period of [redacted] months was proposed for the drug substance when stored at room temperature protected from light in a double-layered low-density polyethylene bag and placed in a high-density polyethylene drum, according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q1E Guidelines (Guidelines on the Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003). Long-term testing will be continued up to [redacted] months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release, film-coated tablets, each containing 25 or 100 mg of drug substance. The drug product contains microcrystalline cellulose, anhydrous dibasic calcium phosphate, sodium starch glycolate, magnesium stearate, [redacted] ([redacted]) (Lorbrena Tablets 25 mg only) and [redacted] ([redacted]) (Lorbrena Tablets 100 mg only) as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through [redacted], tableting, film-coating, and packaging/labeling.

A quality control strategy was developed by a QbD approach, and the following processes were used (Table 3):

- Identification of CQAs
- (a) Identification of CPPs affecting CQAs and (b) determination of PAR of manufacturing process parameters, based on the quality risk assessment and on the experimental design.

Table 3. Outline of the control strategy for the drug product

CQA	Control method
[redacted]	Manufacturing process, [redacted]
[redacted]	Manufacturing process, [redacted]
[redacted]	Manufacturing process, [redacted]
[redacted]	Manufacturing process, [redacted]
[redacted]	Manufacturing process, [redacted]
[redacted]	Manufacturing process, [redacted]

[redacted] and [redacted] have been identified as the critical steps. In-process control parameters and action limits have been established for [redacted] step.

2.2.3 Control of drug product

The proposed specifications for the drug product include content, description, identification (ultraviolet spectroscopy, LC), purity (degradation products [LC]), uniformity of dosage unit (content uniformity [LC]), dissolution (LC), and assay (LC).

2.2.4 Stability of drug product

Table 4 shows the stability studies performed on the drug product. A photostability test showed that the drug product was photostable.

Table 4. Stability studies of drug product

Content	Test	Primary batch	Temperature	Humidity	Storage form	Storage period
25 mg	Long-term testing	3 production scale batches	25°C	60% RH	PTP (3-layered film composed of [redacted]/aluminum foil/[redacted] and aluminum foil)	18 months
	Accelerated testing		40°C	75% RH		6 months
100 mg	Long-term testing		25°C	60% RH		18 months
	Accelerated testing		40°C	75% RH		6 months

Based on the above, the shelf life of 24 months has been proposed for the drug product when stored at room temperature in a press through packaging (PTP) (3-layered film of [redacted]/aluminum foil/[redacted] and aluminum foil) according to ICH Q1E guidelines. Long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

Based on the results of the reviews on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

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

3.1 Primary pharmacodynamics

3.1.1 Inhibition of ALK phosphorylation (CTD 4.2.1.1.1, 4.2.1.1.2, 4.2.1.1.3, 4.2.1.1.4, and 4.2.1.1.5)

3.1.1.1 *In vitro*

The activity of lorlatinib and crizotinib to inhibit human ALK (recombinant) with a resistant mutation[6)] was investigated by electrophoretic mobility shift assay using a fluorescence-labeled substrate. Table 5 shows inhibition constant (Ki) values of lorlatinib and crizotinib determined by the test.

6) Secondary gene mutation within the tyrosine kinase domain of ALK observed in patients treated with a conventional ALK-TKI. The following gene mutations have been reported (*Cancers.* 2018;10:62).
L1196M, leucine at position 1196 replaced by methionine; G1269A, glycine at position 1269 replaced by alanine; F1174L, phenylalanine at position 1174replaced by leucine; C1156Y, cysteine at position 1156 replaced by tyrosine; L1152R, leucine at position 1152 replaced by arginine; 1151Tins, threonine inserted at position 1151; S1206Y, serine at position 1206 replaced by tyrosine; I1171T, isoleucine at position 1171 replaced by threonine; G1202R, glycine at position 1202 replaced by arginine.

Table 5. Activity of lorlatinib and crizotinib to inhibit phosphorylation of ALK with various resistant mutations

Resistant mutation	Lorlatinib		Crizotinib	
	n	Ki (nmol/L)	n	Ki (nmol/L)
None	3	<0.2	127	0.7 [0.7, 0.8]
L1196M	3	0.7 [0.4, 1.3]	143	8.1 [7.6, 8.7]
G1269A	2	0.8, 1	4	20 [18, 23]
F1174L	1	<0.1	3	0.8 [0.7, 0.9]
C1156Y	1	<0.1	3	0.6 [0.1, 3.3]
L1152R	1	<0.1	3	2.2 [1.3, 3.6]
1151Tins	1	0.1	1	2.2
S1206Y	1	0.2	1	1.3
I1171T	1	0.3	1	1.0

Geometric mean [95% confidential interval (CI)], Individual values for n = 1 or 2

The activity of PF-06895751, a metabolite of lorlatinib, to inhibit human ALK (recombinant) phosphorylation was investigated by the fluorescence resonance energy transfer (FRET) method. No inhibitory effect was observed.

Using human NSCLC-derived NCI-H3122 and NCI-H2228 cell lines expressing ALK fusion protein intracellularly, the activity of lorlatinib and crizotinib to inhibit ALK phosphorylation was investigated by enzyme-linked immunosorbent assay (ELISA). Table 6 shows IC_{50} values of lorlatinib and crizotinib determined by the test.

Table 6. Activity of lorlatinib and crizotinib to inhibit ALK phosphorylation in human NSCLC-derived cell lines

Cell line	ALK fusion protein	Lorlatinib		Crizotinib	
		n	IC_{50} (nmol/L)	n	IC_{50} (nmol/L)
NCI-H3122	EML4-ALKv1[*1]	3	2.4 ± 0.3	29	87 ± 9
NCI-H2228	EML4-ALKv3a/b[*2]	3	1.3 ± 0.4	3	206 ± 41

Mean ± standard error (SE), *1 Formed by fusion of exon 13 of *EML4* gene and exon 20 of *ALK* gene, *2 Formed by exon 6 (or exon 6 to which intron 6-derived 33 bases have been added) of *EML4* gene and exon 20 of *ALK* gene

Using 2 types of NCI-H3122 cell lines each expressing ALK fusion protein and 14 types of mouse fibroblast-derived NIH3T3 cell lines each expressing ALK fusion protein, the activity of lorlatinib and crizotinib to inhibit ALK phosphorylation was investigated by ELISA. Table 7 shows IC_{50} values of lorlatinib and crizotinib determined by the test.

Table 7. Activity of lorlatinib and crizotinib to inhibit phosphorylation of ALK fusion proteins expressed in cell lines

Cell line	ALK fusion protein	Resistant mutation	Lorlatinib		Crizotinib	
			n	IC_{50} (nmol/L)	n	IC_{50} (nmol/L)
NCI-H3122	EML4-ALKv1	L1196M	7	11 ± 0.3	6	535 ± 73
		G1269A	3	17 ± 1.9	3	504 ± 135
NIH3T3	EML4-ALKv1	None	5	1.5 ± 0.4	101	80 ± 37
		L1196M	5	21 ± 2.3	101	843 ± 382
		G1269A	2	6, 23	4	605 ± 90
		F1174L	2	0.2, 0.2	4	165 ± 36
		C1156Y	2	0.3, 3	4	478 ± 153
		L1152R	2	2, 16	4	1026 ± 71
		G1202R	4	65 ± 23	4	1148 ± 471
		1151Tins	2	46, 45	2	3000, 3078
		S1206Y	1	4.2	1	626
		I1171T	3	7.1 ± 2.0	3	240 ± 68
	EML4-ALKv2[*1]	None	2	1.3, 1.5	2	100, 92
	EML4-ALKv3a[*2]	None	2	0.8, 0.9	2	58, 53
	EML4-ALKv3b[*3]	None	2	0.9, 1.0	2	89, 63
	KIF5B-ALK[*4]	None	3	0.5 ± 0.2	3	29 ± 6.4

Mean ± SE, Individual values for n = 1 or 2, *[1] Formed by fusion of exon 20 of *EML4* gene and exon 20 of *ALK* gene, *[2] Formed by exon 6 of *EML4* gene and exon 20 of *ALK* gene, *[3] Formed by fusion of exon 6 (to which intron 6-derived 33 bases have been added) of *EML4* gene and exon 20 of *ALK* gene, *[4] Formed by fusion of exon 15 of *KIF5B* gene and exon 20 of *ALK* gene

3.1.1.2 *In vivo*

The activity of lorlatinib to inhibit ALK phosphorylation in tumor tissue was investigated in nude mice subcutaneously transplanted with the following cell lines. Lorlatinib inhibited the phosphorylation in a dose-dependent manner.

- NCI-H3122 Cell line expressing EML4-ALKv1 intracellularly
- NCI-H3122 Cell line expressing EML4-ALKv1^{L1196M} or EML4-ALKv1^{G1269A}
- NIH3T3 Cell line expressing EML4-ALKv1^{I1171T} or EML4-ALKv1^{G1202R}

3.1.2 Inhibition of phosphorylation of kinases other than ALK

3.1.2.1 c-Ros oncogene 1 (ROS1) (CTD 4.2.1.1.1)

The activity of lorlatinib and crizotinib to inhibit phosphorylation of human c-ros oncogene 1 (ROS1) (recombinant) was investigated by electrophoretic mobility shift assay using a fluorescence-labeled substrate. K_i of lorlatinib and crizotinib (geometric mean [95% confidence interval (CI)], n = 2 and 3, respectively) was <0.005 and 0.12 [0.08, 0.19] nmol/L, respectively.

Using human NSCLC-derived HCC78 cell line expressing solute carrier family 34 member 2 (SLC34A2)-ROS1[s][7] and SLC34A2-ROS1[L][8] intracellularly, the activity of lorlatinib and crizotinib to inhibit ROS1 phosphorylation was investigated by ELISA. IC_{50} of lorlatinib and crizotinib (mean ± standard deviation [SD], n = 4 and 10, respectively) was 0.14 ± 0.09 and 96 ± 55 nmol/L, respectively.

Using NIH3T3 cell line expressing ROS1 fusion proteins, the activity of lorlatinib and crizotinib to inhibit ROS1 phosphorylation was investigated by ELISA. Table 8 shows IC_{50} values of lorlatinib and crizotinib.

7) Formed by fusion of exon 12 of *SLC34A2* gene and exon 34 of *ROS1* gene
8) Formed by fusion of exon 12 of *SLC34A2* gene and exon 32 of *ROS1* gene

Table 8. Activity of lorlatinib and crizotinib to inhibit ROS1 fusion proteins expressed in NIH3T3 cell line

ROS1 fusion protein	Lorlatinib		Crizotinib	
	n	IC_{50} (nmol/L)	n	IC_{50} (nmol/L)
CD74-ROS1[s][*1]	4	0.23 ± 0.18	6	16 ± 6
FIG-ROS1[s][*2]	4	0.31 ± 0.41	6	104 ± 48
FIG-ROS1[L][*3]	4	0.29 ± 0.11	5	48 ± 25
SLC34A2-ROS1[s]	6	1.00 ± 1.14	7	61 ± 44
SLC34A2-ROS1[L]	6	1.30 ± 0.55	6	123 ± 42

Mean ± SD; *[1] Formed by fusion of exon 6 of *CD74* gene and exon 34 of *ROS1* gene, *[2] Formed by fusion of exon 7 of *FIG* gene and exon 36 of *ROS1* gene, *[3] Formed by fusion of exon 7 of *FIG* gene and exon 35 of *ROS1* gene

3.1.2.2 Kinases other than ROS1 (CTD 4.2.1.1.1)

The activity of lorlatinib to inhibit phosphorylation of 206 types of kinases (recombinant) was investigated by the FRET method. Table 9 shows kinases with IC_{50} of <60 nmol/L for lorlatinib.

Table 9. Activity of lorlatinib to inhibit various kinases

Kinase	IC_{50} (nmol/L)	Kinase	IC_{50} (nmol/L)
LTK	2.7	PTK2	17
FER	3.3	NTRK1	24
FES	6	NTRK3	46
PTK2B	14	FRK	53
TNK2	17	$EGFR^{T790M/L858R*}$	56

n = 1 (individual value), * Threonine at position 790 and leucine at position 858 of EGFR were replaced by methionine and arginine, respectively.

3.1.3 Inhibition of ALK signaling (CTD 4.2.1.1.4)

3.1.3.1 *In vitro*

Using NCI-H3122 cell line expressing EML4-$ALKv1^{L1196M}$, the activity of lorlatinib to inhibit phosphorylation of ALK, signal transducer and activator of transcription 3 (STAT3), AKT, and extracellular signal-regulated kinase (ERK) was investigated by Western blotting. Lorlatinib inhibited phosphorylation of ALK, STAT3, and ERK in a concentration-dependent manner.

3.1.3.2 *In vivo*

Using nude mice subcutaneously transplanted with NCI-H3122 cell line expressing EML4-$ALKv1^{L1196M}$ (7-9 mice/group), the activity of lorlatinib to inhibit ALK, STAT3, AKT, and ERK in the tumor tissue was investigated by Western blotting. Starting from the time point when the tumor volume reached approximately 400 mm^3, lorlatinib (0.3, 1, 3, or 10 mg/kg) was administered orally *bis in die* (BID) for 4 days, and the expression level of each protein was measured at 1 and 3 hours post-dose of lorlatinib. Lorlatinib inhibited phosphorylation of ALK, STAT3, AKT, and ERK in the 1, 3, and 10 mg/kg groups.

3.1.4 Apoptosis induction (CTD 4.2.1.1.1)

Using NCI-H3122 cell line expressing either of 2 types of ALK fusion protein and NCI-H3122 cell line not expressing the fusion protein, apoptosis-inducing activity of lorlatinib and crizotinib was investigated using the activities of caspase 3 and 7 as the indices. Table 10 shows IC_{50} values of lorlatinib and crizotinib.

Table 10. Apoptosis-inducing activity of lorlatinib and crizotinib in NCI-H3122 cell line

ALK fusion protein	IC_{50} (nmol/L)	
	Lorlatinib	Crizotinib
EML4-ALKv1	4.9 ± 0.2	149 ± 8
EML4-ALKv1^{L1196M}	29 ± 5.7	1520 ± 372
EML4-ALKv1^{G1269A}	28 ± 4.9	1526 ± 291

Mean ± SD, n = 3

3.1.5 Growth inhibitory activity against malignant tumor-derived cell lines

3.1.5.1 *In vitro* (CTD 4.2.1.1.1 and 4.2.1.1.2)

Using NCI-H2228 cell line, NCI-H3122 cell line, NCI-H3122 cell line expressing either of 2 types of ALK fusion proteins, and mouse pro-B cell-derived Ba/F3 cell line expressing EML4-ALKv1^{I1171T}, growth-inhibitory activity of lorlatinib and crizotinib was investigated using adenosine triphosphate (ATP) content in viable cells as the index. Table 11 shows IC_{50} values of lorlatinib and crizotinib.

Table 11. Growth-inhibitory activity of lorlatinib and crizotinib against various malignant tumor-derived cell lines

Cell line	ALK fusion protein	Lorlatinib		Crizotinib	
		n	IC_{50} (nmol/L)	n	IC_{50} (nmol/L)
NCI-H2228	EML4-ALKv3a/b	3	1.3 ± 0.1	3	118 ± 14
NCI-H3122	EML4-ALKv1	4	2.4 ± 0.3	4	108 ± 29
	EML4-ALKv1^{L1196M}	3	30 ± 7	3	838 ± 154
	EML4-ALKv1^{G1269A}	4	30 ± 16	4	623 ± 251
Ba/F3	EML4-ALKv1^{I1171T}	5	14 ± 12	5	225 ± 148

Mean ± SD

Using Ba/F3 cell line expressing CD74-ROS1[s] and HCC78 cell line, growth-inhibitory activity of lorlatinib and crizotinib was investigated with ATP content in viable cells as the index. Table 12 shows IC_{50} values of lorlatinib and crizotinib.

Table 12. Growth-inhibitory activity of lorlatinib and crizotinib against malignant tumor-derived cell lines

Cell line	ROS1 fusion protein	Lorlatinib		Crizotinib	
		n	IC_{50} (nmol/L)	n	IC_{50} (nmol/L)
HCC78	SLC34A2-ROS1	3	2.6 ± 3	3	41 ± 14
Ba/F3	CD74-ROS1[s]	4	0.6 ± 0.5	4	5.9 ± 4.4

Mean ± SD

3.1.5.2 *In vivo*

3.1.5.2.1 Human NSCLC-derived cell lines (CTD 4.2.1.1.4)

Using nude mice subcutaneously transplanted with cell line NCI-H3122 (10-12 mice/group), the tumor growth-inhibitory effect of lorlatinib was investigated. Starting from the time point when the tumor volume reached approximately 280 mm^3, lorlatinib (0.06, 0.2, 0.6, 1.5, or 3 mg/kg/day) was administered subcutaneously for 13 days, and the tumor volume was calculated. A statistically significant tumor growth-inhibitory effect was observed in the lorlatinib 0.2, 0.6, 1.5, and 3 mg/kg/day groups as compared with the control (vehicle[9)]) group (P = 0.00019 in the 0.2 mg/kg/day group; P < 0.00001 in 0.6, 1.5, and 3 mg/kg/day groups; one-way analysis of variance [ANOVA]).

Using nude mice subcutaneously transplanted with NCI-H3122 cell line expressing EML4-ALKv1^{L1196M} (15 mice/group), the tumor growth-inhibitory effect of lorlatinib and crizotinib

9) 45% v/v DMSO, 40% v/v polyethylene glycol (PEG) 400, and 15% v/v polyoxyethylene castor oil

was investigated. Starting from the time point when the tumor volume reached 300 mm^3, lorlatinib (0.3, 1, 3, 10, or 20 mg/kg) or crizotinib (75 mg/kg) was administered orally BID for 13 days, and tumor volume was calculated. A statistically significant tumor growth-inhibitory effect was observed in all lorlatinib groups as compared with the control (37% v/v hydrochloric acid [HCl]) group (Figure 1).

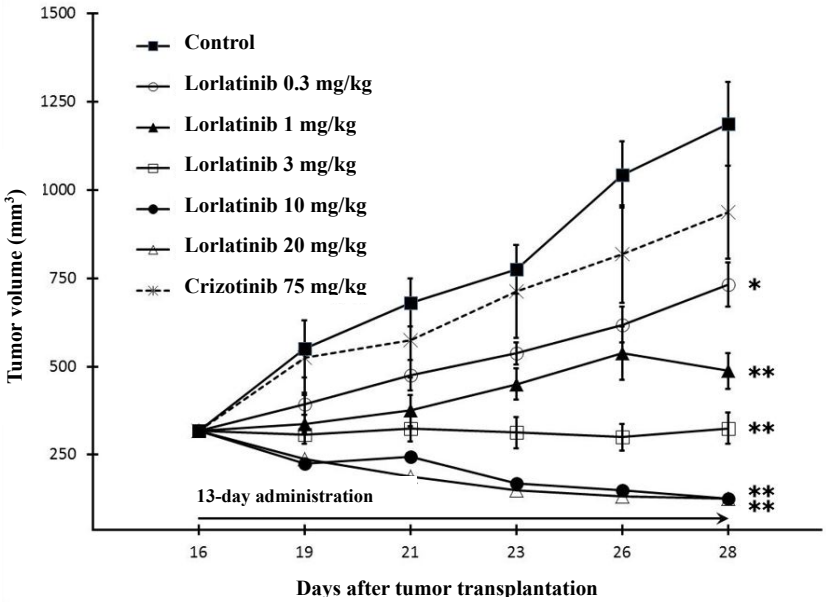

Figure 1. Tumor growth-inhibitory activity of lorlatinib in nude mice subcutaneously transplanted with NCI-H3122 cell line expressing EML4-ALKv1^{L1196M}

n = 15; mean ± SE; * and ** $P < 0.0005$ and $P < 0.00001$, respectively, against the respective control group (one-way ANOVA)

Using nude mice subcutaneously transplanted with NCI-H3122 cell line expressing EML4-ALKv1^{L1196M} (10-12 mice/group), the tumor growth-inhibitory effect of lorlatinib was investigated. Starting from the time point when the tumor volume reached 310 mm^3, lorlatinib (0.5, 1.5, 5, 15, or 40 mg/kg/day) was administered subcutaneously for 13 days, and tumor volume was calculated. A statistically significant tumor growth-inhibitory effect was observed in all lorlatinib groups as compared with the control (vehicle[9)]) group ($P = 0.00342$ in the 0.5 mg/kg/day group; $P < 0.00001$ in the 1.5, 5, 15, and 40 mg/kg/day groups [one-way ANOVA]).

Using nude mice subcutaneously transplanted with NCI-H3122 cell line expressing EML4-ALKv1^{G1269A} (10-12 mice/group), tumor growth-inhibitory activity of lorlatinib was investigated. Starting from the time point when tumor volume reached approximately 220 mm^3, lorlatinib (0.2, 0.6, 2, 6, 20, or 25 mg/kg/day) was administered subcutaneously for 12 days, and tumor volume was calculated. A statistically significant tumor growth-inhibitory effect was observed in the lorlatinib 0.6, 2, 6, 20, and 25 mg/kg/day groups as compared with the control (vehicle[9)]) group. ($P = 0.00069$ in the 0.6 mg/kg/day group, $P = 0.00546$ in the 2 mg/kg/day group, $P < 0.00001$ in the 6, 20, and 25 mg/kg/day groups; one-way ANOVA).

Nude mice intracerebrally transplanted with NCI-H3122 cell line expressing EML4-ALKv1^{L1196M} (5 mice/group) received lorlatinib (5, 10, or 20 mg/kg/day) subcutaneously for 19 days from Day 8 after tumor transplantation, and tumor growth-inhibitory activity of lorlatinib was investigated. Tumor

growth-inhibitory activity was observed in all lorlatinib groups as compared with the control (vehicle[9)]) group.

3.1.5.2.2 Cell lines other than those derived from human NSCLC (CTD 4.2.1.1.2, 4.2.1.1.4, and 4.2.1.1.5)

Using nude mice subcutaneously transplanted with NIH3T3 cell line expressing (a) EML4-ALKv1^{I1171T}, (b) EML4-ALKv1^{G1202R}, or (c) CD74-ROS1, tumor growth-inhibitory activity of lorlatinib was investigated. Results were as follows:

(a) Starting from the time point when the tumor volume reached approximately 240 mm^3, lorlatinib (0.3, 1, or 3 mg/kg/day) was administered subcutaneously for 9 days, and tumor volume was calculated. A statistically significant tumor growth-inhibitory effect was observed in all lorlatinib groups as compared with the control (vehicle[9)]) group ($P < 0.001$; one-way ANOVA).

(b) Starting from the time point when the tumor volume reached approximately 320 mm^3, lorlatinib (0.75, 2.5, 7.5, 20, or 25 mg/kg/day) was administered subcutaneously for 6 days, and tumor volume was calculated. A statistically significant tumor growth-inhibitory effect was observed in the lorlatinib 2.5, 7.5, 20, and 25 mg/kg/day groups as compared with the control (vehicle[9)]) group ($P < 0.005$; one-way ANOVA).

(c) Starting from the time point when the tumor volume reached approximately 250 mm^3, lorlatinib (0.01, 0.03, 0.1, 0.3, 1, or 3 mg/kg) was administered orally BID for 9 days, and tumor volume was calculated. A statistically significant tumor growth-inhibitory effect was observed in the lorlatinib 0.1, 0.3, 1, and 3 mg/kg groups as compared with the control (37% v/v HCl) group ($P = 0.00002$ in the 0.1 mg/kg group, $P < 0.00001$ in the 0.3, 1, and 3 mg/kg groups).

3.2 Secondary pharmacodynamics

3.2.1 Effect on receptors, enzymes, transporters, and ion channels (CTD 4.2.1.2.1 and 4.2.1.2.2)

Inhibitory activity of lorlatinib and its metabolite PF-06895751 against, respectively, 71 and 81 types of receptors, enzymes, transporters, and ion channels was investigated. Lorlatinib showed ≥50% inhibition against epidermal growth factor receptor (EGFR), acetylcholinesterase, aurora kinase A (AURKA), and lymphocyte-specific protein tyrosine kinase (LCK) with IC_{50} (n = 1) of 5.0, 5.3, 3.8, and 65 μmol/L, respectively. In contrast, PF-06895751 did not show ≥50% inhibition against any of the receptors, etc. tested.

The applicant explained that, in light of the observation that IC_{50} values of lorlatinib against the above receptors, etc. were ≥7.7 times the C_{max} (0.495 μmol/L)[10)] of unbound lorlatinib in plasma at the recommended clinical dose (100 mg *quaque die* [QD]), adverse events due to the inhibition of the above receptors, etc. are unlikely to occur during the clinical use of lorlatinib.

[10)] Calculated based on C_{max} (591.1 ng/mL) on Day 15 of Cycle 1 following multiple doses of lorlatinib 100 mg QD in Japanese patients [see Section 6.2.7] and on the fractional ratio of the unbound lorlatinib (0.34) in humans [see Section 4.2.2].

3.3 Safety pharmacology

3.3.1 Effect on central nervous system (CNS) (CTD 4.2.1.3.10)

A single dose of lorlatinib (0.3, 3, 10, or 30 mg/kg) was administered orally to 16 mice, and the effect on clinical signs and cognitive function was investigated. A decrease in memory-retrieval score[11] was observed in the 3, 10, and 30 mg/kg groups.

Based on the above results and the effect on central nervous system (CNS) observed in clinical studies [see Section 7.R.3.4], the applicant explained that the effect of lorlatinib on CNS will be communicated to healthcare professionals through the package insert in an appropriate manner.

3.3.2 Effect on cardiovascular system

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

Using human fetal kidney-derived HEK293 cell line introduced with human *ether-a-go-go* related gene (hERG), the effect of lorlatinib (10, 30, 100, and 300 μmol/L) on hERG potassium current was investigated. Lorlatinib inhibited hERG potassium current by 2.7% ± 0.7%, 11.1% ± 0.9%, 30.7% ± 1.9%, and 60.9% ± 0.4% (mean ± standard error [SE], n = 3), respectively. The inhibitory effect of lorlatinib 30, 100, and 300 μmol/L was statistically significant ($P < 0.05$; Dunnett's multiple comparison) as compared with the control (HEPES-buffered physiological saline containing 0.3% dimethyl sulfoxide [DMSO]), with IC_{50} of 203.1 μmol/L.

3.3.2.2 Effect on type L calcium and sodium channels (CTD 4.2.1.3.7 [non-GLP])

Using ventricular myocytes isolated from guinea pigs, the effect of lorlatinib (10, 30, or 100 μmol/L) on type L calcium channel current and on sodium channel current (delayed and maximum sodium currents) was investigated. Lorlatinib at all concentrations tested showed a statistically significant inhibition of type L calcium channel current as compared with the control (HEPES-buffered saline containing 0.1% DMSO) ($P < 0.01$, 2-way ANOVA) with IC_{50} of 44.0 ± 4.9 μmol/L (mean ± SE, n = 4). Also, lorlatinib 100 μmol/L showed a statistically significant increase in delayed sodium current ($P < 0.01$, 2-way ANOVA) as compared with the control (HEPES-buffered saline containing 0.1% DMSO).

3.3.2.3 Effect on heart rate, blood pressure, and electrocardiogram (CTD 4.2.1.3.12 and 4.2.1.3.13 [both non-GLP])

A single dose of lorlatinib (10 or 30 mg/kg) was administered orally to rats (8 animals/group), and the effect of lorlatinib on systolic blood pressure, diastolic blood pressure, mean blood pressure, and heart rate was investigated. Animals in all lorlatinib groups showed a statistically significant increase in systolic blood pressure, diastolic blood pressure, and mean blood pressure as well as a biphasic change in heart rate as compared with the control (0.001 mol/L HCl) group ($P < 0.05$, analysis of covariance).

Lorlatinib (1 mg/kg) was administered orally BID for 5 days to dogs (4 animals/group) and, after a 2-day withdrawal period, lorlatinib (7.5 mg/kg) was administered orally BID for 12 days. The effect of

[11] Animals were trained to associate food with a specific combination of environment and visual stimulus, and transferred to a different environment where food was unavailable. Then, they were returned to the former environment where food was available, and the effect of lorlatinib was investigated.

lorlatinib on systolic blood pressure, diastolic blood pressure, mean blood pressure, heart rate, and electrocardiogram (RR, PR, QRS, QT, and QTc intervals) was investigated in these animals. Lorlatinib caused a statistically significant decrease in systolic blood pressure, increase in heart rate, shortening of QT interval, and prolongation of PR and QRS intervals as compared with the control (0.001 mol/L HCl) group ($P < 0.05$, analysis of covariance).

The applicant's explanation about the above findings:
C_{max} of unbound lorlatinib in plasma in rats (524 ng/mL) post-dose of lorlatinib 10 mg/kg and in dogs (519 ng/mL) post-dose of lorlatinib 7.5 mg/kg BID was ≥2.6 times the C_{max} of unbound lorlatinib in plasma (201 ng/mL)[10)] at the recommended clinical dose (100 mg QD). These results suggest that lorlatinib is unlikely to pose safety problems in clinical use.

3.3.3 Effect on respiratory system (CTD 4.2.1.3.9)

A single dose of lorlatinib (10, 30, or 100 mg/kg) was administered orally to rats (6 animals/group), and the effect on respiratory rate, tidal volume, and minute ventilation was investigated. Tidal volume decreased by 8% at 60 minutes post-dose of lorlatinib (30 and 100 mg/kg) and by 8% to 15% at 200 to 240 minutes post-dose of lorlatinib (100 mg/kg) as compared with the control (0.001 mol/L HCl) group ($P < 0.05$, ANOVA).

The applicant's explanation about the above findings:
C_{max} of unbound lorlatinib in plasma in rats (1640 and 2270 ng/mL) post-dose of lorlatinib (30 and 100 mg/kg, respectively) was 8.2 and 11 times the C_{max} of unbound lorlatinib in plasma (201 ng/mL)[10)] at the recommended clinical dose (100 mg QD). These findings suggest that lorlatinib is unlikely to pose safety problems in clinical use.

3.R Outline of the review conducted by PMDA

Based on the data submitted and on the results of the reviews in the following sections, PMDA concluded that the applicant's explanations on the nonclinical pharmacology of lorlatinib are acceptable.

3.R.1 Mechanism of action and efficacy of lorlatinib

The applicant's explanation about the mechanism of action of lorlatinib and the efficacy of lorlatinib against *ALK* fusion gene-positive NSCLC resistant to conventional ALK-TKIs:
Many *ALK* fusion gene-positive NSCLC patients acquire resistance to conventional ALK-TKIs. The resistance is induced by the resistant mutation of *ALK* fusion gene (Table 13), the amplification of *ALK* fusion gene, and the mutation of genes such as EGFR and RAS (*Cancers.* 2018;10:62).

Table 13. Resistant mutations of *ALK* fusion genes observed in patients with NSCLC receiving ALK-TKI

	Resistant mutation
Crizotinib	I1151Tins, L1152R, C1156Y, I1171T/N,[*1] L1196M, L1196Q,[*2] G1202R, D1203N,[*3] S1206Y, G1269A
Alectinib	I1171T, V1180L,[*4] G1202R
Ceritinib	L1152P/R,[*5] D1203N, G1202R, F1174C/V,[*6] L1198F,[*7] C1156Y/T[*8]

[*1] Isoleucine at position 1171 is replaced by threonine or asparagine, [*2] Leucine at position 1196 is replaced by glutamine, [*3] Aspartic acid at position 1203 is replaced by asparagine, [*4] Valine at position 1180 is replaced by leucine, [*5] Leucine at position 1152 is replaced by proline or arginine, [*6] Phenylalanine at position 1174 is replaced by cysteine or valine, [*7] Leucine at position 1198 is replaced by phenylalanine, [*8] Cysteine at position 1156 is replaced by tyrosine or threonine.

Lorlatinib is expected to suppress tumor growth in *ALK* fusion gene-positive NSCLC by inhibiting ALK phosphorylation through binding to ATP-binding site within ALK kinase domain (*J Med Chem.* 2014;57:4720-44, etc.) [see Sections 3.1.1, 3.1.3, and 3.1.5]. The following observations indicate that lorlatinib is expected to have efficacy against *ALK* fusion gene-positive NSCLC resistant to conventional ALK-TKIs. It is unknown whether lorlatinib is effective against NSCLC that has become resistant to conventional ALK-TKIs by other than the resistant mutation of ALK fusion gene (e.g., amplification of *ALK* fusion gene, mutation of genes such as EGFR and RAS).

- Lorlatinib suppressed the growth of NSCLC-derived cell lines expressing ALK fusion protein with resistant mutations (L1196M and G1269A) [see Section 3.1.5].

- Lorlatinib suppressed the growth of cell lines expressing ALK fusion protein with G1202R mutation that have gained resistance to crizotinib, alectinib hydrochloride (alectinib), and ceritinib [see Section 3.1.5].

PMDA's view:
The applicant's explanation is acceptable. However, there are limited data about a relationship between the efficacy of lorlatinib and the mechanism of acquisition of resistance to conventional ALK-TKIs. Such data may be important in efficacy predication and appropriate selection of patients for the clinical use of lorlatinib. Investigation should be continued and, once available, new findings should be communicated to healthcare professionals in an appropriate manner.

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

The pharmacokinetics (PK) of lorlatinib in animals was investigated using rats and dogs. Plasma protein binding of lorlatinib, drug-metabolizing enzymes, transporters, etc. were investigated using biomaterials of human or animal origin.

4.1 Absorption

4.1.1 Single-dose administration

A single dose of lorlatinib was administered intravenously (1 mg/kg) or orally (5 mg/kg) to male rats, and plasma lorlatinib concentration was investigated (Table 14). The bioavailability (BA) of lorlatinib following the oral dose of 5 mg/kg was >100%.

A single dose of lorlatinib was administered intravenously (1 mg/kg) or orally (2 mg/kg) to male dogs, and plasma lorlatinib concentration was investigated (Table 14). The BA of lorlatinib following the oral dose of 2 mg/kg was 96.6%.

Table 14. PK parameters of lorlatinib (single intravenous or single oral dose in rats and dogs)

Animal species	Dose (route of administration)	C_{max}* (ng/mL)	t_{max} (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ (h)	CL_{tot} (mL/min/kg)	V_{ss} (L/kg)
Rats	1 mg/kg (i.v.)	670, 799	-	1440, 862	3.4, 2.0	11.6, 19.3	2.54, 2.77
	5 mg/kg (p.o.)	689, 612	4, 7	8570, 8630	4.1, 3.0	-	-
Dogs	1 mg/kg (i.v.)	668, 605	-	1920, 1770	5.4, 3.9	8.68, 9.42	3.09, 2.51
	2 mg/kg (p.o.)	553, 630	0.5, 1	2980, 4170	7.4, 8.7	-	-

n = 2 (individual value), * In the intravenous administration, plasma concentration immediately after dosing, -, Not calculated.

4.1.2 Repeated-dose administration

Lorlatinib was administered orally BID to male rats at 1, 4, and 7.5 mg/kg and to female rats at 0.5, 2, and 7.5 mg/kg for 13 weeks, and plasma lorlatinib concentration was investigated (Table 15). C_{max} and AUC_{24h} of lorlatinib increased roughly dose-proportionally within the dose range investigated. C_{max} and AUC_{24h} of lorlatinib were higher in females than in males in the group receiving 7.5 mg/kg, the dose common to both sexes. The applicant explained that the observed difference was possibly caused by the sex differences in the expression level and isoforms of cytochrome P450 (CYP) in rats (*Drug Metab Rev*. 1998;30:441-98, etc.). The repeated doses did not show any clear effect on C_{max} or AUC_{24h} of lorlatinib.

Table 15. PK parameters of lorlatinib (13-week repeated oral doses in male and female rats)

Day of measurement	Sex	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	AUC_{24h} (ng·h/mL)
1	Male	1	329 ± 121	1.0 ± 0	3750 ± 1160
		4	1610 ± 349	1.0 ± 0	18,600 ± 3420
		7.5	2640 ± 155	1.7 ± 1.2	31,700 ± 1030
	Female	0.5	249 ± 40.5	1.0 ± 0	3660 ± 549
		2	1020 ± 72.3	1.0 ± 0	15,200 ± 1530
		7.5	3940 ± 1180	1.7 ± 1.2	62,400 ± 11,400
91	Male	1	322 ± 113	1.0 ± 0	3920 ± 1310
		4	1460 ± 139	1.0 ± 0	20,600 ± 1740
		7.5	3020 ± 786	1.7 ± 1.2	44,800 ± 10,300
	Female	0.5	388 ± 139	1.0 ± 0	5770 ± 1480
		2	1490 ± 303	1.7 ± 1.2	25,800 ± 4210
		7.5	6600 ± 1630	1.0 ± 0	131,000 ± 34,300

Arithmetic mean ± SD; n = 3

Lorlatinib (1, 3.5, or 12.5 mg/kg) was administered orally BID for 13 weeks to male and female dogs, and plasma lorlatinib concentration was investigated (Table 16). C_{max} and AUC_{24h} of lorlatinib increased roughly dose-proportionally within the range investigated. The PK of lorlatinib did not show any clear sex difference. The repeated doses did not have any clear effect on C_{max} or AUC_{24h} of lorlatinib.

Table 16. PK parameters of lorlatinib (13-week repeated oral doses in male and female dogs)

Day of measurement	Dose (mg/kg)	C_{max} (ng/mL)		t_{max} (h)		AUC_{24h} (ng·h/mL)	
		Male	Female	Male	Female	Male	Female
1	1	307 ± 23.5	252 ± 50.8	1.0 ± 0	1.0 ± 0	2510 ± 411	2530 ± 830
	3.5	1060 ± 60.8	788 ± 204	1.0 ± 0	1.0 ± 0	10,800 ± 1300	9270 ± 2870
	12.5	2980 ± 850	2540 ± 651	1.0 ± 0	1.0 ± 0	32,800 ± 6250	28,700 ± 3800
40	1	325 ± 10.1	274 ± 61.5	1.0 ± 0	1.0 ± 0	2640 ± 328	2420 ± 723
	3.5	1210 ± 105	896 ± 220	1.0 ± 0	1.0 ± 0	10,600 ± 1700	7950 ± 1560
	12.5	4310 ± 136	4920 ± 1170	1.0 ± 0	1.0 ± 0	32,100 ± 6350	37,200 ± 15,000
90	1	348 ± 13.9	287 ± 50.8	1.0 ± 0	1.0 ± 0	2960 ± 183	2680 ± 641
	3.5	1340 ± 181	966 ± 196	1.0 ± 0	1.0 ± 0	12,000 ± 1780	8800 ± 2460
	12.5	3800, 4120[*1]	2850[*2]	1.0, 1.0[*1]	1.0[*2]	37,300, 33,800[*1]	22,000[*2]

Arithmetic mean ± SD; n = 3 (individual values for n = 1 or 2); [*1] n =1, [*2] n = 1

4.1.3 *In vitro* membrane permeability

Using dog kidney-derived MDCKII cell line expressing human P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP), the membrane permeability of lorlatinib was investigated. In the cell line expressing human P-gp or BCRP, apparent permeability in apical to basolateral direction ($P_{app\ A→B}$) of lorlatinib (2 μmol/L) was 25.4 × 10^{-6} cm/s and 28.1 × 10^{-6} cm/s, respectively. The applicant explained that these results and the following observations suggest that lorlatinib has high membrane permeability.

- Compounds with $P_{app\ A→B}$ of >10 × 10^{-6} cm/s are highly permeable (*Drug Metab Dispos.* 2008;36:268-75).

- Lorlatinib is not a substrate for P-gp or BCRP [see Section 4.5.3].

4.2 Distribution

4.2.1 Tissue distribution

A single dose of ^{14}C-labeled lorlatinib (^{14}C-lorlatinib) 10 mg/kg was administered orally to male pigmented rats, and the tissue distribution of radioactivity was investigated by quantitative whole-body autoradiography. The radioactivity was distributed in a wide range of tissues, and the radioactivity concentration reached the maximum level by 8 hours post-dose in all tissues including blood. The radioactivity concentration was higher in the uvea, liver, intervertebral discs, adrenal glands, and Harderian gland than that in blood, and highest in the uvea (C_{max} 49,800 ng Eq./g). Radioactivity at 672 hours post-dose was not detected in blood, whereas that in the uvea was 250 ng Eq./g. The applicant explained that these results suggest that lorlatinib or its metabolites bind to melanin.

4.2.2 Plasma protein binding

(a) Mouse, rat, or rabbit plasma with lorlatinib (2.0 μmol/L) and (b) dog or human plasma with lorlatinib (2.4 μmol/L) were incubated at 37°C for 6 hours, and plasma protein binding of lorlatinib was investigated by equilibrium dialysis. The fractional ratio of the unbound lorlatinib in mice, rats, rabbits, dogs, and humans was 0.239, 0.303, 0.358, 0.287, and 0.340, respectively.

Human serum albumin (600 μmol/L) or human α1-acid glycoprotein (20 μmol/L) was incubated with lorlatinib (2.0 μmol/L) at 37°C for 6 hours, and binding of lorlatinib was investigated by equilibrium

dialysis. The fractional ratio of the unbound lorlatinib was 0.474 for human serum albumin and 0.620 for human α1-acid glycoprotein.

4.2.3 Distribution in blood cells

Blood samples of mice, rats, rabbits, dogs, and humans were incubated with lorlatinib (1.0 μmol/L) at 37°C for 1 hour, and the distribution of lorlatinib in blood cells was investigated. The distribution coefficient between red blood cells and plasma was 0.633, 0.709, 1.12, 0.675, and 0.968, respectively, in mice, rats, rabbits, dogs, and humans. The applicant explained that these results suggest roughly even distribution of lorlatinib between red blood cells and plasma.

4.2.4 Placental and fetal transfer

Placental and fetal transfer of lorlatinib was not investigated. However, in studies of embryo-fetal development in rat and rabbits, fetal toxicities such as increased embryonic loss rate, decreased surviving fetuses, and complex malformations were observed [see Section 5.5]. Based on these findings, the applicant explained that lorlatinib may possibly cross the placenta and be distributed in fetuses.

4.3 Metabolism

4.3.1 *In vitro*

(a) Liver microsomes and (b) hepatocytes of mice, rats, rabbits, dogs, monkeys, and humans were incubated with lorlatinib (10 μmol/L) at 37°C for (a) 1 or (b) 4 hours, and metabolites of lorlatinib were investigated. M2a, M2b (both N-demethylated forms), M6 and M7 (both monoxides) were detected in mice, rats, rabbits, dogs, monkeys, and humans. In humans, M1a (glucuronate conjugate), M5 (monooxygen adduct), M3a, M4a (glucuronate conjugate of M2a and M5, respectively), M12b, M12c (glucuronate conjugate of M6), and M13 (glutathione adduct) were detected in addition to the above.

Human hepatocytes were incubated with lorlatinib (1 μmol/L) in the presence of inhibitors of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A)[12)] and a CYP isoform-nonselective inhibitor (1-aminobenzotriazole) at 37°C for 20 hours to identify CYP isoforms involved in the oxidative metabolism of lorlatinib. The metabolism of lorlatinib was inhibited by 67% in the presence of the CYP isoform-nonselective inhibitor, with the activity of CYP3A, CYP2C19, and CYP2C8 being inhibited by 37%, 21%, and 8.6%, respectively. The applicant explained that the above results demonstrate that, in humans, the oxidative metabolism of lorlatinib is catalyzed mainly by CYP3A.

Also, the applicant explained that glucuronidation of lorlatinib is catalyzed mainly by uridine diphosphate glucuronosyl transferase (UGT) 1A4, judging from the following findings:

- Lorlatinib (40, 200, or 1000 μmol/L) was incubated with recombinant UGT isoforms (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B10, UGT2B15, and UGT2B17) at 37°C for 1 hour. M1a formation was observed in the

[12)] Inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A used were furafylline, phencyclidine, gemfibrozil glucuronide, tienilic acid, esomeprazole, paroxetine, and troleandomycin, respectively.

presence of (a) UGT1A3 or (b) UGT1A4, and the formation rate of M1a at lorlatinib 40, 200 and 1000 μmol/L was (a) 4.62, 12.4, and 11 pmol/min/mg, and (b) 41.7, 112, and 146 pmol/min/mg, respectively.

- Human liver microsomes and lorlatinib (50 μmol/L) were incubated in the presence of an UGT1A4 inhibitor (hecogenin) at 37°C for 30 minutes. M1a formation was decreased by 86% as compared with that in the absence of the UGT1A4 inhibitor.

4.3.2 *In vivo*

A single dose of ^{14}C-lorlatinib (10 mg/kg) was administered orally to bile duct-cannulated and non-cannulated male and female rats, and metabolites in plasma, urine, feces, and bile were investigated. The following results were obtained:

- In non-cannulated rats, mainly unchanged lorlatinib and M2a were detected in plasma samples collected up to 24 hours post-dose, accounting for 37.8% and 54.6%, respectively, of the total plasma radioactivity in males and, in females, 70.1% and 25.7%, respectively.

- In non-cannulated rats, mainly M2a was detected in urine samples up to 168 hours post-dose, which accounted for 5.0% and 10.4%, respectively, of the administered radioactivity in males and females.

- In non-cannulated rats, mainly unchanged lorlatinib and M2a were detected in feces collected up to 168 hours post-dose, accounting for 8.0% and 55.3%, respectively, of the administered radioactivity in males and, in females, 27.8% and 37.5%, respectively.

- In bile duct-cannulated rats, mainly unchanged lorlatinib, M1b (glucuronate conjugate), M2a, M3a, and M3b (glucuronate conjugate of M2a) were detected in the bile collected up to 48 hours post-dose, accounting for 4.8%, 15.2%, 28.5%, 8.5% and 10.6%, respectively, of the administered radioactivity in males and, in females, 10.1%, 43.0%, 4.9%, 5.3%, and 5.7%, respectively.

A single dose of ^{14}C-lorlatinib (10 mg/kg) was administered orally to male and female dogs, and metabolites in plasma, urine, and feces were investigated. The following results were obtained:

- Mainly unchanged lorlatinib and M2a were detected in plasma samples of from male and female dogs collected up to 12 hours post-dose, accounting for 42.6% and 41.6%, respectively, of the plasma radioactivity in males and, in females, 23.3% and 54.4%, respectively.

- Mainly unchanged lorlatinib was detected in urine samples of male and female dogs collected up to 168 hours post-dose. Unchanged lorlatinib accounted for 9.0% and 0.6%, respectively, of the administered radioactivity in males and females.
- Mainly M2a was detected in feces of from male and female dogs collected up to 168 hours post-dose, accounting for 30.3% and 44.5%, respectively, of the administered radioactivity in males and females.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

A single dose of ^{14}C-lorlatinib (10 mg/kg) was administered orally to bile duct-cannulated and non-cannulated male and female rats and dogs, and urinary, fecal, and biliary excretion rates (percentage relative to administered radioactivity) were investigated. The following results were obtained. The applicant explained that the results suggest that lorlatinib is excreted mainly in feces.

- In non-cannulated male and female rats, the urinary and fecal excretion rates up to 168 hours post-dose were 13.6% and 82.4%, respectively, in males and 17.6% and 76.5%, respectively, in females.

- In bile duct-cannulated male and female rats, urinary, fecal, and biliary excretion rates of radioactivity up to 48 hours post-dose were 22.4%, 20.5%, and 47.6%, respectively, in males and 18.8%, 36.5%, and 27.2%, respectively, in females.

- In male and female dogs, urinary and fecal excretion rates of radioactivity up to 168 hours post-dose were 25.5% and 53.0%, respectively, in males and 18.6% and 72.0%, respectively, in females.

4.4.2 Excretion in milk

Excretion of lorlatinib in milk was not investigated. The applicant explained that lorlatinib may possibly be transferred into milk, given the physicochemical properties of lorlatinib (logD at pH 7, 2.47; pKa, 4.92; fractional ratio of the unbound lorlatinib in human plasma, 0.340; molecular weight, 406.41).

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation about the pharmacokinetic interactions mediated by lorlatinib's inhibitory effect on metabolic enzymes:

Based on the C_{max} of steady-state lorlatinib administered by the proposed dosage and administration (0.495 μmol/L[13)]) and the following results, lorlatinib is unlikely to cause pharmacokinetic interactions mediated by the inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C19, or CYP2D6. In contrast, lorlatinib may possibly cause pharmacokinetic interactions mediated by the inhibition of CYP2C9 or CYP3A.

- Lorlatinib (0.1-100 μmol/L) was incubated with substrates of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A)[14)] and human liver microsomes in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), and the inhibitory effect of lorlatinib against each CYP isoform was investigated. Lorlatinib inhibited the metabolism of (a) diclofenac, a substrate of CYP2C9 and (b) testosterone, midazolam, and nifedipine which are

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13) C_{max} of unbound lorlatinib in plasma on Day 15 of Cycle 1 in multiple doses of lorlatinib (100 mg) QD in Japanese patients in phase II of Study 1001.

14) Substrates of (a) CYP1A2, (b) CYP2B6, (c) CYP2C8, (d) CYP2C9, (e) CYP2C19, (f) CYP2D6, and (g) CYP3A used were (a) phenacetin, (b) bupropion, (c) paclitaxel, (d) diclofenac, (e) S-mephenytoin, (f) dextromethorphan, and (g) testosterone, midazolam, and nifedipine, respectively.

substrates of CYP3A, with IC_{50} of (a) 44 μmol/L and (b) 23, 10, and 22 μmol/L, respectively. In contrast, lorlatinib did not show any clear inhibitory effect against the metabolism of the substrates of other CYP isoforms.

- Lorlatinib (0.1-100 μmol/L) was pre-incubated with human liver microsomes in the presence or absence of NADPH, followed by incubation with substrates of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A),[14] and the time-dependent inhibitory effect of lorlatinib against each CYP isoform was investigated. In the presence of NADPH, lorlatinib inhibited the metabolism of testosterone, midazolam, and nifedipine which are substrates of CYP3A, with IC_{50} of 0.81, 0.74, and 0.87 μmol/L, respectively. In contrast, lorlatinib did not show any clear inhibitory effect against the metabolism of the substrates of other CYP isoforms tested.

- Lorlatinib ([a] 0.3-60 μmol/L, [b] 0.1-15 μmol/L) was pre-incubated with human liver microsomes in the presence of NADPH, followed by incubation with CYP3A substrate (a) midazolam or (b) testosterone, and the time-dependent inhibitory effect of lorlatinib against CYP3A was investigated. Lorlatinib inhibited the metabolism of midazolam in a time-dependent manner. The inhibitor concentration at 50% of maximum inhibition rate (K_I) was 2.81 μmol/L and the maximum inactivation rate constant (k_{inact}) was 0.218 min^{-1}. Lorlatinib also inhibited the metabolism of testosterone in a time-dependent manner, but neither K_I nor k_{inact} was calculated because the inhibition was not saturated within the concentration range tested.

Based on the steady-state C_{max} of lorlatinib (0.495 μmol/L[13]) administered by the proposed dosage and administration and the following results, lorlatinib is unlikely to cause pharmacokinetic interactions mediated by the inhibition of UGT1A4, UGT1A6, UGT1A9, UGT2B7, or UGT2B15 in clinical use. In contrast, lorlatinib may possibly cause pharmacokinetic interactions mediated by UGT1A1 inhibition.

- Lorlatinib (1-100 μmol/L), substrates of UGT isoforms (UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7, and UGT2B15),[15] and liver microsomes were incubated in the presence or absence of bovine serum albumin (BSA), and the inhibitory effect of lorlatinib against each UGT isoform was investigated. In the presence of BSA, lorlatinib inhibited the metabolism of the substrates of UGT1A1 and UGT2B7 with IC_{50} of 37 and 64 μmol/L, respectively. In the absence of BSA, lorlatinib inhibited the metabolism of the substrate of UGT1A1 with IC_{50} of 46 μmol/L. Lorlatinib did not show any clear inhibitory effect against the metabolism of the substrates of other UGT isoforms tested.

4.5.2 Enzyme induction

The applicant's explanation about pharmacokinetic interactions mediated by the induction of metabolic enzymes:

Based on the steady-state C_{max} of lorlatinib (0.495 μmol/L[13]) administered by the proposed dosage and administration and the following results, lorlatinib is unlikely to cause pharmacokinetic interactions

[15] The substrates of (a) UGT1A1, (b) UGT1A4, (c) UGT1A6, (d) UGT1A9, (e) UGT2B7, and (f) UGT2B15 used were (a) β-estradiol, (b) trifluoroperazine, (c) 5-hydroxytryptophol, (d) propofol, (e) zidovudine, and (f) oxazepam.

mediated by CYP1A2 induction in clinical use. In contrast, lorlatinib may possible cause pharmacokinetic interactions mediated by the induction of CYP2B6 or CYP3A.

- Human hepatocytes were incubated in the presence of lorlatinib (0.03-125 μmol/L) for 2 days, and the messenger ribonucleic acid (mRNA) expression level and enzyme activity of CYP isoforms (CYP1A2, CYP2B6, and CYP3A) were investigated. The expression level of CYP3A4 mRNA increased in a concentration-dependent manner within the volume range tested, and CYP3A enzyme activity increased in a concentration-dependent manner within the lorlatinib concentrations ranging from 0.03 to 0.5 μmol/L. The CYP2B6 mRNA expression level increased in a concentration-dependent manner at a concentration of ≥0.5 μmol/L, and CYP2B6 enzyme activity increased in a concentration-dependent manner over the lorlatinib concentrations ranging from 0.3 to 3 μmol/L. In contrast, lorlatinib did not cause any clear increase in the CYP1A2 mRNA expression level or enzyme activity.

4.5.3 Transporters

The applicant's explanation about pharmacokinetic interactions of lorlatinib mediated by transporters:
The following study results showed that lorlatinib does not serve as a substrate for P-gp, BCRP, and organic anion transporting polypeptide (OATP) 1B1, or OATP1B3.

- Using MDCK II cell line expressing human P-gp or BCRP, P-gp- or BCRP-mediated transport of lorlatinib (2 μmol/L) was investigated. The ratio of apparent permeability in basolateral to apical direction ($P_{app\ B\rightarrow A}$) to $P_{app\ A\rightarrow B}$ of lorlatinib was 1.8 and 1.3, respectively.

- Using HEK293 cell line expressing human OATP1B1 or OATP1B3, intracellular uptake of lorlatinib (0.03-100 μmol/L) was investigated. The uptake ratio[16)] of lorlatinib was <2 at all concentrations tested.

Based on the steady-state C_{max} of lorlatinib (0.495 μmol/L[13)]) administered by the proposed dosage and administration and the following results, lorlatinib is unlikely to cause pharmacokinetic interactions mediated by organic anion transporter (OAT) 1, organic cation transporter (OCT) 2, or multidrug and toxin extrusion (MATE) 2K induction in clinical use. In contrast, lorlatinib may possibly cause pharmacokinetic interactions mediated by OATP1B1, OATP1B3, OCT1, OAT3, or MATE1. Also, given the estimated lorlatinib concentration (984 μmol/L) in the gastrointestinal tract administered by the proposed dosage and administration, lorlatinib may have pharmacokinetic interactions with the substrates of P-gp and BCRP in the gastrointestinal tract in clinical use.

- Using MDCK II cell line expressing human P-gp or human BCRP, the inhibitory effect of lorlatinib ([a] 0.1-300 μmol/L, [b] 0.00955-300 μmol/L) against (a) P-gp-mediated digoxin (12 μmol/L) transport and (b) BCRP-mediated pitavastatin (2 μmol/L) transport was investigated. Lorlatinib inhibited (a) P-gp-mediated digoxin transport and (b) BCRP-mediated pitavastatin transport, with IC_{50} of (a) 2.99 μmol/L and (b) >94.9 μmol/L, respectively.

16) Ratio of lorlatinib uptake into transporter-expressing cells to lorlatinib uptake into transporter-nonexpressing cells

- Using HEK293 cell line expressing human OATP1B1 or OATP1B3, the inhibitory effect of lorlatinib (0.412-300 μmol/L) against OATP1B1- or OATP1B3-mediated transport of rosuvastatin (5 μmol/L) was investigated. Lorlatinib inhibited OATP1B1- and OATP1B3-mediated transport of rosuvastatin, with IC_{50} of 32.6 μmol/L and >100 μmol/L, respectively.

- Using HEK293 cell line expressing human OCT1, the inhibitory effect of lorlatinib (0.016-50 μmol/L) against OCT1-mediated transport of ^{14}C-metformin (20 μmol/L) was investigated. Lorlatinib inhibited OCT1-mediated transport of ^{14}C-metformin with IC_{50} of 4.21 μmol/L.

- Using HEK293 cell line expressing human OAT1, OAT3, OCT2, MATE1, or MATE2K, the inhibitory effect of lorlatinib (0.0122-50 μmol/L) against OAT1-, OAT3-, OCT2-, MATE1-, or MATE2K-mediated transport of each substrate[17)] was investigated. Lorlatinib did not show any clear inhibitory effect against OAT1-, OCT2-, or MATE2K-mediated transport. In contrast, lorlatinib inhibited OAT3- and MATE1-mediated transport with IC_{50} of 2.72 and 3.71 μmol/L, respectively.

4.R Outline of the review conducted by PMDA

Based on the data submitted and on the results of the reviews in the following subsections, PMDA concluded that the applicant's explanations about the nonclinical pharmacokinetics of lorlatinib are acceptable.

4.R.1 Tissue distribution

Lorlatinib or its metabolite is suggested to bind to melanin [see Section 4.2.1]. PMDA asked the applicant to explain the safety of lorlatinib in melanin-containing tissues (skin and eyes).

The applicant's explanation:
The following observations, etc. suggest that the distribution of lorlatinib and its metabolites in melanin-containing tissues is unlikely to pose safety problems in clinical use.

- The incidence of skin and subcutaneous tissue disorders in phase I and II of Study 1001 was 38.9% (21 of 54 patients) and 30.2% (83 of 275 patients), respectively, but most of them were Grade ≤2 in severity.

- The incidence of eye disorders in phase I and II of Study 1001 was 29.6% (16 of 54 patients) and 19.3% (53 of 275 patients), respectively, but most of them were Grade ≤2 in severity.

PMDA accepted the applicant's explanation.

4.R.2 Pharmacokinetic interactions

Results of *in vitro* studies suggested pharmacokinetic interactions of lorlatinib mediated by the inhibition or induction of the following metabolic enzymes and transporters in clinical use:

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17) ^{3}H-labeled *p*-aminohippuric acid (2 μmol/L) and ^{3}H-labeled estrone-3-sulfate (0.2 μmol/L) were used as substrates for OAT1 and OAT3, respectively, and ^{14}C-labeled metformin (10-25 μmol/L) as the substrate for OCT2, MATE1, and MATE2K.

- Inhibition of CYP2C9, CYP3A, UGT1A1, P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OAT3, and MATE1 [see Sections 4.5.1 and 4.5.3]

- Induction of CYP2B6 and CYP3A [see Section 4.5.2]

The applicant's explanation about the pharmacokinetic interactions of lorlatinib with substrates of the above-mentioned metabolic enzymes and transporters:
In Study 1001, some patients received the substrates of CYP2B6, CYP2C9, UGT1A1, P-gp, BCRP, OATP1B1, OAT1B3, OCT1, OAT3, or MATE1 in combination with lorlatinib. Because they did not show any particular safety problems, the combination of lorlatinib with these substrates is unlikely to pose any safety problems in clinical use. A substudy of Study 1001 is currently ongoing to investigate the pharmacokinetic interactions of lorlatinib with a substrate of CYP2C9 (tolbutamide), a substrate of P-gp (fexofenadine), etc.

PMDA's view:
The applicant's explanation is generally acceptable. However, because information on the pharmacokinetic interactions of lorlatinib mediated by CYP2B6, CYP2C9, UGT1A1, P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OAT3, and MATE1 is critical for the proper use of lorlatinib, relevant data should be further collected and results of the substudy of Study 1001 and other useful information, once available, should be communicated to healthcare professionals appropriately.

The pharmacokinetic interactions of lorlatinib with a substrate of CYP3A (midazolam) are described in Section 6.2.

5. Toxicity and Outline of the Review Conducted by PMDA

In *in vivo* studies, 0.001 mol/L HCl (pH approximately 3) was used as vehicle unless specified otherwise.

5.1 Single-dose toxicity

Single-dose toxicity studies were conducted in rats and dogs (Table 17). In rats, the approximate lethal dose was determined to be 300 mg/kg in males and >150 mg/kg in females based on the acute toxicity after the initial dose in the repeated-dose toxicity study. In dogs, the acute toxicity was determined to be >100 mg/kg based on the results of the single-dose toxicity study.

Table 17. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male rats (Wistar Han)	p.o.	0,[a] 10, 30, 100	100: Decreased physical activity, effect on pancreas (degeneration/necrosis of pancreatic islet/acinus)[b]	>100	Reference 4.2.3.1.1
Male and female rats (Wistar Han)	p.o.	Male: 0,[a] 100, 300 Female :0,[a] 50, 150	Acute toxicity was evaluated by a 2-day repeated-dose toxicity study. Moribund sacrifice: 300 (1 of 3 animals), decreased physical activity/hypotonicity, dyspnoea exertional, prone position, salivation 150, 300 (in the order of female and male): Decreased physical activity, decreased skin elasticity, spread extremities, abnormal fur	300 (male) >150 (female)	Reference 4.2.3.2.1
Male and female dogs (beagle)	p.o. (BID)	25, 50, 100	≥25: Vomiting, watery stool, decreased body weight, increased white blood cell count, neutrophil count, and monocyte count	>100	Reference 4.2.3.1.2

a) Only vehicle was administered.
b) The histopathological test was performed only on the pancreas.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies (14 days, 4 weeks, and 13 weeks) were conducted in rats and dogs (Table 18). Main toxicological target organs were spleen, hepatobiliary system, gastrointestinal tract, and male reproductive organs in both rats and dogs, and peripheral nerves and CNS in rats. Inflammatory changes were observed in skin, lung, oral cavity, etc. of rats and dogs.

Exposure to unbound lorlatinib in plasma (C_{max} and AUC_{24h}) at the no observed adverse effect level (NOAEL) in the 13-week repeated-dose toxicity studies (8 and 4 mg/kg/day, respectively, in male and female rats, 7 mg/kg/day in dogs) were 442 ng/mL and 6240 ng·h/mL, respectively, in male rats, 451 ng/mL and 7820 ng·h/mL in female rats, and 330 ng/mL and 2980 ng·h/mL in dogs, which were 2.2 and 3.5 times (male rats), 2.2 and 4.4 times (female rats), and 1.6 and 1.7 times (dogs) the clinical exposure[18)].

[18)] Exposure to unbound lorlatinib in plasma (C_{max}, 201 ng/mL; AUC_{24h}, 1780 ng·h/mL) calculated based on the exposure to lorlatinib in plasma (C_{max}, 591 ng/mL; AUC_{24h}, 5233 ng·h/mL) on Day 15 of Cycle 1 in the repeated-dose administration of lorlatinib (100 mg) QD in Japanese patients and on the fractional ratio of the unbound lorlatinib in human plasma (0.34) [see Section 4.2.2].

Table 18. Repeated-dose toxicity studies

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male rats (Wistar Han)	p.o.	14 days (BID)	0,[a] 6, 20, 60	Moribund sacrifice: 60 (2 of 5 animals), decreased body weight, edema of anterior stomach, perforated ulcer of glandular stomach, localized peritonitis ≥6: Increased body weight gain, effects on erythrocyte parameters (e.g., decreased red blood cell count, decreased hemoglobin concentration), effects on leucocyte parameters (e.g., increased white blood cell count, increased lymphocyte count, etc.), increased liver weight, increased histiocytes in mesenteric lymph node ≥20: Echocardiographic abnormalities (increased ventricular end-diastolic volume/diastolic volume/stroke volume, enlarged left ventricular cavity, increased left ventricular thickness),[b] increased serum glutamate dehydrogenase (GLDH), enhanced hematopoiesis in spleen/decreased cell count in marginal zone, effects on male reproductive organs (e.g., tissue fragments in epididymal cavity, degeneration of seminiferous tubule in testis, etc.) 60: Decreased physical activity, dehydration, loose stool, emaciation, coarse fur, ptosis, effects on CNS (loss of reflex, prone position, seizure-like activity, circular movement, head bobbing, tremor, abnormal gait, etc.),[c] decreased food consumption, urine coloration, increased urine volume, increased platelet count, increased serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST)/alkaline phosphatase (ALP)/gamma-glutamyltransferase (GGT)/cholesterol/total bilirubin, atrophy of pancreatic acinus, vasodilatation, etc., enlarged liver/bile duct hyperplasia/single-cell necrosis, thymus size reduction and darkening/decreased cellularity of lymphocytes, single-cell necrosis/erosion/ulcer in small and large intestines, increased red blood cells in mesenteric lymph node sinus	20[d]	Reference 4.2.3.2.3
Male and female rats (Wistar Han)	p.o.	4 weeks (BID) + 4-week withdrawal	Male: 0,[a] 2, 8, 30 Female: 0,[a] 1, 4, 15	Moribund sacrifice: 30 (male, 2 of 15 animals), abdominal distention, decreased physical activity/skin elasticity, ataxia, urinary tract infection, severe atrophy of pancreatic acinus, severe decrease in cell count in splenic marginal zone, gastrointestinal distention, cell necrosis in crypt epithelium in small intestine/gastric pyloric gland, etc. ≥1, 2 (in the order of female and male): Effects on erythrocyte parameters (decreased red blood cell count, decreased hemoglobin concentration, etc.), effects on leucocyte parameters (increased white blood cell count/neutrophil count/monocyte count, etc.), increased fibrinogen concentration, increased serum amylase/cholesterol/globulin/glucose/urea nitrogen, increased liver weight, atrophy of pancreatic acinus[e] ≥4, 8: Increased food consumption, increased body weight gain, decreased urine pH, increased	Male: 8[d] Female: 4[d]	4.2.3.2.5

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
				heart weight, increased spleen weight/extramedullary hematopoiesis/decreased cellularity in marginal zone[f)] 15, 30: Effect on clinical signs (abdominal distention, decreased skin elasticity, soft feces, ataxia, soiled fur, piloerection, twisted neck, tremor, etc.), increased serum lipase/bilirubin/ALT/creatinine, skin erosion/ulcer/fibrosis, enlarged spleen, bile duct hyperplasia/centrilobular hepatocellular hypertrophy in liver, single-cell necrosis in glandular stomach, axon degeneration in peripheral nerves, mammary gland atrophy[g)] Reversible[h)]		
Male and female rats (Wistar Han)	p.o.	13 weeks (BID) + 4-week withdrawal	Male: 0,[a)] 2, 8, 15 Female: 0,[a)] 1, 4, 15	≥1, 2: Prothrombin time prolonged, increased heart weight/increased liver weight, extramedullary hematopoiesis in spleen/decreased cellularity in marginal zone,[i)] increased cellularity of hematopoietic cells, pigmentation of mammary gland[g)] ≥4, 8: Abdominal distention, thinning of fur, changes in skin (crust, redness, epidermal inflammation, dermal fibrosis, etc.),[j)] effect on erythrocyte parameters (decreased red blood cell count/hemoglobin concentration, etc.), effects on leukocyte parameters (increased white blood cell count/neutrophil count, etc.), increased fibrinogen concentration, increased serum amylase/lipase/cholesterol/globulin/sodium (Na)/chloride (Cl), decreased serum albumin/decreased albumin/globulin ratio (A/G ratio), decreased urine pH, increased splenic weight, liver darkening, basophilic change of renal tubules/glomerulonephropathy,[k)] findings of lymph nodes (darkening/enlargement/increased hematopoiesis, etc.), decreased salivation 15: Decreased body temperature, decreased frequency of standing up, decreased adrenal weight, increased serum calcium (Ca)/P, atrophy of pancreatic acinus/fibrosis/inflammation, decreased cellularity of lymphocytes in thymus, mammary gland atrophy[g)] 15 (female only): Increased food consumption, increased body weight gain, increased serum AST/ALP/bilirubin/triglycerides, urine analysis abnormal (urine output increased, specific gravity urine decreased, bilirubin urine, etc.), decreased brain/thymus weight, skin ulcer, yellowing of various organs (subcutaneous tissue, etc.), biliary dilatation/wall hypertrophy, splenic enlargement, darkening/smaller adrenals, smaller thymus, enlarged liver/bile duct hyperplasia/single-cell necrosis/centrilobular hepatocellular hypertrophy/increased hematopoiesis, etc., axon degeneration in sciatic nerves, darkening of kidney/pigmentation of renal tubules/degeneration and necrosis of arterial wall, increase in Anichkov's cells in heart, increased cellularity of granulocytes in bone marrow, uterine atrophy/uterine cervical inflammation	Male:8[d)] Female:4[d)]	4.2.3.2.6

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
				Reversible[h] (except bile duct hyperplasia in liver)		
Male and female dogs (beagle)	p.o.	14 days (BID)	0,[a] 5, 15, 50	Moribund sacrifice: 50 (male, 1 of 1 animal), decreased physical activity, isolated spasms, ataxia, head bobbing, ≥5: Soft feces, watery stool, atrophy of pancreatic acinus/vacuolization of cytoplasm/single cell necrosis, etc.[l] ≥15: Abnormalities in telemetry (increased heart rate, decreased blood pressure, transient prolongation in PR interval/QT interval/QTc interval),[m] atrophy of small and large intestines 50: Decreased body weight, vomiting, watery stools, increased serum amylase/lipase/cholesterol, localized ulcer of stomach, dyeable macrophages in thymus	15[d]	Reference 4.2.3.2.4
Male and female dogs (beagle)	p.o.	4 weeks (BID) + withdrawal (4 weeks)	0[a], 2, 7, 25	≥2: Soft feces, mucous stools, watery stool, effects on erythrocyte parameters (decreased red blood cell count/hemoglobin concentration, etc.), effects on leucocyte parameters (increased white blood cell count/lymphocyte count, etc.), increased fibrinogen concentration, increased serum amylase/cholesterol/globulin/ALP, decreased serum albumin/decreased A/G ratio, lung inflammation,[n] atrophy of pancreatic acinus,[o] extramedullary hematopoiesis in spleen, increased cellularity of granulocytes in bone marrow, vacuolization of epididymis ≥7: Increased serum Na/Cl, decreased serum Ca, increased liver weight 25: Vomiting, decreased body weight, soiled fur/anogenital organs, increased platelet count, decreased thymic weight/decreased cellularity of lymphocytes, extramedullary hematopoiesis in liver Reversible[h]	7[d]	4.2.3.2.7
Male and female dogs (beagles)	p.o.	13 weeks (BID)	0[a], 2, 7, 25	Moribund sacrifice: 25 (1 of 3 males, 2 of 3 females), tremor, dyspnoea, inflammation of mandible/lung ≥2: Vomiting, watery stools, increased reticulocyte count, effects on leucocyte parameters (increased white blood cell count/neutrophil count, etc.), increased fibrinogen concentration, increased liver weight, bile duct hyperplasia,[p] findings on lymph nodes (enlargement/inflammation/increased plasma cells in medulla, etc.), small thymus/decreased weight/decreased cellularity of lymphocytes ≥7: Decreased physical activity,[q] hypotonia,[q] abnormal/ataxic gait,[q] increased body weight, changes in skin (redness/swelling/crust/ulcer/inflammation, etc.),[r] effect on erythrocyte parameters (decreased red blood cell count/hemoglobin concentration, etc.), increased platelet count, increased serum ALP/triglycerides/globulin, decreased serum albumin/decreased A/G ratio, pigmentation of	7[d]	4.2.3.2.8

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
				Kupffer's cells in liver, extramedullary hemopoiesis/pigmentation in spleen, subacute inflammation of lung/pleura,[n] effects on male reproductive organs (decreased testicular weight/degeneration/atrophy of seminiferous tubules, decreased epididymal weight/decreased sperm count/azoospermia, etc.) 25: Abdominal distention, darkening of oral cavity/localized compression/inflammation, increased serum albumin, increased weight of spleen, lung, and adrenals, abnormal lung color/stiffness, tracheal inflammation, gallbladder mucosa bleeding, atrophy of gastric mucosa, small intestinal villi/atrophy/degeneration/crypt hyperplasia/subacute inflammation		

a) Only the vehicle was administered.
b) Because of no change in functional parameters did not change, lorlatinib was not considered to have affected the heart directly, and the observed findings were recognized as compensatory changes in response to hypertension and with little toxicological significance.
c) A functional observation battery conducted on Day 3 and 13 showed effects on CNS (e.g., abnormal behaviors, involuntary movement).
d) The findings at doses below the NOAEL were considered of little toxicological significance, judging from their natures and seriousness.
e) The findings in the ≤4 or ≤8 mg/kg/day group were considered of little toxicological significance because they were minimal or mild, and no abnormality in pancreatic exocrine function was observed in these dose groups.
f) The findings in the ≤4 or ≤8 mg/kg/day group were considered of little toxicological significance because they were minimal or mild, and no immune suppression-related findings were observed in these dose groups.
g) The findings were observed only in males in all of the pertinent groups.
h) Including the reversible findings.
i) Findings in all of the pertinent groups were minimal or mild, and no immune suppression-related findings were observed. Therefore, these findings were considered of little toxicological significance.
j) Epithelial inflammation and dermal fibrosis in the 4 or 8 mg/kg/day groups were mild changes observed only in 1 female, and they were thus considered of little toxicological significance.
k) These were minimal changes observed in only 1 female in the 4 or 8 mg/kg/day group, and considered of little toxicological significance, judging from the extent of the change in urinalysis in the pertinent dose groups (minimal decrease in urine pH and ketone bodies, mild increase in urine volume).
l) The findings in the ≤15 mg/kg/day groups were minimal or mild, and no abnormality in pancreatic exocrine function was observed in these dose groups. Therefore, the findings were considered of little toxicological significance.
m) Since the findings were unrelated to t_{max}, their relationship to lorlatinib is unclear. Also, they were considered of little toxicological significance because no abnormality was observed in electrocardiography in dogs in the 13-week repeated-dose toxicity study.
n) The findings in the ≤7 mg/kg/day groups were minimal or mild and localized, and no effect on clinical signs related to respiratory function was observed, from which the findings were considered of little toxicological significance.
o) The findings were minimal or mild, and no abnormality in pancreatic exocrine function was observed, and they were thus considered of little toxicological significance.
p) The findings in the ≤7 mg/kg/day groups were minimal or mild, and no increase in serum total bilirubin, AST, or ALT was observed at these doses. They were thus considered of little toxicological significance.
q) The findings in the 7 mg/kg/day group were sporadic and transient, and no effect was observed on food consumption or water intake in these dose groups. They were thus considered of little toxicological significance.
r) The findings in any dose groups were minimal or mild and localized, and they were thus considered of little toxicological significance.

5.3 Genotoxicity

In vitro genotoxicity studies consisted of a bacterial reverse mutation assay and a micronucleus assay in mammalian cells, and a micronucleus assay in rodents was conducted as an *in vivo* genotoxicity study (Table 19). Both *in vitro* and *in vivo* micronucleus assays showed positive results, and lorlatinib was identified as genotoxic. The applicant explained that the positive results with micronucleus assays were due to an aneuploidy-inducing effect of lorlatinib.

Table 19. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentration (μg/plate, μg/mL, or μmol/L[a]) Dose (mg/kg/day)	Results	Attached document CTD
In vitro	Bacterial reverse mutation assay (Ames assay)	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	S9-/+	0,[b] 100, 250, 1000, 2500, 5000	Negative	4.2.3.3.1.1
		Escherichia coli WP2 *uvrA* pKM101				
	Micronucleus assay in mammalian cells	Human lymphoblast TK6 cell line	S9-/+ (4 hours)	0,[b] 293, 345, 406	Positive (≥293)	4.2.3.3.1.3
			S9- (27 hours)	0,[b] 18.5, 25.6, 57.8	Negative[c]	
	Micronucleus assay using fluorescent *in situ* hybridization method	Human lymphoblast TK6 cell line	S9-/+ (4 hours + 40-hour recovery period)	1000	Positive centromere signal in ≥75% of micronuclei[d]	Reference 4.2.3.3.1.2
			S9- (27 hours)	269	Positive centromere signal in ≥70% of micronuclei[d]	
In vivo	Micronucleus assay in rodents	Male and female rat (Wistar Han) bone marrow		0,[e] 10, 30, 100 (p.o., 2 days)	Positive (100)[f]	4.2.3.3.2.1

a) In the micronucleus assay using the fluorescent *in situ* hybridization method, the concentration is expressed in μmol/L.
b) Only the vehicle (DMSO) was added.
c) A statistically significant increase in micronucleus count was observed at 25.6 μg/mL. However, the increase was within the historical range and considered of little toxicological significance.
d) A statistically significant increase in micronucleus count was observed as compared with the control group. The assay was thus considered an appropriate testing method for investigating the mechanism of micronuclei induction.
e) Only the vehicle was administered.
f) A statistically significant increase in micronucleus count was observed in the ≤30 mg/kg/day groups as well. However, the increase was within the historical range and thus considered of little toxicological significance.

5.4 Carcinogenicity

Because lorlatinib is an antineoplastic drug intended to treat patients with advanced cancer, no carcinogenicity study was conducted.

5.5 Reproductive and developmental toxicity

Because lorlatinib is an antineoplastic drug intended to treat patients with advanced cancer, studies on fertility and early embryonic development to implantation were not conducted.

The applicant's explanation about the effect of lorlatinib on fertility, based on the effect on male and female reproductive organs in repeated-dose toxicity studies [see Section 5.2]:

- Effects on male reproductive organs (decreased testicular weight, degeneration and atrophy of seminiferous tubules, tissue fragments in epididymal lumen, and decreased sperm count) were observed at a dose equivalent to 4.2 times the clinical exposure[18)] in rats and at a dose equivalent to below the clinical exposure[18)] in dogs. These results suggest the possibility that lorlatinib affects male fertility in humans as well. Accordingly, this possibility and the observed effects on male reproductive organs in rats and dogs will be communicated to healthcare professionals through the package insert in an appropriate manner.

- In rats, effects on female reproductive organs (uterine atrophy and uterine cervical inflammation) were observed at a dose equivalent to 22 times the clinical exposure.[18)] However, the changes were

minimal and reversible, and no other effect on female reproductive organs was observed in rats or dogs. Lorlatinib is thus unlikely to affect female reproductive organs in humans.

Studies on embryo-fetal development were conducted in rats and rabbits (Table 20). Both rats and rabbits showed increased embryonic loss rate, decreased surviving fetuses, and complex malformations (gastroschisis, dilatation of lateral ventricle, etc.) and visceral anomalies (malposition and malformation of the kidney, etc.).

The exposure to unbound lorlatinib in plasma (C_{max} and AUC_{24h}) at the NOAEL for embryo-fetal development (1 mg/kg/day in rats,[19] 1 mg/kg/day in rabbits) was 82.4 ng/mL and 2060 ng·h/mL, respectively, in rats and 13.5 ng/mL and 195 ng·h/mL, respectively, in rabbits. All values were equal to or lower than the clinical exposure.[18]

[19] In rats, the NOAEL for embryo-fetal development was <1 mg/kg/day. Therefore, the minimum toxicity dose was used instead.

Table 20. Reproductive and developmental toxicity studies

Study type	Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings[b)]	NOAEL (mg/kg/day)	Attached document CTD
Embryo-fetal development study	Female rats (Wistar Han)	p.o.	Gestation day 6 to 17 (BID)	0,[a)] 1, 4, 15, 30	Maternal animals: Moribund sacrifice: 30 (3 of 6 animals), progression of clinical signs, decreased body weight and food consumption ≥15: Hypersensitive reaction, dehydration-like symptom, enlarged spleen 30: Abnormal gait, decreased physical activity, hunchback position, abnormal fur (piloerection, yellow fur, etc.), eyelid closure, yellowing of tongue, spread/stiff/swollen hindlimb, vaginal secretion Fetuses: ≥1: Increased embryonal loss rate before and after implantation, increased early resorptions, increased late resorptions,[c)] decreased live fetuses,[c)] decreased fetal weight,[c)] complex malformations (abnormal rotation of hindlimb, polydactylia of left forelimb, gastroschisis),[c)] abnormalities of visceral organs (small kidney, aortic arch interruption)[c)] 4≥: Total embryonal loss	Maternal animals (general toxicity): 4 Embryo-fetal development: <1	4.2.3.5.2.3

Embryo-fetal development study	Female rabbits (NZW)	p.o.	Gestation day 7 to 19 (BID)	0,[a] 1, 4, 15, 30	Maternal animals: Moribund sacrifice: 15, 30 (4 of 8 animals in each group), abortion, decreased body weight and food consumption, loss of fur, decreased feces, etc. ≥1: Increased body weight gain, liquid stool ≥4: Soft feces, decreased grooming frequency Fetuses: ≥4: Increased embryonal loss rate before and after implantation, increased early resorptions, increased late resorptions,[d] decreased live fetuses,[d] complex malformations (dome-shaped head due to enlarged lateral ventricle and third ventricle, abduction of forelimb, overdistension of fore limb),[d] abnormalities of visceral organs (malposition/malformation of the kidney, subclavian artery behind trachea)[d] ≥15: Total embryonal loss	Maternal animals (general toxicity): 4[e] Embryo-fetal development: 1	4.2.3.5.2.4

a) Only the vehicle (acidified deionized water) was administered.
b) No skeletal examination was conducted.
c) Because total loss of embryos occurred in the ≥4 mg/kg/day groups, these changes were identified only in the 1 mg/kg/day group.
d) Because total loss of embryos occurred in the ≥15 mg/kg/day groups, these changes were identified only in the 4 mg/kg/day group.
e) The findings in the ≤4 mg/kg/day groups were mild and were therefore considered of little toxicological significance.

5.6 Local tolerance

Local tolerance studies were conducted (Table 21). No findings suggestive of irritability were observed. Lorlatinib was considered unlikely to have an irritant effect on intravenous or perivascular tissues.

Table 21. Local tolerance studies

Test system	Site of application	Testing method	Main findings	Attached document CTD
Female rabbits (NZW)	Intravenous	Single dose of 1 mL of lorlatinib solution (0.2 mg/mL)	None	Reference 4.2.3.6.1
	Perivascular	Single dose of 0.05 mL of lorlatinib solution (0.2 mg/mL)	None	

5.7 Other studies

5.7.1 Photosafety

Because lorlatinib has an absorption band between 290 and 700 nm and has affinity to pigmented tissues, a phototoxicity study was conducted in rats (Table 22). There were no findings suggestive of phototoxicity, indicating that lorlatinib is unlikely to be phototoxic.

Table 22. Phototoxicity study

Type of study	Test system	Method	Main findings	Attached document CTD
Phototoxicity study	Female rats (Long-Evans)	Lorlatinib (0[a] 1, 4, or 15 mg/kg/day) was administered orally for 3 days. Approximately 1 hour after the last dose, ultraviolet A (UV-A), ultraviolet B (UV-B), and visible light were irradiated to the skin and eyes for 42 to 44 minutes. Clinical signs and skin condition score were evaluated at 1 and 4 hours, and 1, 2, and 3 days after the irradiation. Body weight measurement, ophthalmological test, and ocular histopathologic examination were performed 3 days after the irradiation.	No abnormality was observed in the skin or eyes.	4.2.3.7.7.3

a) Only vehicle was administered.

5.7.2 Toxicity of impurities

Impurities (Related Substances A, B, C, and D) that are present at levels exceeding the qualification threshold specified in ICH guidelines Q3A and Q3B were evaluated for general toxicity and genotoxicity.

No new general toxicity was observed in tests with each impurity spiked (Table 23). The impurities were not judged to pose safety problems when not exceeding the specified upper limit level.

Genotoxicity of the impurities was evaluated based on the results of the *in silico* (quantitative) structure-activity relationship ([Q]SAR) and genotoxicity studies (Table 24). The impurities contained in lorlatinib were unlikely to have genotoxicity.

Table 23. General toxicity studies of impurities

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	Attached document CTD
Male and female rats (Wistar Han)	p.o.	4 weeks (BID)	0,[a] 2	In both the group treated with lorlatinib alone and the groups treated with lorlatinib with each impurity spiked,[b] effects on hematological and clinical chemistry results (increased leukocyte parameter values, increased cholesterol, etc.) and increased liver weight were observed. Spiking with impurities did not cause any new toxicity nor aggravation.	4.2.3.7.6.9

a) Only the vehicle (ultra-pure water) was administered.
b) In each group, lorlatinib was spiked with (a) Related Substance A ([redacted]%) and Related Substance B ([redacted]%), (b) Related Substance C ([redacted]%), and (c) Related Substance D ([redacted]%), respectively.

Table 24. Genotoxicity studies of impurities

Study type		Test system	Metabolic activation (treatment)	Concentration (μg/plate)	Results	Attached data CTD
In vitro	Bacterial reverse mutation assay on Related Substance C	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* WP2 *uvrA* pKM101	S9-/+	0,[a] 15, 50, 150, 500, 1500, 5000	Negative	Reference 4.2.3.7.6.2
	Bacterial reverse mutation assay on Related Substance E	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	S9-	0[a], 15, 50, 150, 500, 1500[b)c)], 5000[b)c)]	Negative	Reference 4.2.3.7.6.3
		Escherichia coli WP2 *uvrA* pKM101	S9+	0[a], 15, 50, 150, 500,[b)c)] 1500,[b)c)] 5000[b)c)]		
	Bacterial reverse mutation assay on Related Substance F	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* WP2 *uvrA* pKM101	S9-/+	0,[a] 15, 50, 150, 500, 1500, 5000[b)]	Negative	Reference 4.2.3.7.6.4
	Bacterial reverse mutation assay on Related Substance G	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* WP2 *uvrA* pKM101	S9-/+	0,[a] 492, 878, 1568, 2800, 5000	Negative	4.2.3.7.6.6
	Bacterial reverse mutation assay on Related Substance H	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* WP2 *uvrA* pKM101	S9-/+	0,[a] 154, 275, 492, 1180,[b)] 2800[b)d)]	Negative	4.2.3.7.6.7
	Bacterial reverse mutation assay on Related Substance I	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* WP2 *uvrA* pKM101	S9-/+	0,[a] 100, 333, 1000, 3330, 5000	Negative	4.2.3.7.6.8

a) Only the vehicle (DMSO) was added.
b) Precipitation of the test substance was observed.
c) Cytotoxicity was observed.
d) Due to the extensive precipitation of the test substance, reverse mutant colonies could not be counted.

5.7.3 Toxicity of metabolites

PF-06895751, the main metabolite of lorlatinib in human, was subjected to *in vitro* bacterial reverse mutation and micronucleus assays in mammalian cells (Table 25). The results were negative, and it was concluded that PF-06895751 is unlikely to be genotoxic.

Table 25. Toxicity studies of metabolite

Assay		Test system	Metabolic activation (treatment)	Concentration (μg/plate, μg/mL)	Results	Attached document CTD
In vitro	Bacterial reverse mutation assay on PF-06895751	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 *Escherichia coli* WP2 *uvrA* pKM101	S9-/+	0,[a] 100, 250, 1000, 2500, 5000	Negative	4.2.3.7.6.10
	Micronucleus assay on PF-06895751 in human lymphoblast	Human lymphoblast cell line TK6	S9-/+ (4 hours) S9- (27 hours)	118, 147, 184	Negative	4.2.3.7.6.11

a) Only the vehicle (DMSO) was added.

5.R Outline of the review conducted by PMDA

Based on the data submitted and the discussions in the following subsections, PMDA concluded that the applicant's explanations about the toxicity of lorlatinib are acceptable.

5.R.1 Inflammation of skin, lung, etc.

The applicant explained, in light of the following observations, that the inflammation of skin, lung, etc. observed in the repeated-dose toxicity studies of lorlatinib is unlikely to pose safety problems in clinical use from the toxicological point of view:

- Inflammation was observed in the skin and uterine cervix of rats and the lymph nodes, skin, lung, trachea, oral cavity, and gastrointestinal tract of dogs. The inflammation affected white blood cell parameters (increased white blood cell count, increased lymphocyte count, etc.) and increased cellularity in lymph nodes and bone marrow. The affected sites are bacterial infection-prone and the inflammation could have been due to decreased local immune response, but the exact mechanism of inflammation is unclear. Lorlatinib caused atrophy, decreased weight, and decreased cellularity in thymus in rats and dogs, but these findings are unlikely to be related to inflammation because the involvement of acquired immunity is limited in the early stage of localized bacterial infection.

- A 13-week repeated-dose study administering lorlatinib was conducted in rats and dogs. Over the long time period, inflammation was observed in skin and uterine cervix of rats and in lymph nodes, skin, lung, trachea, oral cavity, and gastrointestinal tract of dogs, but was slight or mild in most of the affected animals. Inflammation-related findings attributed to the toxicity of lorlatinib, such as moderate or severe inflammation, were observed at doses equivalent to 22 times (inflammation of skin in rats) or 5 times (inflammation of lung and oral cavity in dogs) the clinical exposure.[18)] In addition, moderate inflammation of pancreas was observed in rats at the dose equivalent to 7.6 times the clinical dose[18)] accompanied by the atrophy of acinar cells and increased lipase and amylase.

- ALK-TKIs other than lorlatinib also caused inflammation. For example, ceritinib caused inflammation of extrahepatic bile duct in rats and monkeys (Review Report on Zykadia capsules 150 mg dated March 3, 2016). However, no consistent tendency was observed in the site of the inflammation.

PMDA's view:

Given the severity of inflammation in the toxicity studies, comparison with the clinical exposure, occurrences of inflammatory changes in the clinical studies, etc., the inflammation observed in rat pancreas and dog lung is a risk warranting caution in clinical use of lorlatinib [see Sections 7.R.3.5 and 7.R.3.7].

5.R.2 Bile duct hyperplasia

The applicant's explanation about the bile duct hyperplasia observed in the repeated-dose toxicity studies of lorlatinib:

- In light of the observations that lorlatinib activates pregnane X receptor (PXR) [see Section 6.R.3] and that PXR activation triggers the inhibition of bile acid metabolism (e.g., *Drug Metab Rev*.

2013;45:145-55), bile duct hyperplasia may possibly be a change secondary to the change in the bile acid metabolism.

- Given the following observations, bile duct hyperplasia is unlikely to pose safety problems in clinical use of lorlatinib.
  (a) (i) Lorlatinib and its main metabolite were negative for bacterial reverse mutation assay [see Sections 5.3 and 5.7.3]. (ii) Although lorlatinib was positive for micronucleus assay [see Section 5.3], bile duct hyperplasia is unlikely to be attributable to the genotoxicity of lorlatinib, and lorlatinib is unlikely to be carcinogenic in clinical use, given the following facts:
    - The positive results of the micronucleus assay are considered attributable to the aneuploidy induction.
    - Bile duct hyperplasia occurred at exposure to unbound lorlatinib in plasma lower than that (C_{max}, 2180 ng/mL; AUC_{24h}, 31,600 ng·h/mL) at the NOAEL in the *in vivo* micronucleus assay (30 mg/kg/day).
    - No cellular atypia was observed in hyperplastic epithelial cells.

  (b) In the clinical studies, increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) occurred and were possibly related to bile duct hyperplasia [see Section 7.R.3.6], but most of the events were Grade ≤2.

PMDA's view:
The applicant's above explanation is acceptable from the toxicological aspect. The safety of lorlatinib in clinical use is described in Section 7.R.3.6.

5.R.3 Lorlatinib administration in pregnant or possibly pregnant women

PMDA asked the applicant to explain treatment with lorlatinib in pregnant women or women who may possibly be pregnant.

The applicant's explanation:
In the studies on the effect of lorlatinib on embryo-fetal development of rats and rabbits, increased embryonic loss rate, decreased surviving fetuses, complex malformations, visceral anomalies, etc. were observed at doses equivalent to or below the clinical exposure.[18)] In rats, the NOAEL on embryo-fetal development was not determined [see Section 5.5]. These results suggest that lorlatinib may possibly affect fetuses of pregnant women or women who may possibly be pregnant. However, relapsed NSCLC is a life-threatening disease, and the administration of lorlatinib to pregnant women or women who may possibly be pregnant is allowed only when the expected therapeutic benefit outweighs the possible risks associated with the treatment and the possible impact of lorlatinib on the fetus is fully explained to the patient and her family members. Lorlatinib is not only teratogenic but also genotoxic [see Section 5.3]. The results of the studies on the effect of lorlatinib on embryo-fetal development and the genotoxicity studies will be communicated through the package insert, with cautionary advice that (a) women of childbearing potential and (b) male patients who have women of childbearing potential must take appropriate contraceptive measures during lorlatinib treatment and for a certain period after the last dose.

PMDA accepted the applicant's explanation.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Oral formulations of lorlatinib are available in tablets (containing maleate [Crystalline Form 1], acetic acid solvate [Crystalline Form 3], and free base [Crystalline Form 7]), oral solution, and oral solution containing ^{14}C-lorlatinib. PK, etc. of lorlatinib was investigated using these formulations and lorlatinib injection (Table 26). The proposed commercial formulations are 25 and 100 mg tablets.

Table 26. Formulations used in clinical studies

Formulation	Study
Simple oral solution containing ^{14}C-lorlatinib (acetic acid solvate [Crystalline Form 3])	Foreign phase I study (Study 1004)
Simple oral solution (free base [Crystalline Form 7])	Foreign phase I study (Study 1008)
Injection (free base [Crystalline Form 7])	Foreign phase I study (Study 1007)
Simple tablets (maleate [Crystalline Form 1]) (100 mg)	Foreign phase I study (Study 1005)
Tablets (acetic acid solvate [Crystalline Form 3]) (5, 25, and 100 mg)*	Phase I part of global phase I/II study (Study 1001), foreign phase I study (Study 1005)
Simple tablets (free base [Crystalline Form 7]) (100 mg)	Foreign phase I study (Study 1005)
Clinical study tablets (free base [Crystalline Form 7]) (25 mg)	Phase II of global phase I/II study (Study 1001), foreign phase I study (Studies 1007, 1008, 1011, 1012, and 1016)
Commercial image tablets (free base [Crystalline Form 7]) (25, 50, and 100 mg)	Foreign phase I study (Study 1016)

* 5 and 25 mg tablets were used in Study 1001, and 100 mg tablets in Studies 1001 and 1005.

6.1.1 Assay

The amount of lorlatinib in human plasma and urine was determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation was 2.50 ng/mL in both types of samples.

6.1.2 Foreign clinical studies

6.1.2.1 Foreign phase I study (CTD 5.3.1.1.2, Study 1007 [June to September 2016])

A 2-treatment, 2-period cross-over study was conducted in 11 healthy adults (all included in the PK analysis) to investigate the absolute BA. A single dose of lorlatinib was administered orally (100 mg) or intravenously (50 mg), with a ≥10-day washout period between treatment periods.

Absolute BA [90% CI] of lorlatinib calculated from AUC_{inf} was 80.8% [75.7%, 86.2%].

6.1.2.2 Foreign phase I study (CTD 5.3.1.2.1, Study 1016 [November 2016 to February 2017])

A 4-treatment, 4-period cross-over study was conducted in 20 healthy adults (all included in the PK analysis) in order to investigate the bioequivalence between commercial image tablets (25, 50, and 100 mg) and clinical study tablets (free base [Crystalline Form 7]) (25 mg). A single dose of lorlatinib (100

mg) was administered orally in the fasting state,[20] with a ≥10-day washout period between treatment periods.

The geometric mean ratio [90% CI] of C_{max} and AUC_{last} of lorlatinib after the administration of (a) 25 mg, (b) 50 mg, and (c) 100 mg commercial image tablets relative to those after the administration of clinical study tablets was (a) 1.07 [0.96, 1.18] and 1.01 [0.97, 1.04], (b) 1.01 [0.92, 1.12] and 1.01 [0.97, 1.04], and (c) 1.07 [0.97, 1.18] and 1.04 [1.01, 1.08], respectively, all which met the criteria for bioequivalence (0.80-1.25).

The applicant explained that the above results demonstrated the bioequivalence between the commercial image tablets (25, 50, and 100 mg) and the clinical study tablets (free base [Crystalline Form 7]) (25 mg).

6.1.2.3 Foreign phase I study (CTD 5.3.1.1.3, Study 1008 [December 2015 to April 2016])

A cross-over study was conducted in 27 healthy adults (all included in the PK analysis) to investigate the effect of food and rabeprazole sodium (rabeprazole) on the PK of lorlatinib. A single dose of lorlatinib (100 mg) was administered orally in the fasting state[20] or after the consumption of a high-fat meal (with lipids accounting for approximately 50% of the total calorie [1000 kcal]) or, alternatively, a single dose of lorlatinib (100 mg) was administered orally in the fasting state[20] after multiple oral doses of rabeprazole (20 mg) QD from 5 until 1 day before the administration of lorlatinib. A ≥10-day washout period was allowed between the treatment periods.

The geometric mean ratio [90% CI] of C_{max} and AUC_{inf} following the administration after a high-fat meal relative to that following the administration under fasting conditions was 0.91 [0.85, 0.97] and 1.05 [1.01, 1.08], respectively. Based on the above results, the applicant explained that lorlatinib may be administered regardless of food consumption.

The geometric mean ratio [90% CI] of C_{max} and AUC_{inf} of lorlatinib following the concomitant use with rabeprazole relative to that following the administration of lorlatinib alone was 0.71 [0.66, 0.76] and 1.01 [0.98, 1.04], respectively. Although rabeprazole reduced C_{max} of lorlatinib, the efficacy of lorlatinib did not show any tendency of difference between patients receiving drugs affecting intragastric pH, such as proton pump inhibitors (PPIs), and patients not receiving such drugs in Study 1001. The applicant explained that, given these observations, the concomitant use is unlikely to pose any clinical problem.

6.2 Clinical pharmacology

The PK of lorlatinib in healthy adults and patients with cancer was investigated in lorlatinib monotherapy as well as in combination therapy of lorlatinib with itraconazole or rifampicin.

[20] Lorlatinib was administered after a ≥10-hour fasting (overnight), followed by a ≥4-hour fasting.

6.2.1 Global clinical studies

6.2.1.1 Global phase I/II study (CTD 5.3.5.2.1, Study 1001 [ongoing since January 2014 (data cut-off March 15, 2017)])

An open-label, uncontrolled study was conducted in 334 patients with *ALK* or *ROS1* fusion gene-positive, relapsed NSCLC (55 patients in phase I, 54 patients included in the PK analysis; 279 patients in phase II, 277 patients included in the PK analysis) in order to investigate the PK, etc. of lorlatinib. Lorlatinib was administered according to the following dosage regimen in each 21-day treatment cycles, and plasma lorlatinib concentration was investigated (Table 27).

- Phase I
  A single dose of lorlatinib (10-200 mg) was administered orally at 7 days before the start of Cycle 1,[21)] followed by multiple oral doses QD from Day 1 of Cycle 1.

- Phase II
  A single dose of lorlatinib (100 mg) was administered orally at 7 days before the start of Cycle 1, followed by multiple oral doses QD from Day 1 of Cycle 1.

C_{max} and AUC of lorlatinib following the single-dose increased roughly dose-proportionally. C_{max} of lorlatinib in multiple administration increased roughly dose-proportionally, whereas AUC increased less than dose-proportionally. The applicant explained that the less than dose-proportional increase was due to the induction of lorlatinib-metabolizing enzymes during the multiple administration. The accumulation rate[22)] during 100 mg treatment was 1.07 in phase I and 1.08 in phase II.

21) In lorlatinib 25 and 150 mg groups, lorlatinib was not administered on 7 days before Cycle 1.
22) Ratio of AUC_{24h} on Day 15 in Cycle 1 to that on Day 7 in Cycle 1

Table 27. PK parameters of lorlatinib

	Dose (mg)	Day of measurement	n	C_{max} (ng/mL)	t_{max} [*1] (h)	AUC_{24h} (ng·h/mL)	AUC_{inf} (ng·h/mL)	$t_{1/2}$ [*2] (h)	CL/F (L/h)	V_z/F (L)
Phase I part	10	Day −7 in Cycle 1	3	50.8 (17)	1.98 (1.00, 2.97)	488.2 (21)	698.0[*3]	18.0[*3]	14.3[*3]	373[*3]
		Day 15 in Cycle 1	3	67.3 (18)	1.00 (1.00, 1.08)	752.1 (26)	-	-	13.3 (26)	-
	25	Day 1 in Cycle 1	3	149.2 (71)	2.00 (0.500, 2.05)	1387 (35)	-	-	-	-
		Day 15 in Cycle 1	3	138.1 (35)	1.00 (1.00, 2.00)	1701 (29)	-	-	14.7 (29)	-
	50	Day −7 in Cycle 1	2	390, 423	1.25 (0.500, 2.00)	3310, 3880	7210, 7240	16.6, 30.8	6.91, 6.94	166, 307
		Day 15 in Cycle 1	3	359.7 (27)	2.00 (1.92, 2.75)	3367 (39)	-	-	14.8 (39)	-
	75	Day −7 in Cycle 1	12	489.1 (45)	1.09 (0.500, 4.03)	3990 (55)	7663 (79)[*4]	27.2 ± 8.30[*4]	9.79 (79)[*4]	368 (54)[*4]
		Day 15 in Cycle 1	12	429.6 (48)	1.03 (0.500, 2.00)	4107 (53)	-	-	17. 7 (48)	-
	100	Day −7 in Cycle 1	16	595.5 (37)	1.96 (0.517, 4.33)	5110 (28)	8236 (25)[*5]	20.9 ± 5.03[*5]	12.1 (25)[*5]	356 (39)[*5]
		Day 15 in Cycle 1	16	550.2 (32)	1.13 (1.00, 4.00)	5121 (30)	-	-	19.5 (30)	-
	150	Day 1 in Cycle 1	3	760.0 (58)	1.05 (1.00, 3.00)	7474 (73)	-	-	-	-
		Day 15 in Cycle 1	3	541.0 (42)	1.30 (1.00, 24.0)	6157 (9)	-	-	24.4 (9)	-
	200	Day −7 in Cycle 1	3	1201 (19)	2.00 (1.18, 3.00)	11,410 (43)	18,340 (61)	19.8 ± 3.30	10.9 (61)	308 (41)
		Day 15 in Cycle 1	2	760, 1430	1.61 (1.22, 2.00)	4480, 12,900	-	-	15.5, 44.6	-
Phase II part	100	Day −7 in Cycle 1	19	695.2 (40)	1.15 (0.500, 4.02)	5308 (36)	9088 (35)	23.6 ± 9.37	11.0 (35)	352 (37)
		Day 15 in Cycle 1	22	576.5 (42)	1.96 (0.500, 22.7)	5650 (39)	-	-	17.7 (39)	-

Geometric mean (geometric coefficient of variation [%]) (individual values for n = 1 or 2); *[1] Median (range), *[2] Arithmetic mean ± SD, *[3] n = 1, *[4] n = 11, *[5] n = 15, -: Not calculated.

6.2.2 Foreign clinical study

6.2.2.1 Foreign phase I study (CTD 5.3.3.1.1, Study 1004 [September to November 2015])

An open-label, uncontrolled study was conducted in 6 healthy adults (all included in the PK analysis) to investigate the mass balance of lorlatinib. A single dose of ^{14}C-lorlatinib (100 mg) was administered orally, and radioactivity concentrations in plasma, urine, and feces were investigated.

Mainly the unchanged lorlatinib was detected in the plasma (44.4% of total radioactivity in plasma) up to 288 hours post-dose. Main metabolites were M1a (pyridine N-glucuronide of unchanged lorlatinib), M2a (pyrazole N-demethylate), M6 (pyridine N-oxide), and PF-06895751 (8.0%, 2.3%, 4.5%, and 21.0%, respectively, of total radioactivity in plasma).

The excretion rate of radioactivity (percentage relative to the administered radioactivity) within 288 hours post-dose was 88.6%, with the urinary and fecal excretion rate (percentage relative to the administered radioactivity) being 47.7% and 40.9%, respectively. Main radioactive compounds detected in feces within 192 hours post-dose were the unchanged lorlatinib and M2a (9.1% and 6.4%, respectively, of the administered radioactivity). Main radioactive compounds detected in urine within 168 hours post-dose were M1a and M6 (10.9% and 16.3%, respectively, of the administered radioactivity). The unchanged lorlatinib excreted in urine within 168 hours post-dose was <1% of the

administered radioactivity. Based on these results, the applicant explained that mainly the hepatic metabolism is involved in the clearance of lorlatinib, with renal excretion contributing to only a limited extent.

6.2.3 Drug-drug interactions

6.2.3.1 Interactions with rifampicin (CTD 5.3.3.4.1, Study 1011 [July to October 2016])

A 2-period, open-label study was conducted in 12 healthy adults (all included in the PK analysis) to investigate the effect of rifampicin (a CYP3A inducer) on the PK of lorlatinib. In Period 1, a single dose of lorlatinib (100 mg) was administered orally in on Day 1. In Period 2, rifampicin (600 mg) was administered orally QD from Day 1 to 12, and a single dose of lorlatinib (100 mg) was administered orally on Day 8. The washout interval between the treatment periods was ≥10 days.

The geometrical mean ratio [90% CI] of C_{max} and AUC_{inf} of lorlatinib following the concomitant use of lorlatinib with rifampicin (lorlatinib/rifampicin) relative to that following the lorlatinib monotherapy was 0.24 [0.22, 0.26] and 0.15 [0.13, 0.17], respectively.

Moderate or severe hepatic dysfunction[23)] was observed in all 12 subjects on Day 9 of Period 2. Therefore, rifampicin was discontinued on Day 10. None of the 12 subjects met Hy's law,[24)] and all recovered from the hepatic dysfunction.

6.2.3.2 Interactions with itraconazole (CTD 5.3.3.4.2, Study 1012 [August 2016 to May 2017])

A 2-period, open-label study was conducted in 16 healthy adults (all included in the PK analysis) in order to investigate the effect of itraconazole (a CYP3A inhibitor) on the PK of lorlatinib. In Period 1, lorlatinib (50, 75, or 100 mg) was administered orally in a single dose on Day 1. In Period 2, itraconazole (200 mg) was administered orally QD from Day 1 to 11, and lorlatinib (50, 75, or 100 mg) was administered orally in a single dose on Day 5. The washout interval between the treatment periods was ≥10 days.

Table 28 shows the PK parameters of lorlatinib obtained. The geometrical mean ratio [90% CI] of C_{max} and AUC_{inf} of lorlatinib following the concomitant use of lorlatinib with itraconazole (lorlatinib/itraconazole) relative to that following the lorlatinib (100 mg) monotherapy was 1.24 [1.10, 1.40] and 1.42 [1.29, 1.56], respectively. Based on the results, the applicant explained that cautionary advice should be given on the concomitant use of lorlatinib with a CYP3A inhibitor.

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23) The range of maximum AST and ALT levels in patients was 80 to 1307 and 118 to 1338 IU/L, respectively. AST and ALT exceeded 20 times the upper limit of normal (ULN) in 5 and 4 patients, respectively.

24) Defined according to "Guidance for industry. Drug-Induced Liver Injury: premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009."

Table 28. PK parameters of lorlatinib

Lorlatinib (mg)	Itraconazole	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{inf} (ng·h/mL)	$t_{1/2}$*2 (h)	CL/F (L/h)	V_z/F (L)
50	Concomitant use without	2	274, 219	1.00, 2.00	4280, 4900	20.2, 33.5	11.7, 10.2	341, 493
	Concomitant use with	2	339, 301	2.00, 2.00	6700, 8850	32.6, 50.0	7.46, 5.65	351, 408
75	Concomitant use without	2	441, 459	2.00, 1.02	6180, 5110	20.4, 17.5	12.1, 14.7	357, 371
	Concomitant use with	2	685, 732	1.00, 2.00	9290, 8300	18.1, 14.3	8.07, 9.04	211, 187
100	Concomitant use without	12	414 (24)	1.50 (1.00, 4.00)	7338 (37)	23.1 ± 4.88	13.6 (37)	444 (33)
	Concomitant use with	12	514 (24)	1.50 (1.00, 8.00)	10,400 (31)	29.8 ± 6.34	9.61 (31)	405 (25)

Geometric mean (geometric coefficient of variation [%]) (individual values for n = 2); *1 Mean (range), *2 Arithmetic mean ± SD

6.2.3.3 Interactions with midazolam (CTD 5.3.5.2.1, Substudy of Study 1001 [ongoing since January 2014 (data cut-off March 15, 2017)])

An open-label, uncontrolled study was conducted in 6 patients with *ALK* or *ROS1* fusion gene-positive advanced and/or recurrent NSCLC (all included in the PK analysis) in order to investigate the effect of lorlatinib on the PK of midazolam (a substrate of CYP3A). Lorlatinib (25 or 150 mg) was administered orally QD, and a single dose of midazolam (2 mg) was administered orally 7 days before the start of treatment and Day 15 of treatment with lorlatinib. Plasma concentration of midazolam in these patients was investigated.

The geometrical mean ratios [90% CI] of C_{max} and AUC_{inf} of midazolam following the concomitants use of midazolam with lorlatinib (25 mg)[25] to that following the midazolam monotherapy were 0.60 [0.37, 0.98] and 0.39 [0.26, 0.59], respectively.

These results and the results of the *in vitro* studies [see Section 4.5.2] suggested that lorlatinib induces CYP3A in clinical use. The applicant explained that this should be communicated to healthcare professionals.

6.2.4 Relationship between exposure and variation of QT/QTc interval

A relationship between plasma lorlatinib concentration and QT interval adjusted by Fridericia correction formula (QTcF) was investigated by the linear mixed-effects model using data obtained from 12 patients in whom plasma lorlatinib concentration was measurable during electrocardiogram in the foreign phase I study (Study 1012).

At the C_{max} of lorlatinib 100 mg obtained in phase II part of Study 1001 [see Section 6.2.1], difference from placebo in changes from baseline in QTcF (ΔQTcF) [95% CI] (ms) was estimated to be (a) −25.9 [−30.1, −21.3] following a single oral dose and (b) −21.4 [−24.9, −7.7] following repeated oral doses (QD).

[25] The ratio [90% CI] of the geometrical mean of the C_{max} of midazolam following the combined administration of midazolam and lorlatinib (150 mg) relative to that following the administration of midazolam alone was 0.50 [0.19, 1.26]. The geometrical mean of AUC_{inf} was not calculated because of n = 2.

Based on the above results, the applicant explained that QT interval prolongation is unlikely to occur in clinical use of lorlatinib.

6.2.5 Population pharmacokinetics (PPK) analysis

A population pharmacokinetics (PPK) analysis was performed using the non-linear mixed-effects model (software used, NONMEM Ver. 7.3.0), based on the PK data of lorlatinib (5806 measuring time points in 425 patients) obtained from foreign phase I studies (Studies 1004, 1005, 1007, 1008, 1011, and 1016) and a global phase I/II study (Study 1001). The PK of lorlatinib was described by a 2-compartment model with first and zero order absorption processes.

In this analysis, possible covariates for CL were age, sex, disease, genotype (CYP2C19, CYP3A5, or CYP2C9), total daily dose, race, serum albumin, alkaline phosphatase (ALP), total bilirubin, triglycerides, hepatic impairment,[26)] renal impairment,[27)] creatinine clearance (CrCL), and ALT. Possible covariates for volume of distribution of the central compartment (V_2) were age, sex, renal impairment, triglycerides, race, and CrCL. Possible covariates for absorption rate constant (K_a) were dietary conditions, dosage form (tablets [acetic acid solvate], tablets [free base], or injection), and concomitant use with a PPI. Possible covariates for relative bioavailability (F_{rel}) were dietary conditions, dosage form (tablets [acetic acid solvate], tablets [free base], or injection), concomitant use with a PPI, total daily dose, hepatic impairment, renal impairment, CrCL, ALT, and genotype (CYP2C19, CYP 3A5, or CYP2C9).

Serum albumin, CrCL, and total daily dose were identified as significant covariates for CL, and concomitant use with PPI as a significant covariate for K_a.

The applicant's explanation about the above results:

- The results suggested that, in the single oral dose or multiple oral QD doses of lorlatinib (100 mg), the estimated CL increases with an increase in serum albumin. However, the estimated CL in patients with a serum albumin level of 3.2 mg/dL and 4.6 mg/dL (10 and 90 percentile, respectively, of the data set used for the PPK analysis) was lower only by 5.3% and higher only by 4%, respectively, than the level in patients with a serum albumin level of 4.0 mg/dL (median value of the data set used for the PPK analysis). This indicates that the effect of serum albumin on CL is limited and thus the effect of serum albumin on the PK of lorlatinib is clinically insignificant.

- The estimated CL in the single oral dose or multiple oral QD doses of lorlatinib (100 mg) tended to decrease with increasing renal impairment assessed by CrCl. However, the distribution range of CL in patients with mild to moderate renal impairment overlapped with that in patients with normal renal function (Table 29). The effect of CrCL on the PK of lorlatinib is thus clinically insignificant.

- CL was suggested to increase with an increase in total daily dose. This is considered due to the increased amount of metabolic enzymes induced by lorlatinib.

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26) Classified according to US National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG).
27) Classified according to US Kidney Disease Outcomes Quality Initiative.

- K_a was suggested to decrease when a PPI is concomitantly administered. However, in Study 1001, there was no clear different tendency in the efficacy of lorlatinib between patients receiving a drug affecting intragastric pH, such as PPI, and patients not receiving such drug. The effect of concomitant use with a PPI on the PK of lorlatinib is considered clinically insignificant.

Table 29. CL classified by severity of renal impairment (L/h)

Severity of renal impairment*	n	Single dose	n	Multiple doses
Normal	226	9.80 (6.35, 17.09)	133	15.17 (10.15, 23.09)
Mild	120	8.04 (5.84, 11.42)	103	12.70 (9.33, 18.25)
Moderate	45	7.22 (5.38, 9.87)	41	11.61 (8.60, 15.77)
Severe	1	4.81	1	7.68

Median (range) (individual value for n = 1); * Normal, CrCL ≥90 mL/min; mild, CrCL ≥60 mL/min and <90 mL/min; moderate, CrCL ≥30 mL/min and <60 mL/min; severe, CrCL ≥15 mL/min and <30 mL/min.

6.2.6 Relationship of exposure to lorlatinib with efficacy and safety

6.2.6.1 Relationship between exposure and efficacy

Based on the data obtained from phase I part and phase II part (Cohorts 2-5) of Study 1001, a relationship between exposure to lorlatinib[28)] (AUC_{24h}, AUC [cumulative value of Cycle 1], C_{max} [Cycle 1], and plasma lorlatinib concentration [mean of Cycle 1, concentration before administration on Day 1 of Cycle 2]) and the overall response rate or response rate of intracranial lesion was investigated by population pharmacokinetic (PPK) and pharmacodynamic (PD) analyses. Results did not show any clear relationship between the exposure to lorlatinib and the overall response rate or response rate of intracranial lesion.

6.2.6.2 Relationship between exposure and safety

Based on the data obtained from phase I part and phase II part (Cohorts 1-6) of Study 1001, a relationship between exposure to lorlatinib[28)] (AUC_{ss}, AUC [after single-dose administration, cumulative value (Cycle 1, the cycle with event, the cycle before the occurrence of event, and 21 days during which the maximum total daily dose was administered at steady state), C_{max} (Cycle 1 and before the event), and plasma lorlatinib concentration (mean during Cycle 1, before administration on Day 16 of Cycle 1, and before administration on Day 1 of Cycle 2)]) and Grade ≥2 effect on mood, Grade ≥2 effect on speech, Grade ≥2 effect on cognition, Grade ≥3 hypercholesterolaemia, Grade ≥3 hypertriglyceridaemia, Grade ≥2 weight increase, and all adverse events[29)] of Grade ≥3 was investigated by the PPK and PD analyses. The results revealed the following significant relationship between the exposure and adverse events:

- The incidence of Grade ≥3 hypercholesterolaemia increases with increasing exposure to lorlatinib (C_{max} [before the event]).

- The incidence of Grade ≥3 adverse events was suggested to increase with increasing exposure to lorlatinib (AUC [cumulative value following 21-day administration at the maximum total daily dose at steady state]).

28) Estimated by the PPK analysis [see Section 6.2.5].

29) Adverse events to be analyzed were selected from among those observed in Study 1001 based on the seriousness, incidence (>10%), and the effect on RP2D of lorlatinib, etc.

6.2.7 Difference in PK between Japanese and non-Japanese patients

The applicant's explanation:

There is no clear difference in the PK of lorlatinib between Japanese and non-Japanese patients, based on the following results:

- In phase II part of Study 1001, there was no clear difference between Japanese and non-Japanese patients in the PK parameters of lorlatinib (100 mg) following a single oral administration or multiple oral QD administration (Table 30).

Table 30. PK parameters of lorlatinib

	Day of measurement	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{24h} (ng·h/mL)	CL/F (L/h)
Japanese	Day −7 of Cycle 1	4	783.2 (20)	2.50 (0.500, 4.02)	5913 (19)	10.18 (13)
	Day 15 of Cycle 1	7	591.1 (33)	2.00 (1.00, 3.08)	5233 (41)	19.11 (42)
Non-Japanese	Day −7 of Cycle 1	15	673.5 (43)	1.02 (0.500, 2.00)	5158 (39)	11.30 (41)*2
	Day 15 of Cycle 1	15	569.8 (46)	1.07 (0.500, 22.7)	5856 (39)	17.08 (39)

Geometric mean (geometric coefficient of variation [%]); *1 Median (range), *2 n = 12

- The PPK analysis did not identify race as a significant covariate for the PK parameters of lorlatinib [see Section 6.2.5].

6.R Outline of the review conducted by PMDA

Based on the data submitted and the results of the reviews in the following subsections, PMDA concluded that the applicant's explanations about the clinical pharmacology, etc. of lorlatinib are acceptable.

6.R.1 Administration in patients with hepatic impairment

The applicant's explanation about the administration of lorlatinib in patients with hepatic impairment:

Given the following observations, etc., the dose adjustment of lorlatinib is not necessary for patients with mild hepatic impairment. On the other hand, lorlatinib should be administered carefully to patients with moderate or severe hepatic impairment because of the lack of use experience in this patient group. A clinical study (Study 1009) is planned to be conducted in patients with moderate or severe hepatic impairment to investigate the PK of lorlatinib in this patient group.

- In the PPK analysis, neither ALT nor total bilirubin was identified as a significant covariate for the PK parameters of lorlatinib [see Section 6.2.5].

- In patients with normal hepatic function (Class A) and in patients with mild hepatic impairment[30] (Classes B1 and B2) in Study 1001, the incidence of (a) all-Grade adverse events, (b) Grade ≥3 adverse events, and (c) serious adverse events was (a) 96.7%, 100%, and 87.5%, (b) 41.3%, 50.0%, and 37.5%, and (c) 35.1%, 37.5%, and 25.0%, respectively, showing no clear difference in the

[30] Hepatic function was rated as normal (class A) if both total bilirubin and AST were below ULN, mild impairment (class B1) if total bilirubin was below ULN and AST was above ULN, and mild impairment (class B2) if total bilirubin was <1.0 to 1.5 times the ULN.

incidences of adverse events between patients with normal hepatic function and patients with mild hepatic impairment.

PMDA's view:
Taking account of the above explanation of the applicant and the observation that hepatic metabolism is mainly involved in the clearance of lorlatinib [see Section 6.2.2.1], the explanation of the applicant is acceptable. The results of Study 1009 should be communicated to healthcare professionals in an appropriate manner once available.

6.R.2 Administration of lorlatinib in patients with renal impairment

The applicant's explanation about the administration of lorlatinib in patients with renal impairment:
Given the following findings, renal impairment is unlikely to affect the PK of lorlatinib. A clinical study (Study 1010) is planned to be conducted in patients with severe renal impairment to investigate the PK of lorlatinib in this patient group.

- Renal excretion is suggested to have minimal contribution to the clearance of lorlatinib [see Section 6.2.2.1].

- The estimated CL following a single or multiple oral doses of lorlatinib (100 mg) tended to decrease with the increasing severity of renal impairment. However, the distribution of CL in patients with mild to moderate renal impairment overlapped with that in patients with normal renal function, which suggests that the effect of mild to moderate renal impairment on the PK of lorlatinib is clinically insignificant [see Section 6.2.5].

- In Study 1001, the incidence of (a) all-Grade adverse events in patients with normal renal function, and patients with mild, moderate, and severe renal impairment was, respectively, 95.7%, 97.5%, 100%, and 100%, (b) Grade ≥3 adverse events, respectively, 34.4%, 47.5%, 56.3%, and 100%, and (c) serious adverse events, respectively, 30.1%, 39.2%, 43.8%, and 0%, showing no clear difference between patients with normal renal function and patients with mild or moderate renal impairment, except Grade ≥3 and serious adverse events.

PMDA's view:
PMDA accepted the explanation of the applicant. Once available, the results of Study 1010 should be communicated to healthcare professionals in an appropriate manner.

6.R.3 Concomitant use with CYP3A inducers

The explanation's applicant about the concomitant use of lorlatinib with (a) rifampicin, (b) a potent CYP3A inducer other than rifampicin, and (c) a moderate or weak CYP3A inducer:

(a) In Study 1011, moderate or severe hepatic dysfunction occurred in all of the 12 patients receiving lorlatinib/rifampicin [see Section 6.2.3.1], suggesting the necessity of contraindicating the concomitant use of lorlatinib and rifampicin.

(b) The mechanism of hepatic dysfunction caused by the lorlatinib/rifampicin therapy is unclear. However, given the following facts, hepatic dysfunction may be caused also by the concomitant use of lorlatinib with a potent CYP3A inducer other than rifampicin. Therefore, the combination of lorlatinib and a non-rifampicin potent CYP3A inducer should also be contraindicated. In Study 1001, no hepatic dysfunction-related adverse events were reported by the 2 patients receiving lorlatinib and phenytoin (a potent CYP3A inducer) during the combination therapy.

- Lorlatinib has an equivalent level of PXR-activating effect to that of rifampicin,[31)] and there are clinical cases of hepatic dysfunction caused by the concomitant use of a PXR-activating drug (*Clin Pharmacokinet*. 2002;41:681-90, etc.).
- There is a correlation between CYP3A-inducing activity and the PXR-activating effect (*Drug Metab Dispos*. 2011;39:151-9).

(c) Given the following observations, it is unnecessary to contraindicate the concomitant use of lorlatinib with a moderate or weak CYP3A inducer. A clinical study is planned to be conducted to investigate the safety and PK in the concomitant use of lorlatinib with a moderate CYP3A inducer.

- In Study 1001, only 3 patients received lorlatinib in combination with a moderate CYP3A inducer (modafinil). The small number of patients experiencing the combination therapy precludes an immediate conclusion on the safety of combination of lorlatinib with a moderate CYP3A inducer. Of the 3 patients, 1 patient showed increased hepatic enzyme levels supposedly caused by the combination therapy, but the adverse event was mild and transient.
- In Study 1001, hepatic enzyme levels increased in 25 of 85 patients receiving lorlatinib (100 mg) QD in combination with a weak CYP3A inducer However, the event of most of affected patients was Grade ≤2.

PMDA's view:

PMDA accepted the applicant's explanation (a) about the lorlatinib/rifampicin therapy. Meanwhile, the contraindication of the concomitant use of lorlatinib with a potent CYP3A inducer other than rifampicin is inappropriate. Considering an unknown mechanism of lorlatinib/rifampicin-induced hepatic dysfunction and the occurrence of adverse events following the combination therapy with a CYP3A inducer in Study 1001, the explanation about the contraindication is less than convincing.

At the same time, a concomitant CYP3A inducer was shown to decrease exposure to lorlatinib, and thus the use of the combination therapy should be avoided wherever possible [see Section 6.2.3.1]. The results of the clinical study on the safety and PK of the combination therapy of lorlatinib with a moderate CYP3A inducer should be provided to healthcare professionals in an appropriate manner as soon as available.

31) Human hepatocytes were incubated with (a) lorlatinib (0.01-100 μmol/L) or (b) rifampicin (0.1-30 μmol/L) at 37°C for 24 hours, and PXR activity was investigated. EC_{50} and E_{max} were (a) 2.85 μmol/L and 13.8 times the baseline, respectively and (b) 2.76 μmol/L and 13 times the baseline, respectively.

6.R.4 Concomitant use with CYP3A inhibitors

The applicant's explanation about the concomitant use of lorlatinib with a CYP3A inhibitor:
Given the following observations, the "Precautions for Dosage and Administration" section should advise that the dose of lorlatinib be reduced to 75 mg when used with a potent CYP3A inhibitor, while dose adjustment is unnecessary when lorlatinib is combined with a moderate or weak CYP3A inhibitor.

- Based on the results of Study 1012, exposure to lorlatinib following the concomitant use of lorlatinib (75 mg) with a potent CYP3A inhibitor was estimated to be similar to that following the administration of lorlatinib (100 mg) alone [see Section 6.2.3.2].

- Based on the results of Study 1012, exposure to lorlatinib following the concomitant use of lorlatinib (100 mg) with a moderate or weak CYP3A inhibitor was lower than that following the administration of lorlatinib (150 mg) alone that led to treatment interruption or dose reduction [see Section 7.R.5.1].

PMDA's view:
A concomitant CYP3A inhibitor increased exposure to lorlatinib [see Section 6.2.3.2], suggesting the possibility that the dose of lorlatinib be reduced when used with a CYP3A inhibitor. Therefore, the use of a CYP3A inhibitor with lorlatinib should be avoided wherever possible. When there is no alternative, the combination therapy must be given probably with a reduced dose of lorlatinib, and patients must be closely monitored for adverse events. There are no clinical study data available on the efficacy or safety of lorlatinib at an adjusted dose used with a potent CYP3A inhibitor, and therefore, the optimal dose of lorlatinib in combination with a potent CYP3A inhibitor remains unknown at present, and there is no need to give any cautionary advice on the specific dose.

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

The applicant submitted the results from 1 global phase I/II study for efficacy and safety evaluation as shown in Table 31. The applicant also submitted the results of 7 foreign phase I studies shown in Table 31 as reference data.

Table 31. List of clinical studies on efficacy and safety

Data category	Region	Study ID	Phase	Study population	Number of enrollments	Dosage regimen[*3]	Main endpoint
Evaluation	Global	1001	I/II	Patients with NSCLC [Phase I] *ALK* or *ROS1* fusion gene-positive patients [Phase II] *ALK* or *ROS1* fusion gene-positive patients (a) Cohort 1: *ALK* fusion gene-positive patients without prior chemotherapy[*1] (b) Cohort 2: *ALK* fusion gene-positive patients with disease progression after treatment with crizotinib (c) Cohort 3A: *ALK* fusion gene-positive patients with disease progression after treatment with crizotinib and 1 or 2 chemotherapies (d) Cohort 3B: *ALK* fusion gene-positive patients with disease progression after treatment with an ALK-TKI other than crizotinib[*2] (e) Cohort 4: *ALK* fusion gene-positive patients with disease progression after treatment with 2 ALK-TKIs[*2] (f) Cohort 5: *ALK* fusion gene-positive patients with disease progression after treatment with 3 ALK-TKIs[*2] (g) Cohort 6: *ROS1* fusion gene-positive patients	[Phase I] 55 [Phase II] 276 (a) 30 (b) 27 (c) 32 (d) 28 (e) 66 (f) 46 (g) 47	[Phase I] Lorlatinib was administered orally QD at 10, 25, 50, 75, 100, 150, or 200 mg, or BID at 35, 75, or 100 mg. [Phase II] Lorlatinib (100 mg) was administered orally QD.	Efficacy Safety PK
Reference	Foreign	1004	I	Healthy adults	6	^{14}C-lorlatinib (100 mg) was administered orally as a single dose.	PK
		1005	I	Healthy adults	20	3 types of lorlatinib formulations[*4] (tablets, 100 mg) were administered orally as a single dose.	PK
		1007	I	Healthy adults	11	A single dose of lorlatinib was administered under fasting conditions intravenously at 50 mg or orally at 100 mg.	PK

Data category	Region	Study ID	Phase	Study population	Number of enrollments	Dosage regimen[*3]	Main endpoint
		1008	I	Healthy adults	27	(a) A single dose of lorlatinib (tablets, 100 mg) was administered orally under fasting conditions. (b) A single dose of lorlatinib (tablets, 100 mg) was administered orally after a high-fat meal. (c) Rabeprazole (20 mg) was administered orally QD on Days 1 to 5, followed by a single oral administration of lorlatinib on Day 6 (tablets, 100 mg) under fasting conditions. (d) A single dose of lorlatinib (solution, 100 mg) was administered orally under fasting conditions.	PK
		1011	I	Healthy adults	12	A single dose of lorlatinib (100 mg) was administered orally under fasting conditions. After a ≥10-day washout period, rifampicin (600 mg) was administered orally QD on Days 1 to 12 and lorlatinib (100 mg) was administered orally as a single dose on Day 8.	Safety, PK
		1012	I	Healthy adults	16	A single dose of lorlatinib (50, 75, or, 100 mg) was administered orally. After a ≥10-day washout period, itraconazole (200 mg) was administered orally QD on Days 1 to 11 and lorlatinib (50, 75, or, 100 mg) was administered orally as a single dose on Day 5.	PK
		1016	I	Healthy adults	20	4 types of lorlatinib formulations (tablets[*5], 100 mg) were administered orally as a single dose under fasting conditions.	PK

[*1] Includes ALK-TKI, [*2] Regardless of prior chemotherapy other than ALK-TKI, [*3] The washout period was ≥7 days in Study 1005 and ≥10 days in Studies 1007, 1008, and 1016. The study drug was administered according to a cross-over design. [*4] Acetic acid solvate, free base, and maleate of lorlatinib were used. [*5] 25-mg clinical study tablets and commercial image tablets (25, 50, and 100 mg) were used.

Each of clinical study is summarized below.

Major adverse events other than deaths observed in each clinical study are described in Section "7.3 Adverse events, etc. observed in clinical studies," and PK-related data are described in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase I/II study (CTD 5.3.5.2, Study 1001 [ongoing since January 2014 (data cut-off March 15, 2017)])

An open-label, uncontrolled study was conducted in patients with *ALK* fusion gene-positive advanced and/or recurrent NSCLC (target sample size, 50 in phase I, 260 in phase II[32)]) to investigate the efficacy, safety, PK., etc. of lorlatinib in 47 study sites in 13 countries and regions including Japan.

In phase I, lorlatinib was administered orally QD (10, 25, 50, 75, 100, 150, or 200 mg) or BID (35, 75, or 100 mg). In phase II, lorlatinib (100 mg) was administered orally QD until the criteria for disease progression or study discontinuation met.

Of 55 patients enrolled in phase I of the study, 54 patients receiving lorlatinib were included in the safety analysis in phase I. Of 276 patients enrolled in phase II (199 in Cohorts 2-5), (i) 274 patients who received lorlatinib and were positive for *ALK* fusion gene or *ROS1* fusion gene (197 in Cohorts 2-5) and (ii) 165 patients receiving lorlatinib who were positive for *ALK* fusion gene or *ROS1* fusion gene and had CNS metastasis (132 in Cohorts 2-5) were included in the efficacy analysis in the study. Of 276 patients enrolled in phase II, 275 patients were included in the safety analysis in phase II, except 1 patient who did not receive lorlatinib.

In phase I, the dose limiting toxicity (DLT) evaluation period was until Day 21 after the start of administration of lorlatinib. DLT (Grade 2 aphasia and dementia, Grade 1 visual impairment) was observed in 1 of 3 patients in the 200 mg QD group, and the recommended phase II dose (RP2D) was determined to be 100 mg QD.[33)]

The primary endpoints of phase II of the study were (a) response rate by central assessment based on Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1 and (b) intracranial response rate by central assessment based on the revised RECIST.[34)] No evaluation based on statistical hypothesis testing was performed on Cohorts 1 to 5 which enrolled patients with *ALK* fusion gene-positive advanced and/or recurrent NSCLC.

Tables 32 and 33 show results of the primary endpoints i.e., (a) and (b)[35)] (data cut-off March 15, 2017) obtained by the efficacy analysis. Of the efficacy analysis populations in phase II (197 in [i] and

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32) In phase II, the following patients were enrolled in each cohort. Cohorts 3B, 4, and 5 enrolled patients regardless of the prior chemotherapy, except ALK-TKI.
Cohort 1: *ALK* fusion gene-positive patients without prior chemotherapy
Cohort 2: *ALK* fusion gene-positive patients with disease progression after treatment with crizotinib
Cohort 3A: *ALK* fusion gene-positive with disease progression after treatment with crizotinib and not more than 2 chemotherapies
Cohort 3B: *ALK* fusion gene-positive patients with disease progression after treatment with an ALK-TKI other than crizotinib
Cohort 4: *ALK* fusion gene-positive patients with disease progression after treatment with 2 ALK-TKIs
Cohort 5: *ALK* fusion gene-positive patients with disease progression after treatment with 3 ALK-TKIs
Cohort 6: *ROS1* fusion gene-positive patients

33) Prior to the enrollment of Japanese patients in phase II, a Japanese cohort study (3 patients) was conducted to confirm the tolerability and safety of lorlatinib in Japanese patients with *ALK* or *ROS1* fusion gene-positive. As a result, no DLT was observed in patients receiving oral lorlatinib (100 mg) QD, confirming the tolerability of this dosage regimen in Japanese patients.

34) An intracranial lesion of ≥5 mm was identified by contrast-enhanced magnetic resonance imaging (MRI) with a 1 mm-thick slices and was added as a measurable lesion.

35) Among 276 patients enrolled in phase II, those treated with lorlatinib who were positive for *ALK* fusion gene- or *ROS1* fusion gene and had CNS metastasis were subjected to the analysis.

132 in [ii]), who were enrolled in Cohorts 2 to 5 (the cohorts enrolling *ALK* fusion gene-positive patients with disease progression after treatment with ALK-TKI)

Table 32. Best overall response and response rate in Cohorts 2 to 5 (RECIST ver. 1.1, efficacy analysis population, central assessment, data cut-off March 15, 2017)

Best overall response	Entire population						Japanese population
	Cohort 2	Cohort 3A	Cohort 3B	Cohort 4	Cohort 5	Cohorts 2-5	Cohorts 2-5
	N = 27	N = 32	N = 27	N = 65	N = 46	N = 197	N = 31
CR	1 (3.7)	0	1 (3.7)	2 (3.1)	0	4 (2.0)	3 (9.7)
PR	19 (70.4)	21 (65.6)	8 (29.6)	25 (38.5)	16 (34.8)	89 (45.2)	13 (41.9)
SD	4 (14.8)	6 (18.8)	10 (37.0)	22 (33.8)	16 (34.8)	58 (29.4)	11 (35.5)
PD	3 (11.1)	3 (9.4)	6 (22.2)	10 (15.4)	10 (21.7)	32 (16.2)	4 (12.9)
NE	0	2 (6.3)	2 (7.4)	6 (9.2)	4 (8.7)	14 (7.1)	0
Responsive[*1] (response rate [95% CI[*2]] [%])	20 (74.1 [53.7, 88.9])	21 (65.6 [46.8, 81.4])	9 (33.3 [16.5, 54.0])	27 (41.5 [29.4, 54.4])	16 (34.8 [21.4, 50.2])	93 (47.2 [40.1, 54.4])	16 (51.6 [33.1, 69.8])

[*1] CR + PR, [*2] Exact method

Table 33. Best overall response of intracranial lesion and intracranial response rate in Cohorts 2 to 5 (revised RECIST ver. 1.1, efficacy analysis population,[*1] central assessment, data cut-off March 15, 2017)

Best overall response	Entire population						Japanese population
	Cohort 2	Cohort 3A	Cohort 3B	Cohort 4	Cohort 5	Cohorts 2-5	Cohorts 2-5
	N = 17	N = 20	N = 12	N = 45	N = 38	N = 132	N = 15
CR	6 (35.3)	4 (20.0)	1 (8.3)	15 (33.3)	9 (23.7)	35 (26.5)	6 (40.0)
PR	4 (23.5)	11 (55.0)	4 (33.3)	10 (22.2)	6 (15.8)	35 (26.5)	1 (6.7)
SD	6 (35.3)	3 (15.0)	3 (25.0)	13 (28.9)	15 (39.5)	40 (30.3)	7 (46.7)
PD	1 (5.9)	1 (5.0)	3 (25.0)	4 (8.9)	2 (5.3)	11 (8.3)	1 (6.7)
NE	0	1 (5.0)	1 (8.3)	3 (6.7)	6 (15.8)	11 (8.3)	0
Responsive[*2] (response rate [95% CI[*3]] [%])	10 (58.8 [32.9, 81.6])	15 (75.0 [50.9, 91.3])	5 (41.7 [15.2, 72.3])	25 (55.6 [40.0, 70.4])	15 (39.5 [24.0, 56.6])	70 (53.0 [44.2, 61.8])	7 (46.7 [21.3, 73.4])

[*1] Among 276 patients enrolled in phase II, patients treated with lorlatinib who were positive for *ALK* fusion gene or *ROS1* fusion gene and had CNS metastasis, [*2] CR + PR, [*3] Exact method

Deaths occurred during or within 28 days post-dose of lorlatinib in 7 of 54 patients (13.0%) in phase I (1 of 3 in the 10 mg QD group, 1 of 3 in the 25 mg QD group, 3 of 17 in the 100 mg QD group, 1 of 3 in the 150 mg QD group, 1 of 3 in the 75 mg BID group) and 26 of 275 patients (9.5%) in phase II. The causes of deaths except disease progression (6 patients in phase I [1 in the 10 mg QD group, 1 in the 25 mg QD group, 3 in the 100 mg QD group, 1 in the 75 mg BID group], 18 patients in phase II), were hypoxia in 1 patient in the 150 mg QD group in phase I, and myocardial infarction, general physical health deterioration, pneumonia, lung infection, acute pulmonary oedema, respiratory distress, peripheral artery embolism, and embolism in 1 patient each in phase II. A causal relationship to lorlatinib was ruled out for all events.

7.2 Reference data

7.2.1 Clinical pharmacology studies

The applicant submitted the results of the following 7 clinical pharmacology studies in healthy adults. No death occurred during or within 30 days after the study drug administration in any of the studies.

7.2.1.1 Foreign phase I study (CTD 5.3.3.1.1, Study 1004 [September 2015 to November 2015])

7.2.1.2 Foreign phase I study (CTD 5.3.3.1.1, Study 1005 [March 2015 to May 2015])

7.2.1.3 Foreign phase I study (CTD 5.3.1.1.2, Study 1007 [June 2016 to September 2016])

7.2.1.4 Foreign phase I study (CTD 5.3.1.1.3, Study 1008 [December 2015 to April 2016])

7.2.1.5 Foreign phase I study (CTD 5.3.3.4.1, Study 1011 [July 2016 to October 2016])

7.2.1.6 Foreign phase I study (CTD 5.3.3.4.2, Study 1012 [August 2016 to May 2017])

7.2.1.7 Foreign phase I study (CTD 5.3.1.2.1, Study 1016 [November 2016 to February 2017])

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA decided that the most important data submitted for the evaluation of the efficacy of lorlatinib in patients with *ALK* fusion gene-positive advanced and/or recurrent NSCLC progressed after ALK-TKI therapy would be those of Cohorts 2 to 5 in phase II of the global phase I/II study (Study 1001) conducted to investigate the efficacy and safety of lorlatinib in patients with *ALK* fusion gene-positive advanced and/or recurrent NSCLC. Therefore, the review focused on the study on these cohorts. The safety of lorlatinib was evaluated mainly based on the results in the phase II of Study 1001.

7.R.2 Efficacy

After the reviews in the subsections below, PMDA concluded that lorlatinib has a certain level of efficacy in patients with *ALK*-fusion gene-positive unresectable advanced and/or recurrent NSCLC progressed after ALK-TK1 therapy.

7.R.2.1 Efficacy endpoints and evaluation results

The applicant's explanation about the primary endpoints in phase II of Study 1001 and the efficacy of lorlatinib in patients with *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC progressed after ALK-TK1 therapy:

Patients with unresectable relapsed NSCLC who respond to lorlatinib are expected to have improved clinical symptoms accompanying the disease progression (*J Clin Oncol.* 2006;24:3831-7, *JAMA.* 2003;290:2149-58, etc.). Because response achievement in these patients is of clinical significance, the response rate was included as a primary endpoint in phase II of Study 1001.

The response rate [95% CI] in the pooled analysis of data from Cohorts 2 to 5 in phase II of Study 1001 was 47.2% [40.1%, 54.4%] [see Section 7.1.1.1]. Both the response rate [95% CI] of lorlatinib in each cohort [see Section 7.1.1.1] and the response rate in patients classified by the type of ALK-TKI given as a prior treatment (Table 34) showed the tumor-shrinking effect of lorlatinib in patients with *ALK* fusion gene-positive NSCLC progressed after ALK-TKI therapy, regardless of the type or number of prior treatments with ALK-TKI[36)] given as prior treatment.

36) Crizotinib, alectinib, and ceritinib

Table 34. Best overall response and response rate[*1] classified by type of ALK-TKI administered as prior treatment

(RECIST ver. 1.1, central assessment, data cut-off March 15, 2017)

Best overall response	Crizotinib only[*2]	Alectinib only	Ceritinib only	Crizotinib and alectinib	Crizotinib and ceritinib	Alectinib and ceritinib	Crizotinib, alectinib, and ceritinib
	N = 58	N = 13	N = 13	N = 37	N = 34	N = 3	N = 16
CR	1 (1.7)	1 (7.7)	0	1 (2.7)	1 (2.9)	0	0
PR	39 (67.2)	3 (23.1)	5 (38.5)	15 (40.5)	12 (35.3)	0	4 (25.0)
SD	10 (17.2)	5 (38.5)	5 (38.5)	11 (29.7)	12 (35.3)	2 (66.7)	8 (50.0)
PD	6 (10.3)	3 (23.1)	3 (23.1)	8 (21.6)	7 (20.6)	0	3 (18.8)
NE	2 (3.4)	1 (7.7)	0	2 (5.4)	2 (5.9)	1 (33.3)	1 (6.3)
Responsive[*3] (response rate [95% CI[*4]] [%])	40 (69.0 [55.5, 80.5])	4 (30.8 [9.1, 61.4])	5 (38.5 [13.9, 68.4])	16 (43.2 [27.1, 60.5])	13 (38.2 [22.2, 56.4])	0	4 (25.0 [7.3, 52.4])

[*1] Regardless of a prior chemotherapy other than ALK-TKI or of the number of times of treatment with the same ALK-TKI. A total of 23 patients with a prior treatment with ALK-TKI other than crizotinib, alectinib, and ceritinib are excluded. [*2] One patient with a prior treatment with the study drug, AT13387-05 (HSP90 inhibitor) is excluded.[*3] CR + PR, [*4] Exact method

The response rate [95% CI] in the Japanese population in Cohorts 2 to 5 according to the central assessment based on RECIST ver. 1.1 was 51.6% [33.1%, 69.8%] (16 of 31 patients).

Taking account of the results in Cohorts 2 to 5 of the phase II part of Study 1001, as well as the facts that (a) lorlatinib targets at the oncogenic driver and that (b) lorlatinib is effective in patients with G1202R[6)] mutation in ALK-TKI, a mutation reported to confer resistance to conventional ALK-TKIs, lorlatinib is expected to be effective in patients with *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC progressed after conventional ALK-TKI therapy.

PMDA's view:

A relationship between response rate and overall survival (OS), the true endpoint, in patients with *ALK* fusion gene-positive advanced and/or recurrent NSCLC is unclear. It is therefore practically impossible to evaluate the life-prolonging effect of lorlatinib based on the response rate assessed as a primary endpoint in Study 1001. However, the applicant's explanation about the efficacy of lorlatinib is acceptable, and results of the response rate in Study 1001, etc. demonstrated a certain level of efficacy of lorlatinib in patients with *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC progressed after conventional ALK-TKI therapy. Because of only a small number of Japanese patients included in the efficacy analysis of lorlatinib, there is limitation to the evaluation of efficacy of lorlatinib in Japanese patients. Nevertheless, in Cohorts 2 to 5 of phase II of Study 1001, lorlatinib was as effective in the Japanese population as in the entire population of the cohorts. Lorlatinib is concluded to have promising efficacy in Japanese patients as well.

7.R.3 Safety (for adverse events, see Section "7.3 Adverse events, etc. observed in clinical studies")

PMDA's conclusion made after the review in the following subsections:

Adverse events requiring particular attention in treatment with lorlatinib in patients with *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC progressed after ALK-TKI therapy are QT interval prolongation, CNS disorder, pancreatitis, hepatic dysfunction, and interstitial lung disease (ILD). Particular caution should be exercised against these adverse events in using lorlatinib.

Besides these adverse events, hyperlipidaemia and cardiac disorders (except QT interval prolongation) are also subject to particular attention. Lorlatinib is, however, tolerable for patients where their safety is secured by appropriate actions of physicians with adequate knowledge and experience in cancer chemotherapy, i.e., monitoring and controlling adverse events, dose adjustment of lorlatinib, with utmost attention and control measures for serious adverse events such as ILD.

7.R.3.1 Safety profile of lorlatinib

The applicant's explanation about the safety profile of lorlatinib, based on the safety data obtained from phase II of Study 1001:

Table 35 shows the outline of safety in phase II of Study 1001.

Table 35. Outline of safety profile (phase II of Study 1001)

	Number of patients (%) 275
All adverse events	274 (99.6)
Grade ≥3 adverse events	175 (63.6)
Adverse events resulting in death	26 (9.5)
Serious adverse events	89 (32.4)
Adverse events leading to treatment discontinuation	21 (7.6)
Adverse events leading to treatment interruption	125 (45.5)
Adverse events leading to dose reduction	64 (23.3)

In phase II of Study 1001, all-Grade adverse events with an incidence of ≥10% were hypertriglyceridaemia in 155 patients (56.4%), hypercholesterolaemia in 145 patients (52.7%), oedema peripheral in 113 patients (41.1%), blood cholesterol increased in 96 patients (34.9%), dyspnoea in 64 patients (23.3%), weight increased in 57 patients (20.7%), arthralgia in 54 patients (19.6%), diarrhoea in 49 patients (17.8%), cough in 47 patients (17.1%), dizziness and headache in 42 patients (15.3%) each, nausea in 40 patients (14.5%), constipation in 39 patients (14.2%), fatigue and paraesthesia in 37 patients (13.5%) each, AST increased and pain in extremity in 32 patients (11.6%) each, anaemia and neuropathy peripheral in 31 patients (11.3%) each, ALT increased in 29 patients (10.5%), and back pain in 28 patients (10.2%). Grade ≥3 adverse events with an incidence of ≥3% were hypertriglyceridaemia in 42 patients (15.3%), hypercholesterolaemia in 27 patients (9.8%), disease progression in 22 patients (8.0%), blood cholesterol increased in 19 patients (6.9%), lipase increased in 14 patients (5.1%), dyspnoea in 12 patients (4.4%), and hypertension in 10 patients (3.6%). Serious adverse events with an incidence of ≥2% were disease progression in 22 patients (8.0%), pyrexia and dyspnoea in 6 patients (2.2%) each. There were no adverse events leading to treatment discontinuation with an incidence of ≥1%. Adverse events leading to treatment interruption with an incidence of ≥2% were oedema peripheral and hypertriglyceridaemia in 12 patients (4.4%) each, dyspnoea in 7 patients (2.5%), and cognitive disorder in 6 patients (2.2%). Adverse events leading to dose reduction with an incidence of ≥2% were oedema peripheral in 11 patients (4.0%), and cognitive disorder in 6 patients (2.2%).

PMDA's view:

Adverse events with a high incidence and serious or Grade ≥3 adverse events in Study 1001 are likely to occur following the administration of lorlatinib. Patients receiving lorlatinib should be monitored

for these adverse events while taken into consideration a possible relationship with lorlatinib. However, most of these adverse events were controllable by treatment interruption, dose reduction, etc. Accordingly, lorlatinib is tolerated as long as physicians with adequate knowledge and experience in cancer chemotherapy continue to follow by monitoring and controlling the adverse events and interruption and dose reduction of lorlatinib.

7.R.3.2 Difference in safety profile between Japanese and non-Japanese patients

The applicant's explanation about the difference in the lorlatinib safety profile between Japanese patients and non-Japanese patients based on the safety data from phase II of Study 1001:

Table 36 shows the outline of the safety profiles of Japanese and non-Japanese patients in phase II of Study 1001.

Table 36. Outline of safety profile (phase II of Study 1001)

	Number of patients (%)	
	Japanese patients 39	Non-Japanese patients 236
All adverse events	39 (100)	235 (99.6)
Grade ≥3 adverse events	25 (64.1)	150 (63.6)
Adverse events resulting in death	4 (10.3)	22 (9.3)
Serious adverse events	7 (17.9)	82 (34.7)
Adverse events leading to treatment discontinuation	1 (2.6)	20 (8.5)
Adverse events leading to treatment interruption	21 (53.8)	104 (44.1)
Adverse events leading to dose reduction	7 (17.9)	57 (24.2)

In phase II of Study 1001, all-Grade adverse events with ≥15% higher incidence in Japanese patients than in non-Japanese patients were hypertriglyceridaemia (30 Japanese patients [76.9%], 125 non-Japanese patients [53.0%]), blood cholesterol increased (23 [59.0%], 73 [30.9%]), and peripheral sensory neuropathy (13 [33.3%], 9 [3.8%]). The Grade ≥3 adverse event with a ≥10% higher incidence was hypertriglyceridaemia (10 [25.6%], 32 [13.6%]). There were no adverse events resulting in death, serious adverse events, adverse events leading to treatment discontinuation, adverse events leading to treatment interruption, or adverse events leading to dose reduction that occurred at ≥10% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's view:

A small number of Japanese patients treated with lorlatinib precludes an adequate comparison of the safety profile between Japanese and non-Japanese patients. However, adverse events such as hypertriglyceridaemia, blood cholesterol increased, peripheral sensory neuropathy, etc. occurred more frequently in Japanese patients than in non-Japanese patients but were rarely serious or led to treatment discontinuation or dose reduction. Therefore, lorlatinib is tolerated in Japanese patients as well, premising that lorlatinib is administered by physicians with adequate knowledge and experience in cancer chemotherapy.

In the following subsections, PMDA reviewed major adverse events observed in Study 1001 while taking account of the known events observed with crizotinib, alectinib, and ceritinib, drugs with ALK tyrosine kinase-inhibitory activities as with lorlatinib.

7.R.3.3 QT interval prolongation

The applicant's explanation about QT interval prolongation associated with lorlatinib:
Adverse events related to QT interval prolongation were tabulated based on event terms classified under a Medical Dictionary for Regulatory Activities (MedDRA) SMQ of "torsade de pointes/QT prolongation (narrow and broad)".

Table 37 shows the incidences of QT interval prolongation in phase II of Study 1001.

Table 37. Incidences of QT interval prolongation (phase II of Study 1001)

PT (MedDRA ver. 20.0)	Number of patients (%) 275	
	All Grades	Grade ≥3
QT interval prolonged	26 (9.5)	6 (2.2)
Electrocardiogram QT prolonged	19 (6.9)	1 (0.4)
Presyncope	4 (1.5)	1 (0.4)
Syncope	2 (0.7)	2 (0.7)
Cardiac arrest	1 (0.4)	1 (0.4)
Loss of consciousness	1 (0.4)	1 (0.4)

In phase II of Study 1001, there was no QT interval prolongation that resulted in death. Serious QT interval prolongation was observed in 3 of 275 patients (1.1%; cardiac arrest, presyncope, and syncope in 1 patient each). A causal relationship to lorlatinib could not be ruled out for presyncope in 1 patient. QT interval prolongation led to treatment discontinuation in 1 of 275 patients (0.4%; loss of consciousness in 1 patient). QT interval prolongation leading to treatment interruption was observed in 4 of 275 patients (1.5%; cardiac arrest, electrocardiogram QT prolonged, presyncope, and syncope in 1 patient each). QT interval prolongation leading to dose reduction was observed in 1 of 275 patients (0.4%; presyncope in 1 patient).

In phase II of Study 1001, the median time to the first episode of QT interval prolongation (range) was 15.0 days (1-149 days).

Table 38 shows changes in QTcF following the administration of lorlatinib in phase II of Study 1001. None of the patients showing changes in QTcF value experienced serious symptoms related to QT interval prolongation.

Table 38. Changes in QTcF following administration of lorlatinib (phase II of Study 1001)

	Number of patients (%) 275
Maximum level	
>480 ms	25 (9.1)
>500 ms	6 (2.2)
>550 ms	1 (0.4)
Increase from baseline (maximum value)	
>30 ms	118 (42.9)
>60 ms	19 (6.9)
>100 ms	5 (1.8)
Mean maximum increase from baseline [90% CI] (ms)	31.0 [28.8, 33.1]

PMDA's view:

In phase II of Study 1001, most of lorlatinib-induced QT interval prolongation was Grade ≤2. However, Study 1001 excluded patients with the risk of QT interval prolongation and there were several patients who showed increased QTcF by ≥60 ms from baseline after lorlatinib administration. Caution should be exercised against possible QT interval prolongation during the use of lorlatinib. Therefore, the criteria for treatment interruption, dose reduction, and treatment discontinuation used in the clinical studies due to QT interval prolongation and the incidences of QT prolongation in the clinical studies should be appropriately communicated to healthcare professionals using the package insert. Electrolyte determination and electrocardiography should be performed regularly during treatment, and lorlatinib should be withheld or any other appropriate actions should be taken following QT interval prolongation or arrhythmia. This should be advised in the package insert appropriately.

7.R.3.4 CNS disorders

The applicant's explanation about lorlatinib-induced CNS disorders:

Adverse events related to CNS disorders were tabulated according to MedDRA HLGTs of "mental impairment disorders," "cognitive and attention disorders and disturbances," "deliria (including confusion)," "mood disorders and disturbances," "anxiety disorders and symptoms," "depressed mood disorders and disturbances," "personality disorders and disturbances in behavior," "manic and bipolar mood disorders and disturbances" and a MedDRA HLT of "speech and language disorders."

Table 39 shows the incidences of CNS disorders in phase II of Study 1001.

Table 39. Incidences of CNS disorders (phase II of Study 1001)

PT (MedDRA ver. 20.0)	Number of patients (%) 275	
	All Grades	Grade ≥3
CNS disorders	107 (38.9)	7 (2.5)
Memory impairment	24 (8.7)	0
Cognitive disorder	18 (6.5)	2 (0.7)
Irritability	16 (5.8)	2 (0.7)
Amnesia	16 (5.8)	0
Anxiety	15 (5.5)	1 (0.4)
Depression	12 (4.4)	1 (0.4)
Dysarthria	10 (3.6)	0
Confusional state	9 (3.3)	2 (0.7)
Slow speech	7 (2.5)	1 (0.4)
Affect lability	7 (2.5)	0
Disturbance in attention	7 (2.5)	0
Speech disorder	6 (2.2)	0
Personality change	5 (1.8)	0
Mood swings	3 (1.1)	0
Agitation	2 (0.7)	1 (0.4)
Mental impairment	2 (0.7)	0
Affective disorder	2 (0.7)	0
Aggression	2 (0.7)	0
Mood altered	2 (0.7)	0
Dementia	1 (0.4)	0
Delirium	1 (0.4)	0
Depressed mood	1 (0.4)	0
Euphoric mood	1 (0.4)	0
Mania	1 (0.4)	0

In phase II of Study 1001, there were no CNS disorders resulting in death. Serious CNS disorders occurred in 2 of 275 patients (0.7%; cognitive disorder and confusional state in 1 patient each). A causal relationship to lorlatinib could not be ruled out for either event. CNS disorders led to treatment discontinuation in 4 of 275 patients (0.4%; cognitive disorder, anxiety, confusional state, and affect lability in 1 patient each). CNS disorders led to treatment interruption in 18 of 275 patients (6.5%; cognitive disorder in 6 patients, memory impairment in 4 patients, depression, irritability, and affect lability in 2 patients each, amnesia, disturbance in attention, dysarthria, agitation, anxiety, confusional state, and personality change in 1 patient each [some patients had >1 adverse event]). CNS disorders led to dose reduction in 15 of 275 patients (5.5%; cognitive disorder in 6 patients, affect lability in patients 2, amnesia, dysarthria, memory impairment, agitation, anxiety, depression, irritability, mood swings, and personality change in 1 patient each [some patients had >1 adverse event]).

In phase II of Study 1001, the median time to the first episode of CNS disorders (range) was 43.0 days (1-452 days).

PMDA asked the applicant to explain the mechanism of the onset of CNS disorders, risk factors, and reversibility.

The applicant's explanation:
CNS disorders was presumably caused by lorlatinib transported to the CNS through the blood-brain barrier. However, its underlying mechanism is unclear and a clear risk factor remains unknown. No histopathological changes were observed in the CNS in the nonclinical studies, and that the CNS disorders observed in Study 1001 resolved after dose reduction, treatment interruption, or discontinuation of lorlatinib. CNS disorders are thus considered reversible.

PMDA's view:
In phase II of Study 1001, most of the lorlatinib-induced CNS disorders are Grade ≤2 and reversible. However, CNS disorders were observed at a certain frequency after the administration of lorlatinib, and there were serious CNS disorders for which a causal relationship to lorlatinib could not be ruled out. Lorlatinib-induced CNS disorders is thus subject to attention. Therefore, incidences of CNS disorders in the clinical studies should be appropriately communicated to healthcare professionals using the package insert. CNS disorders are events unique to lorlatinib and not common to other ALK-TKIs, and its risk factor remains unknown. Post-marketing data on CNS disorders should be collected and measures to reduce risks of CNS disorders should be further investigated.

7.R.3.5 Pancreatitis

The applicant's explanation about lorlatinib-induced pancreatitis:
The MedDRA SMQ of "acute pancreatitis (narrow)" in and the preferred terms (PTs) of "pancreatic enzyme abnormality," "amylase increased," "lipase increased," "lipase urine increased," "lipase abnormal," "pancreatic enzymes abnormal," "pancreatic enzymes increased," "blood trypsin increased," "amylase abnormal," "amylase creatinine clearance ratio abnormal," "hyperamylasaemia," and "hyperlipasaemia" were tabulated.

Table 40 shows the incidences of pancreatitis in phase II of Study 1001.

Table 40. Incidences of pancreatitis (phase II of Study 1001)

PT (MedDRA ver. 20.0)	Number of patients (%) 275	
	All Grades	Grade ≥3
Pancreatitis	38 (13.8)	19 (6.9)
Lipase increased	26 (9.5)	14 (5.1)
Amylase increased	21 (7.6)	8 (2.9)
Pancreatitis	1 (0.4)	1 (0.4)
Pancreatic enzymes increased	1 (0.4)	0

In phase II of Study 1001, there was no pancreatitis resulting in death. Serious pancreatitis was observed in 1 of 275 patients (0.4%; pancreatitis in 1 patient), and its causal relationship to lorlatinib could not be ruled out. There was no pancreatitis leading to treatment discontinuation. Pancreatitis leading to treatment interruption was observed in 8 of 275 patients (2.9%; lipase increased in 5 patients, amylase increased in 4 patients, and pancreatitis in 1 patient [some patients had >1 adverse event]). Pancreatitis leading to dose reduction was observed in 4 of 275 patients (1.5%; lipase increased in 3 patients, amylase increased in 2 patients, and pancreatitis in 1 patient [some patients had >1 adverse event]).

In phase II of Study 1001, the median time to the first episode of pancreatitis (range) was 77.5 days (1-316 days).

PMDA's view:
In phase II of Study 1001, pancreatitis was observed in >1 patient. However, most patients experienced only increased pancreatic enzymes, and only 1 patient suffered lorlatinib-induced pancreatitis. Even so, in light of the following facts, the occurrence of pancreatitis in the clinical studies should be communicated to healthcare professionals in an appropriate manner, and data on pancreatitis should be collected further. Once available, new safety data should be communicated to healthcare professionals for precautions in an appropriate manner.

- In Study 1001, serious pancreatitis was observed and a causal relationship to lorlatinib could not be ruled out for the event.

- Pancreatitis is an adverse event requiring caution in the use of ceritinib, an ALK-TKI (see "Review Report on Zykadia capsules 150 mg dated February 16, 2016").

7.R.3.6 Hepatic dysfunction

The applicant's explanation about lorlatinib-induced hepatic dysfunction:
MedDRA PTs of "acute hepatic failure," "hepatic failure," "hepatitis," "hepatitis acute," "hepatotoxicity," "jaundice," "jaundice cholestatic," "jaundice hepatocellular," "hypertransaminasaemia," "drug-induced liver injury," "ALT abnormal," "ALT increased," "AST abnormal," "AST increased," "bilirubin conjugated increased," "blood bilirubin increased," "blood bilirubin unconjugated increased," "liver function test abnormal," "transaminases increased," "blood

bilirubin abnormal," "hepatic enzyme increased," "hepatic enzyme abnormal," "transaminases abnormal," "total bile acids increased," or "bilirubin conjugated abnormal" were tabulated.

Table 41 shows the incidences of hepatic dysfunction in phase II of Study 1001.

Table 41. Incidences of hepatic dysfunction (phase II of Study 1001)

PT (MedDRA ver. 20.0)	Number of patients (%) 275	
	All Grades	Grade ≥3
Hepatic dysfunction	44 (16.0)	5 (1.8)
AST increased	32 (11.6)	3 (1.1)
ALT increased	29 (10.5)	3 (1.1)
Jaundice	1 (0.4)	1 (0.4)
Blood bilirubin increased	1 (0.4)	0
Transaminases increased	1 (0.4)	0
Hepatic enzyme increased	1 (0.4)	0

In phase II of Study 1001, there was no hepatic dysfunction resulting in death. Serious hepatic dysfunction was observed in 3 of 275 patients (1.1%; AST increased and ALT increased in 2 patients each, jaundice in 1 patient [some patients had >1 adverse event]), and a causal relationship to lorlatinib could not be ruled out in 1 of 275 patients (0.4%; AST increased and ALT increased in one and the same patient). There was no hepatic dysfunction leading to treatment discontinuation. Hepatic dysfunction leading to treatment interruption was observed in 4 of 275 patients (1.5%; ALT increased in 3 patients, AST increased and jaundice in 1 patient each [some patients had >1 adverse event]). Hepatic dysfunction leading to dose reduction was observed in 1 of 275 patients (0.4%; ALT increased in 1 patient).

In phase II of Study 1001, the median time to the first occurrence of hepatic dysfunction (range) was 15.0 days (1-223 days).

In phase II of Study 1001, hepatic dysfunction with laboratory values meeting the criteria of Hy's law[24)] was observed in 1 of 275 patients. This patient showed increases in AST and ALT exceeding 23 times the upper limit of the reference range on Day 371 after the start of administration of lorlatinib and total bilirubin exceeding 18 times the upper limit of the reference range and ALP exceeding 16 times the upper limit of the reference range on Day 380. A causal relationship to lorlatinib was ruled out for events. Lorlatinib was however discontinued because the patient was infected with influenza virus at that time. The patient died of disease progression on Day 385 before recovery of laboratory values. Also, in phase I of Study 1001, hepatic dysfunction with laboratory values meeting the criteria for Hy's law was reported in 1 patient with *ROS1*-positive NSCLC. A causal relationship of the hepatic dysfunction to lorlatinib could not be ruled out in this patient.

PMDA's view:
In phase II of Study 1001, both all-Grade and Grade ≥3 hepatic dysfunction occurred in only a limited number of patients, and a relationship between lorlatinib and hepatic dysfunction still remains unclear. Taking account of the following observations, the incidences of hepatic dysfunction in the clinical studies should be communicated to healthcare professionals in an appropriate manner, and data on

hepatic dysfunction should be further collected. Once available, new safety findings should be communicated to healthcare professionals in an appropriate manner.

- Serious hepatic dysfunction was observed and its causal relationship to lorlatinib could not be ruled out.

- Hepatic dysfunction meeting Hy's law criteria was observed.

- Hepatic dysfunction is an attention-requiring event in the use of conventional ALK-TKIs, namely, crizotinib, alectinib, and ceritinib ("Review Report on Xalkori Capsules 200 mg, Xalkori Capsules 250 mg, dated February 20, 2012," "Review Report Alecensa Capsules 20 mg, Alecensa Capsules 40 mg, dated May 16, 2014," and "Review Report on Zykadia Capsules 150 mg, dated February 16, 2016").

7.R.3.7 ILD

The applicant's explanation about lorlatinib-induced ILD:
PTs falling under the MedDRA SMQ of "interstitial lung disease (narrow and broad)" were tabulated.

Table 42 shows the incidences of ILD in phase II of Study 1001.

Table 42. Incidences of ILD (phase II of Study 1001)

PT (MedDRA ver. 20.0)	Number of patients (%) 275	
	All Grades	Grade ≥3
ILD	4 (1.5)	3 (1.1)
Pneumonitis	3 (1.1)	2 (0.7)
ILD	1 (0.4)	1 (0.4)

In phase II of Study 1001, there was no ILD resulting in death. Serious ILD was observed in 3 of 275 patients (1.1%; pneumonitis in 2 patients, ILD in 1 patient). A causal relationship to lorlatinib could not be ruled out in 2 of 275 patients (0.7%; pneumonitis and ILD in 1 patient each). ILD led to treatment discontinuation in 1 of 275 patients (0.4%; pneumonitis in 1 patient) and treatment interruption in 1 of 275 patients (0.4%; ILD in 1 patient). There was no ILD leading to dose reduction.

In phase II of Study 1001, the median time to the first episode of ILD (range) was 73.5 days (33-105 days).

Table 43 shows the details of patients who had serious ILD in phase II of Study 1001.

Table 43. Patients who had serious ILD (phase II of Study 1001)

Sex	Age	PT (MedDRA ver. 20.0)	Grade	Date of onset	Duration (days)	Lorlatinib treatment	Causal relationship	Outcome
Male	54	ILD	3	69	3	Interrupted	Not related	Resolved
Male	42	Pneumonitis	3	105	4	Continued	Not related	Resolved
Male	54	Pneumonitis	4	33	5	Discontinued	Related	Resolved with sequelae

PMDA's view:

ILD is an adverse event known to be induced by ALK-TKI. In light of the observation that serious ILD occurred post-dose of lorlatinib in phase II of Study 1001, physicians must be advised to monitor patients for possible ILD during the treatment with lorlatinib so that appropriate measures are taken against at its onset. Because of the limited number of patients who experienced the disease, neither the characteristic manifestation nor a risk factor of lorlatinib-induced ILD is known. The incidence of lorlatinib-induced ILD, at least in the clinical studies on lorlatinib, did not tend to be higher than the incidence of ILD in the clinical studies on conventional ALK-TKIs, i.e., crizotinib, alectinib, and ceritinib ("Review Report on Xalkori Capsules 200 mg, Xalkori Capsules 250 mg, dated February 20, 2012," "Review Report on Alecensa Capsules 20 mg, Alecensa Capsules 40 mg, dated May 16, 2014," and "Review Report on Zykadia Capsules 150 mg, dated February 16, 2016").

7.R.3.8 Hyperlipidaemia

The applicant's explanation about lorlatinib-induced hyperlipidaemia:

MedDRA PTs of "blood cholesterol increased," "blood triglycerides increased," "hypercholesterolaemia," or "hypertriglyceridaemia" were tabulated.

Table 44 shows the incidences of hyperlipidaemia in phase II of Study 1001.

Table 44. Incidences of hyperlipidaemia (phase II of Study 1001)

PT (MedDRA ver. 20.0)	Number of patients (%) 275	
	All Grades	Grade ≥3
Hyperlipidaemia	236 (85.8)	71 (25.8)
Hypertriglyceridaemia	155 (56.4)	42 (15.3)
Hypercholesterolaemia	145 (52.7)	27 (9.8)
Blood cholesterol increased	96 (34.9)	19 (6.9)
Blood triglycerides increased	17 (6.2)	3 (1.1)

In phase II of Study 1001, there was no hyperlipidaemia resulting in death or leading to treatment discontinuation. Serious hyperlipidaemia was observed in 2 of 275 patients (0.7%; hypertriglyceridaemia and blood cholesterol increased in 1 patient each), and a causal relationship to lorlatinib could not be ruled out in both patients. Hyperlipidaemia leading to treatment interruption was observed in 17 of 275 patients (6.2%; hypertriglyceridaemia in 12 patients, blood cholesterol increased in 5, hypercholesterolaemia in 3 patients, and blood triglycerides increased in 2 patients [some patients had >1 adverse event]). Hyperlipidaemia leading to dose reduction was observed in 7 of 275 patients (2.5%; hypertriglyceridaemia in 5 patients and hypercholesterolaemia in 2 patients).

Table 45 shows the details of patients who had serious hyperlipidaemia in phase II of Study 1001.

Table 45. Patients who had serious hyperlipidaemia (phase II of Study 1001)

Sex	Age	PT (MedDRA ver. 20.0)	Grade	Time of onset (days)	Duration (days)	Lorlatinib treatment	Administration of hypolipidemic agent	Causal relationship	Outcome
Female	53	Blood cholesterol increased	4	21	7	Interrupted	Used	Related	Resolved
Male	52	Hypertriglyceridaemia	4	104	14	Interrupted	Used	Related	Resolved

A cholesterol- or triglyceride-lowering drug was administered in 222 of 236 patients (94.1%) who had hyperlipidaemia.

In phase II of Study 1001, the median time to the first episode of hyperlipidaemia (range) was 15.0 days (1-148 days). The median duration was 217 days for hypercholesterolaemia and 210 days for hypertriglyceridaemia.

PMDA's view:
In phase II of Study 1001, there were no patients who discontinued lorlatinib and only a limited number of patients experienced serious adverse events. Therefore, adverse events are controllable where appropriate measures such as dose adjustment of lorlatinib are taken. However, taking account that (a) hyperlipidaemia occurred frequently following the administration of lorlatinib, (b) a causal relationship to lorlatinib could not be ruled out for serious hyperlipidaemia in some patients, and (c) the incidence of hyperlipidaemia was higher in Japanese patients than non-Japanese patients [see Section 7.R.3.2], attention should be paid to possible lorlatinib-induced hyperlipidaemia, and the incidences of hyperlipidaemia in clinical studies should be communicated to health professionals through the package insert.

7.R.3.9 Cardiac disorders (except QT interval prolongation)

The applicant's explanation about lorlatinib-induced cardiac disorders:
PTs falling under the MedDRA system organ class (SOC) "cardiac disorders" in were tabulated.

Table 46 shows the incidences of cardiac disorders in phase II Study 1001.

Table 46. Incidences of cardiac disorders (phase II Study 1001)

PT (MedDRA ver. 20.0)	Number of patients (%) 275	
	All Grades	Grade ≥3
Cardiac disorders	44 (16.0)	12 (4.4)
Tachycardia	11 (4.0)	0
Sinus tachycardia	7 (2.5)	0
Pericardial effusion	6 (2.2)	3 (1.1)
Palpitations	5 (1.8)	0
Atrial fibrillation	4 (1.5)	2 (0.7)
Bradycardia	4 (1.5)	1 (0.4)
Sinus bradycardia	3 (1.1)	0
Atrioventricular block first degree	2 (0.7)	0
Arrhythmia	1 (0.4)	1 (0.4)
Atrioventricular block complete	1 (0.4)	1 (0.4)
Cardiac arrest	1 (0.4)	1 (0.4)
Cardiac failure	1 (0.4)	1 (0.4)
Cardiac tamponade	1 (0.4)	1 (0.4)
Myocardial infarction	1 (0.4)	1 (0.4)
Supraventricular tachycardia	1 (0.4)	1 (0.4)
Right ventricular dysfunction	1 (0.4)	1 (0.4)
Cardiac failure congestive	1 (0.4)	0
Cyanosis	1 (0.4)	0
Myocardial ischaemia	1 (0.4)	0
Left ventricular dysfunction	1 (0.4)	0
Sinus node dysfunction	1 (0.4)	0

In phase II of Study 1001, cardiac disorder resulted in death in 1 of 275 patients (0.4%; myocardial infarction in 1 patient), but its causal relationship to lorlatinib was ruled out. Serious cardiac disorder occurred in 9 of 275 patients (3.3%; pericardial effusion in 3 patients, atrial fibrillation in 2 patients, atrioventricular block complete, cardiac arrest, myocardial infarction, supraventricular tachycardia, and sinus node dysfunction in 1 patient each [some patients had >1 adverse event]), and a causal relationship to lorlatinib was ruled out in all patients. Cardiac disorder leading to treatment discontinuation occurred in 1 of 275 patients (0.4%; myocardial infarction in 1 patient). Cardiac disorder leading to treatment interruption occurred in 12 of 275 patients (4.4%; atrial fibrillation and pericardial effusion in 3 patients each, arrhythmia, atrioventricular block complete, cardiac arrest, cardiac failure, cardiac tamponade, supraventricular tachycardia, and sinus node dysfunction in 1 patient each [some patients had >1 adverse event]). Cardiac disorder leading to dose reduction occurred in 1 of 275 patients (0.4%; cardiac tamponade in 1 patient).

In phase II of Study 1001, the median time to the first episode of cardiac disorder (range) was 42.0 days (1-323 days).

PMDA's view:

In phase II of Study 1001, most of lorlatinib-induced cardiac disorders were Grade ≤2. Serious cardiac disorder occurred in only a limited number of patients and a causal relationship to lorlatinib was ruled out for all events. These results preclude a clear conclusion about lorlatinib-induced cardiac disorders. However, in light of the facts that cardiac disorder is identified as an adverse event requiring caution in administering conventional ALK-TKIs of crizotinib and ceritinib, (see "Review Report on Xalkori Capsules 200 mg, Xalkori Capsules 250 mg, dated February 20, 2012" and "Review Report on Zykadia Capsules 150 mg, dated February 16, 2016"), the occurrence of cardiac disorder in the clinical studies should be communicated to healthcare professionals through the package insert and

that information on cardiac disorder should be collected further. New safety findings should be communicated to healthcare professionals in an appropriate manner.

7.R.4 Clinical positioning and indication

The proposed indication of lorlatinib was "*ALK* fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitor(s)." The "Precautions for Indications" section included the following description:

- The efficacy and safety of lorlatinib in post-operative adjuvant therapy have not been established.

Based on the reviews in Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the following discussion in this section, PMDA concluded that the indication of lorlatinib should be "*ALK* fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer progressed after therapy with ALK tyrosine kinase inhibitor(s)," with the following cautions in the "Precautions for Indication" section:

- The efficacy and safety of lorlatinib in the first-line therapy have not been established.

- The efficacy and safety of lorlatinib in the post-operative adjuvant therapy have not been established.

- Physicians should select patients to be treated with lorlatinib based on their good understanding of the "Clinical Studies" section of the package insert and of the efficacy and safety of lorlatinib, after due consideration of other treatment options.

7.R.4.1 Clinical positioning and indication of lorlatinib

Descriptions on lorlatinib was not found in the latest Japanese or foreign clinical practice guidelines or representative textbooks on clinical oncology.

PMDA asked the applicant to explain the clinical positioning and indication of lorlatinib in patients with *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC.

The applicant's explanation:
Based on the results in Cohorts 2 to 5 in phase II of Study 1001, lorlatinib is recognized as a treatment option for patients with *ALK*- fusion gene-positive unresectable advanced and/or recurrent NSCLC resistant or intolerant to ALK-TKI. Currently, clinical study results are unavailable on the efficacy and safety of lorlatinib as a post-operative adjuvant therapy, and treatment with lorlatinib in a post-operative adjuvant therapy is not recommended.

Based on the above, the indication was proposed as "*ALK* fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitor(s)," with the caution in the "Precautions for Indication" section that the efficacy and safety of lorlatinib as a post-operative adjuvant therapy have not been established.

In patients with *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC, appropriate choice between lorlatinib and crizotinib, alectinib, and ceritinib, conventional ALK-TKIs, is currently unclear because of no clinical study comparing the efficacy and safety of these drugs. The following study is currently ongoing:

- Global phase III study (Study 1006)
  An open-label, randomized study to compare the efficacy and safety of lorlatinib and crizotinib in patients with *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC without prior chemotherapy (target sample size, 280 patients).

PMDA's view:
PMDA generally accepted the applicant's explanation. However, taking into account that (a) no clinical data are available on the efficacy and safety of lorlatinib in patients with *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC without prior chemotherapy, and (b) efficacy of lorlatinib was evaluated mainly based on the response rate without data on the life-prolonging effect, and treatment options other than lorlatinib should also be considered, lorlatinib should be indicated for "*ALK* fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer progressed after therapy with ALK tyrosine kinase inhibitor(s)," with the following cautionary advice in the "Precautions for Indication" section:

- The efficacy and safety of lorlatinib in the first-line therapy have not been established.

- Physicians should select patients to be treated with lorlatinib based on their good understanding of the "Clinical Studies" section of the package insert and of the efficacy and safety of lorlatinib, after due consideration of other treatment options.

Data on the choice among lorlatinib, crizotinib, alectinib, and ceritinib should be collected from the ongoing Study 1006 and other sources. Once available, new findings should be appropriately communicated to healthcare professionals.

7.R.5 Dosage and administration

The proposed dosage and administration for lorlatinib were "The usual adult dosage is 100 mg of lorlatinib administered orally once daily. The dose may be adjusted according to the patient's condition." Also, the following descriptions were included in the "Precautions for Dosage and Administration" section:

- Criteria for treatment interruption, dose reduction, discontinuation of lorlatinib in case of an adverse drug reaction.

- The dose of lorlatinib should be reduced to 75 mg once daily when it is combined with a potent CYP3A inhibitor.

After the reviews on Sections "6.R.4 Concomitant use with CYP3A inhibitors," "7.R.2 Efficacy," and "7.R.3 Safety," and in the following subsections, PMDA concluded that the dosage regimen should be defined as per the proposal, along with the following information in the "Precautions for Dosage and Administration" section.

- Criteria for treatment interruption, dose reduction, discontinuation of lorlatinib in case of an adverse drug reaction

7.R.5.1 Dosage and administration of lorlatinib

The applicant's explanation about justification for the proposed dosage and administration of lorlatinib:

Phase II of Study 1001 was conducted using the dosage regimen determined based on the following study results. The results demonstrated the clinical benefits of lorlatinib in patients with *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC. Therefore, the dosage and administration of lorlatinib were proposed as above, based on the dosage regimen used in phase II of Study 1001.

- In phase I of Study 1001, lorlatinib was administered orally QD at 10, 25, 50, 75, 100, 150, or 200 mg, or orally BID at 35, 75, or 100 mg. Although the maximum tolerated dose (MTD) of lorlatinib was not determined, there were adverse events leading to treatment interruption or dose reduction in 3 of 3 patients (100%) and 2 of 3 patients (67%), respectively, in the 150 mg QD group. Therefore, RP2D of lorlatinib was determined to be 100 mg QD oral administration.

- In Japanese lead-in cohort (LIC) in Study 1001, no DLT was observed during 100 mg QD oral administration of lorlatinib, showing that oral lorlatinib 100 mg QD is well tolerated in Japanese patients.

PMDA accepted the explanation of the applicant.

7.R.5.2 Criteria for treatment interruption, dose reduction, and discontinuation of lorlatinib

The applicant's explanation about the criteria for treatment interruption, dose reduction, and discontinuation of lorlatinib:

Study 1001 had clearly specified criteria for treatment interruption, dose reduction, and discontinuation of lorlatinib, and results demonstrated the clinical benefits of lorlatinib. Based on these criteria with the following modification, the criteria for treatment interruption and discontinuation of lorlatinib and specific guidelines for the treatment of adverse drug reactions will be presented in the "Precautions for Dosage and Administration" section:

- The dose adjustment criteria for pancreatitis, ILD, QT interval prolongation, and decreased left ventricular ejection fraction (LVEF) were stipulated in Study 1001 but will not be included because there were only a few patients who experienced serious adverse events.

- Various CNS disorder-related adverse events occurred in Study 1001. In response, dose reduction is accepted clearly in the criteria even for patients experiencing a Grade 1 CNS disorder.

PMDA's view:
PMDA accepted the applicant's explanation about the criterion for CNS disorder, in light of various lorlatinib-induced adverse events observed in Study 1001 and the high stringency of modified criteria as compared with those used in Study 1001. However, for adverse events other than CNS disorders, criteria for treatment interruption, dose reduction, and discontinuation used in Study 1001 was defined with specific values based on the Grades of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), and the tolerability and safety of lorlatinib were confirmed when the criteria were followed. The table below shows dose adjustment criteria defined based on the Study 1001 criteria, and it should be provided in the "Precautions for Dosage and Administration" section.

- In case of a lorlatinib-induced adverse drug reaction, treatment should be interrupted or discontinued, or the dose of lorlatinib should be reduced according to the following criteria.

Doses in case of a dose reduction/discontinuation

Dose reduction level	Dose
Normal dose	100 mg/day
1st step dose reduction	75 mg/day
2nd step dose reduction	50 mg/day
Discontinuation	Discontinue administration if the dose of 50 mg/day is intolerable.

Criteria for treatment interruption, dose reduction, and discontinuation following an adverse drug reaction

Adverse drug reaction	Severity[Note1)]	Action
Pancreatitis	Grade ≤2 amylase and lipase increased, and evidence of pancreatitis in diagnostic imaging	Withhold lorlatinib until the imaging diagnosis normalizing to baseline while lipase and amylase increased remaining Grade ≤2. After recovery, resume lorlatinib at the next lower dose.
	Glade 3 or 4	Discontinue lorlatinib.
ILD	Grade 1 and symptomatic	• Withhold lorlatinib until recovery to baseline. After recovery, resume lorlatinib at the same dose. • Discontinue lorlatinib at relapse or persistence after 6-week withdrawal despite appropriate treatment.
	Grade 2	• Withhold lorlatinib until recovery to baseline. After recovery, resume lorlatinib at the next lower dose. • Discontinue lorlatinib at relapse or persistence after 6-week withdrawal despite appropriate treatment.
	Grade 3 or 4	Discontinue lorlatinib.
QT interval prolongation	Grade 3	Withhold lorlatinib until recovery to Grade ≤1. After recovery, resume lorlatinib at the next lower dose.
	Grade 4	Discontinue lorlatinib.
LVEF decreased	Grade 3 or 4	Discontinue lorlatinib.
Atrioventricular block	Atrioventricular block first degree	Symptomatic: Withhold lorlatinib until recovery to asymptomatic. After recovery, resume lorlatinib at the same dose or next lower dose.
	Atrioventricular block second degree	• Asymptomatic: Withhold lorlatinib until recovery of second degree atrioventricular block. After recovery, resume lorlatinib at the same dose or next lower dose. • Symptomatic: Withhold lorlatinib until recovery to asymptomatic and first degree or no block. After recovery, resume lorlatinib at the next lower dose. [Note2)]
	Atrioventricular block complete	Withhold lorlatinib until recovery to asymptomatic with PR interval of ≤200 msec. After recovery, resume lorlatinib at the next lower dose.[Note2)]
CNS disorder (including language disorder, memory impairment, sleep disorder, and cognitive disorder), visual disturbance	Grade 1	Continue lorlatinib at the same dose or withhold lorlatinib until recovery to baseline. After recovery, resume lorlatinib at the same dose or next lower dose.
	Grade 2 or 3	Withhold lorlatinib until recovery to Grade ≤1. After recovery, resume lorlatinib at the next lower dose.
	Grade 4	Discontinue lorlatinib.
Hyperlipidaemia (cholesterol total or triglycerides increased)	Grade 3	Continue lorlatinib at the same dose or withhold lorlatinib until recovery to Grade ≤2. After recovery, resume lorlatinib at the same dose.
	Grade 4	Withhold lorlatinib until recovery to Grade ≤2. After recovery, resume lorlatinib at the next lower dose.
Other nonhematological toxicity	Grade 3	Withhold lorlatinib until recovery to Grade ≤1 or baseline.[Note3)] After recovery, resume lorlatinib at the same dose or next lower dose.
	Grade 4	Withhold lorlatinib until recovery to Grade ≤1 or baseline.[Note3)] After recovery, resume lorlatinib at the next lower dose or discontinue lorlatinib.
Lymphopenia	Grade 3 or 4	Continue lorlatinib at the same dose[Note4)] or withhold lorlatinib until recovery to Grade ≤1 or baseline. After recovery, resume lorlatinib at the same dose or next lower dose.
Other hematological toxicity	Grade 3 or 4	Withhold lorlatinib until recovery to Grade ≤1 or baseline. After recovery, resume lorlatinib at the same dose or next lower dose.

Note 1): According to NCI-CTCAE ver. 4.03
Note 2): After pacemaker placement, resume lorlatinib at the same dose.
Note 3): Lorlatinib may be continued during asymptomatic Grade 4 hyperuricaemia or Grade 3 hypophosphataemia. Adjust the dose when Grade 3 to 4 nausea, vomiting, or diarrhoea persists.
Note 4): In the absence of infection or clinically significant toxicological findings

7.R.6 Post-marketing investigations

The applicant's explanation about their post-marketing surveillance plan:

In Study 1001, the incidence of CNS disorder was higher after the administration of lorlatinib than that of conventional ALK-TKIs in Japanese patients. CNS disorder will be defined as safety specification,

and a post-marketing survey will be conducted to investigate risk factors for CNS disorder. The survey will cover all patients receiving lorlatinib as post-marketing surveillance.

The planned sample size is 651. This sample size will allow the identification of risk factors of CNS disorder by comparing patient characteristics between patients who experience CNS disorder and those who do not, based on the occurrence of CNS disorder.

The follow-up period is 52 weeks. Most patients experienced the first episode of CNS disorder within 52 weeks after the start of lorlatinib treatment in Study 1001.

PMDA's view:
The discussion in Section "7.R.3 Safety," indicate the importance of investigation of risk factors for CNS disorders in the post-marketing surveillance. The applicant's plan is thus acceptable.

Because of limited data on the safety of lorlatinib treatment, relevant data should be collected promptly in an unbiased manner. Available safety data should be provided to healthcare professionals early. Therefore, the post-marketing surveillance should cover all patients receiving lorlatinib for a certain period.

To ensure post-marketing safety against ILD, etc., another risk minimization activity, i.e., condition setting for use of the drug (requirements for physicians and medical institutions, explanation to patients or their family members given by the prescribing physician, and request to pharmacists for collaboration) should be added because (a) there is only limited use experience in Japan, (b) there were patients who had a fatal or serious outcome after the administration of lorlatinib, as with conventional ALK-TKIs, and (c) a phase III study of lorlatinib (Study 1006) is currently ongoing. Whether to retain this additional activity should be reviewed when necessary, e.g., before the submission of periodic safety reports.

7.3 Adverse events, etc. observed in clinical studies

Deaths reported in the safety evaluation data were detailed in Sections "7.1 Evaluation data" and in "7.2 Reference data." The following subsections summarize major non-fatal adverse events.

7.3.1 Global phase I/II study (Study 1001)

7.3.1.1 Phase I

Adverse events occurred in 3 of 3 patients (100%) in the 10 mg QD group, 3 of 3 patients (100%) in the 25 mg QD group, 3 of 3 patients (100%) in the 50 mg QD group, 12 of 12 patients (100%) in the 75 mg QD group, 17 of 17 patients (100%) in the 100 mg QD group, 3 of 3 patients (100%) in the 150 mg QD group, 3 of 3 patients (100%) in the 200 mg QD group, 3 of 3 patients (100%) in the 35 mg BID group, 3 of 3 patients (100%) in the 75 mg BID group, and 4 of 4 patients (100%) in the 100 mg BID group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 3 of 3 patients (100%) in the 10 mg QD group, 3 of 3 patients (100%) in the 25 mg QD group, 3 of 3 patients (100%) in the 50 mg QD group, 11 of 12 patients (91.7%) in the 75 mg QD group, 16 of 17 patients (94.1%) in the 100 mg QD group, 3 of 3 patients (100%) in the 150 mg QD

group, 3 of 3 patients (100%) in the 200 mg QD group, 1 of 3 patients (33.3%) in the 35 mg BID group, 3 of 3 patients (100%) in the 75 mg BID group, and 4 of 4 patients (100%) in the 100 mg BID group. Adverse events with an incidence of ≥50% in any group were oedema peripheral in 3 patients (100%), amylase increased, electrocardiogram QT prolonged, lipase increased, aphasia, and neuropathy peripheral in 2 patients (66.7%) each in the 10 mg QD group; vomiting, hypercholesterolaemia, hypophosphataemia, paraesthesia, and cough in 2 patients (66.7%) each in the 25 mg QD group; asthenia in 2 patients (66.7%) in the 50 mg QD group; hypercholesterolaemia in 7 patients (58.3%) and blood cholesterol increased in 6 patients (50.0%) in the 75 mg QD group; hypercholesterolaemia in 12 patients (70.6%) and oedema peripheral in 9 patients (52.9%) in the 100 mg QD group; anaemia, oedema peripheral, and hypomagnesaemia in 3 patients (100%) each, fatigue, lung infection, blood creatinine increased, ejection fraction decreased, hypercholesterolaemia, hypokalaemia, cognitive disorder, confusional state, and hallucination in 2 patients (66.7%) each in the 150 mg QD group; hypercholesterolaemia in 3 patients (100%), constipation, diarrhoea, oedema, upper respiratory tract infection, urinary tract infection, AST increased, hypertriglyceridaemia, back pain, neuropathy peripheral, and haemoptysis in 2 patients (66.7%) each in the 200 mg QD group; dyspnoea in 2 patients (66.7%) in the 35 mg BID group; anaemia and oedema peripheral in 2 patients (66.7%) each in the 75 mg BID group; and diarrhoea, fatigue and oedema peripheral in 3 patients (75.0%) each, anaemia, abdominal pain upper, nausea, vomiting, gamma-glutamyltransferase (GGT) increased, weight increased, decreased appetite, back pain, headache, paraesthesia, cough, and dyspnoea in 2 patients (50.0%) each in the 100 mg BID group.

Serious adverse events occurred in 3 of 3 patients (100%) in the 10 mg QD group, 1 of 3 patients (33.3%) in the 25 mg QD group, 1 of 3 patients (33.3%) in the 50 mg QD group, 4 of 12 patients (33.3%) in the 75 mg QD group, and 9 of 17 patients (52.9%) in the 100 mg QD group, 3 of 3 patients (100%) in the 150 mg QD group, 1 of 3 patients (33.3%) in the 200 mg QD group, 2 of 3 patients (66.7%) in the 35 mg BID group, 2 of 3 patients (66.7%) in the 75 mg BID group, and 2 of 4 patients (50.0%) in the 100 mg BID group. The serious adverse event reported by ≥2 patients in any group was disease progression in 3 patients (17.6%) in the 100 mg QD group, and a causal relationship to the study drug was ruled out in either of them.

Adverse events led to treatment discontinuation in 1 of 3 patients (33.3%) in the 10 mg QD group, 2 of 3 patients (66.7%) in the 150 mg QD group, and 2 of 4 patients (50.0%) in the 100 mg BID group. There were no adverse events leading to treatment discontinuation reported by ≥2 patients in any group.

7.3.1.2 Phase II

Adverse events were observed in 274 of 275 patients (99.6%). Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 261 of 275 patients (94.9%). Table 47 shows adverse events with an incidence of ≥15%.

Table 47. Adverse events with an incidence of ≥15%

SOC PT (MedDRA ver. 20.0)	Number of patients 275	
	All Grades	Grade ≥3
All adverse events	274 (99.6)	175 (63.6)
Gastrointestinal disorders		
Diarrhoea	49 (17.8)	2 (0.7)
General disorders and administration site conditions		
Oedema peripheral	113 (41.1)	4 (1.5)
Investigations		
Blood cholesterol increased	96 (34.9)	19 (6.9)
Weight increased	57 (20.7)	6 (2.2)
Metabolism and nutrition disorders		
Hypercholesterolaemia	145 (52.7)	27 (9.8)
Hypertriglyceridaemia	155 (56.4)	42 (15.3)
Musculoskeletal and connective tissue disorders		
Arthralgia	54 (19.6)	0
Nervous system disorders		
Dizziness	42 (15.3)	2 (0.7)
Headache	42 (15.3)	2 (0.7)
Respiratory, thoracic and mediastinal disorders		
Cough	47 (17.1)	0
Dyspnoea	64 (23.3)	12 (4.4)

Serious adverse events occurred in 89 of 275 patients (32.4%). Serious adverse events reported by ≥3 patients were disease progression in 22 patients (8.0%), pyrexia and dyspnoea in 6 patients (2.2%) each, pneumonia in 5 patients (1.8%), pericardial effusion, mental status changes, and pulmonary embolism in 3 patients (1.1%) each. A causal relationship to the study drug could not be ruled out for pneumonia and mental status changes (1 patient each).

Adverse events led to treatment discontinuation in 21 of 275 patients (7.6%). Adverse events leading to treatment discontinuation reported by ≥2 patients were acute respiratory failure, dyspnoea, and respiratory failure in 2 patients (0.7%) each, and a causal relationship to the study drug was ruled out for all events.

7.3.2 Foreign phase I study (Study 1004)

Adverse events occurred in 5 of 6 patients (83.3%). A causal relationship to the study drug could not be ruled out in 3 of 6 patients (50.0%). The adverse event with an incidence of ≥50% was diarrhoea in 3 patients (50.0%).

There were no serious adverse events or adverse events leading to treatment discontinuation.

7.3.3 Foreign phase I study (Study 1005)

Adverse events occurred in 5 of 19 patients (26.3%) during the treatment with 100 mg of lorlatinib (acetic acid solvate formulation), 6 of 19 patients (31.6%) during the treatment with 100 mg of lorlatinib (free base formulation), and 3 of 19 patients (15.8%) during the treatment with 100 mg of lorlatinib (maleate formulation). A causal relationship to the study drug could not be ruled out in 2 of 19 patients (10.5%), 1 of 19 (5.3%), and 2 of 19 (10.5%), respectively. The adverse event with an incidence of ≥10% in any period was headache occurred in 2 patients (10.5%) during the treatment with free base lorlatinib 100 mg.

There were no serious adverse events or adverse events leading to treatment discontinuation.

7.3.4 Foreign phase I study (Study 1007)

Adverse events occurred in 4 of 11 patients (36.4%) during the period of intravenous lorlatinib 50 mg and 4 of 11 patients (36.4%) during the period of oral lorlatinib 100 mg. A causal relationship to the study drug could not be ruled out in 3 of 11 patients (27.3%) and 3 of 11 (27.3%), respectively. Adverse events with an incidence of ≥10% in either period were headache in 2 patients (18.2%) during the period of intravenous lorlatinib 50 mg and headache in 2 patients (18.2%) during the period of oral lorlatinib 100 mg.

There were no serious adverse events or adverse events leading to treatment discontinuation.

7.3.5 Foreign phase I study (Study 1008)

The study consisted of treatment periods with lorlatinib tablets 100 mg in the fasted state (a), lorlatinib tablets 100 mg after a high-fat meal (b), lorlatinib tablets 100 mg + rabeprazole in the fasted state (c), or lorlatinib solution 100 mg in the fasted state (d). Adverse events occurred in 19 of 24 patients (79.2%) with (a), 15 of 23 patients (65.2%) with (b), 9 of 23 patients (82.6%) with (c), and 16 of 24 patients (66.7%) with (d). A causal relationship to the study drug could not be ruled out in 19 of 24 patients (79.2%) with (a), 15 of 23 patients (65.2%) with (b), 19 of 23 patients (82.6%) with (c), and 16 of 24 patients (66.7%) with (d). The adverse event with an incidence of ≥30% observed in any treatment period was headache in 7 patients (30.4%) with (c), lorlatinib tablet 100 mg + rabeprazole administered in the fasted state.

No serious adverse events were reported.

Adverse events led to treatment discontinuation in 1 of 24 patients (4.2%) with (a), 1 of 23 patients (4.3%) with (b), and 1 of 23 patients (4.3%) with (c). These adverse events were atrioventricular block second degree with (a), atrioventricular block first degree with (b), and tonsillitis with (c). A causal relationship to the study drug could not be ruled out for atrioventricular block second degree with (a) and atrioventricular block first degree with (b).

7.3.6 Foreign phase I study (Study 1016)

The study consisted of treatment periods with lorlatinib in 25-mg clinical study tablets (a), lorlatinib in 25-mg commercial image tablets (b), lorlatinib in 50-mg commercial image tablets (c), or lorlatinib in a 100-mg commercial image tablet (d). Adverse events occurred in 13 of 20 patients (65.0%) with (a), 14 of 20 patients (70.0%) with (b), 12 of 20 patients (60.0%) with (c), and 14 of 20 patients (70.0%) with (d). A causal relationship to the study drug could not be ruled out in 12 of 20 patients (60.0%) with (a), 11 of 20 patients (55.0%) with (b), 10 of 20 patients (50.0%) with (c), and 13 of 20 patients (65.0%) with (d). The adverse event with an incidence of ≥20% in any treatment period was dry skin in 5 patients (25.0%) with (b).

There were no serious adverse events or adverse events leading to treatment discontinuation.

7.3.7 Foreign phase I study (Study 1011)

The study consisted of treatment periods with lorlatinib alone (a), rifampicin alone (b), or lorlatinib + rifampicin (c). Adverse events occurred in 1 of 12 patients (8.3%) with (a), 5 of 12 patients (41.7%) with (b), and 12 of 12 patients (100%) with (c). A causal relationship to the study drug could not be ruled out in 1 of 12 patients (8.3%) with (a), 4 of 12 patients (33.3%) with (b), and 12 of 12 patients (100%) with (c). Adverse events with an incidence of ≥30% in any treatment period were drug-induced liver injury in 12 patients (100%) and nausea in 9 (75.0%) occurring during the treatment with lorlatinib + rifampicin.

Serious adverse events occurred in 5 of 12 patients (41.7%) during the treatment with lorlatinib + rifampicin. The observed serious adverse event was drug-induced liver injury in 5 patients (41.7%). A causal relationship to the study drug could not be ruled out for the event in all patients.

Adverse events led to treatment discontinuation in 12 of 12 patients (100%) during the treatment with lorlatinib + rifampicin. The adverse event leading to treatment discontinuation in ≥2 patients was drug-induced liver injury observed in 11 patients (91.7%), and a causal relationship to the study drug could not be ruled out for the event in all patients.

7.3.8 Foreign phase I study (Study 1012)

The study consisted of treatment periods with lorlatinib alone (a), itraconazole alone (b), or lorlatinib + itraconazole (c). Adverse events occurred in 6 of 12 patients (50.0%) with (a), 8 of 12 patients (66.7%) with (b), and 11 of 12 patients (91.7%) with (c). Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 5 of 12 patients (41.7%) with (a), 8 of 12 patients (66.7%) with (b), and 11 of 12 patients (91.7%) with (c). Adverse events with an incidence of ≥30% in any treatment period were diarrhoea in 5 patients (41.7%) with (b) and diarrhoea and headache in 5 patients (41.7%) each with (c).

There were no serious adverse events or adverse events leading to treatment discontinuation.

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

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

The assessment is ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

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

The assessment is ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC progressed after ALK-TKI therapy, and that the product has acceptable safety in view of its benefits. Lorlatinib is the new active ingredient expected to have an inhibitory effect even against ALK fusion protein with

mutation that confers resistance to conventional ALK-TKIs. The product has clinical significance as a treatment option for *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC progressed after ALK-TKI therapy. The indication, conditions of approval, post-marketing investigations, etc. are subject to further discussion.

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

Review Report (2)

August 16, 2018

Product Submitted for Approval

Brand Name	Lorbrena Tablets 25 mg Lorbrena Tablets 100 mg
Non-proprietary Name	Lorlatinib
Applicant	Pfizer Japan Inc.
Date of Application	January 30, 2018

List of Abbreviations

See attachment.

1. Content of the Review

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

1.1 Efficacy

Following the review on Section "7.R.2 Efficacy" of the Review Report (1), PMDA concluded that the efficacy of lorlatinib was demonstrated in patients with *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC progressed after ALK-TKI therapy, by the response rate, etc. in Cohorts 2 to 5[37)] in phase II of the global phase I/II study (Study 1001) in patients with *ALK* fusion gene-positive advanced and/or recurrent NSCLC, by taking account of the following:

- Lorlatinib is an inhibitor targeted at ALK, the oncogenic driver, created based on the theoretical rationale derived from molecular diagnosis.

37) In phase II, the following patients were enrolled in each cohorts. Cohorts 3B, 4, and 5 enrolled patients regardless of the prior chemotherapy, except ALK-TKI.
Cohort 1: *ALK* fusion gene-positive patients without prior chemotherapy
Cohort 2: *ALK* fusion gene-positive patients with disease progression after treatment with crizotinib
Cohort 3A: *ALK* fusion gene-positive patients with disease progression after treatment with crizotinib and not more than 2 chemotherapies
Cohort 3B: *ALK* fusion gene-positive patients with disease progression after treatment with an ALK-TKI other than crizotinib
Cohort 4: *ALK* fusion gene-positive patients with disease progression after treatment with 2 ALK-TKIs
Cohort 5: *ALK* fusion gene-positive patients with disease progression after treatment with 3 ALK-TKIs
Cohort 6: *ROS1* fusion gene-positive patients

- Lorlatinib exhibited efficacy in patients with G1202R mutation,[38)] etc., which are known to confer resistance to conventional ALK-TKIs.

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

1.2 Safety

Following the review in Section "7.R.3 Safety" of the Review Report (1), PMDA concluded that the treatment with lorlatinib in patients with *ALK* fusion gene-positive unresectable advanced and/or recurrent NSCLC progressed after ALK-TKI therapy requires particular attention to QT interval prolongation, CNS disorders, pancreatitis, hepatic dysfunction, and ILD.

Besides the above-mentioned adverse events, hyperlipidaemia and cardiac disorders (except QT interval prolongation) are also subject to particular attention. PMDA concluded that lorlatinib is, however, tolerable for patients where their safety is secured by appropriate actions of physicians with adequate knowledge and experience in the treatment of cancer chemotherapy, i.e., monitoring and controlling adverse events, dose adjustment of lorlatinib, with utmost attention and control measures for serious adverse events such as ILD.

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

1.3 Clinical positioning and indication

In response to the review on Section "7.R.4 Clinical positioning and indication" of the Review Report (1), PMDA concluded that lorlatinib is a treatment option for patients with *ALK* fusion gene-positive NSCLC progressed after ALK-TKI therapy, and therefore that lorlatinib should be indicated for "*ALK* fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer progressed after therapy with ALK tyrosine kinase inhibitor(s)." Because (a) there are no clinical data available on the efficacy and safety of lorlatinib in patients without prior chemotherapy and (b) no information is currently available on the life-prolonging effect of lorlatinib, the "Precautions for Indications" section of the package insert should present the cautionary statements shown below.

In phase II of Study 1001, 11 patients intolerant to conventional ALK-TKI were included in Cohorts 2 to 5. Lorlatinib was effective in 4 of 10 patients evaluable for efficacy, suggesting that patients intolerant to ALK-TKI are eligible for lorlatinib treatment. However, the indications of many other anti-neoplastic agents are presented without "intolerance" clearly mentioned. Accordingly, the term "with resistance or intolerance to ALK tyrosine kinase inhibitor(s)" in the proposed indication is to be modified to "progressed after therapy with ALK tyrosine kinase inhibitor(s)."

Precautions for Indications

- The efficacy and safety of lorlatinib in the first-line therapy have not been established.

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38) Secondary gene mutation within the tyrosine kinase domain of ALK observed in patients treated with conventional ALK-TKI. The following gene mutations have been reported (*Cancers*. 2018;10:62):
L1196M, Leucine at position 1196 is replaced by methionine; G1269A, Glycine at position 1269 is replaced by alanine; F1174L, Phenylalanine at position 1174 is replaced by leucine; C1156Y, Cysteine at position 1156 is replaced by tyrosine; L1152R, Leucine at position 1152 is replaced by arginine; 1151Tins, Threonine is inserted at position 1151; S1206Y, Serine at position 1206 is replaced by tyrosine; I1171T, Isoleucine at position 1171 is replaced by threonine; G1202R, Glycine at position 1202 is replaced by arginine.

- The efficacy and safety of lorlatinib in the post-operative adjuvant therapy have not been established.

- Physicians should select patients to be treated with lorlatinib based on their good understanding of the "Clinical Studies" section of the package insert and of the efficacy and safety of lorlatinib, after due consideration of other treatment options.

The above opinions of PMDA were supported by the expert advisors at the Expert Discussion. Meanwhile, the following comment was raised from the expert advisors:

- The modified indication is rather unclear in terms of whether it includes patients intolerant to conventional ALK-TKIs. Therefore, the applicant's proposed indication, i.e., "*ALK* fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitor(s)" is also an option.

PMDA's view:
As commented by the Expert Advisors, the applicant's proposed indication, that is, "*ALK* fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitor(s)," is acceptable.

Accordingly, PMDA instructed the applicant to finalize the descriptions in the "Precautions for Indications" section as above and to define the indication for lorlatinib as "*ALK* fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitor(s)." The applicant agreed.

1.4 Dosage and administration

Following the review in Section "7.R.5 Dosage and administration" of the Review Report (1), PMDA concluded that the dosage and administration should be defined as "The usual adult dosage is 100 mg of lorlatinib administered orally once daily. The dose may be adjusted according to the patient's condition," as proposed by the applicant. The "Precautions for Dosage and Administration" section should give reminders on the criteria for treatment interruption, dose reduction, and discontinuation of lorlatinib in case of adverse drug reactions.

Also, following the review in Section "6.R.3 Concomitant use with CYP3A inducers" of the Review Report (1), PMDA concluded that the "Drug Interactions" section of the package insert should contraindicate the concomitant use of rifampicin with lorlatinib and to advise to avoid the concomitant use with other CYP3A inducers wherever possible.

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

Accordingly, PMDA instructed the applicant to define the dosage and administration as well as "Precautions for Dosage and Administration" section as above. The applicant agreed.

1.5 Risk management plan (draft)

The applicant plans to define CNS disorder as a safety specification and conduct post-marketing surveillance covering all patients receiving lorlatinib to investigate risk factors for CNS disorder, with the planned sample size of 651 and follow-up period of 52 weeks.

Following the review in Section "7.R.6 Post-marketing investigations" in Review Report (1), PMDA concluded that there is no problem in conducting the post-marketing surveillance as proposed by the applicant.

Further, PMDA concluded that additional risk minimization activities would be required. At present, the conventional ALK-TKIs are used under the conditions as additional risk minimization activities (defining requirements for physicians and medical institutions, the prescribing physician's explanation to patients or their family members, and requesting pharmacies for cooperation). Similarly, these additional risk minimization activities should be implemented for lorlatinib.

The above conclusion of PMDA was supported by the expert advisors. Meanwhile, the following comments were raised:

- In study 1011, all 12 patients who received both lorlatinib and rifampicin, a potent CYP3A inducer, experienced moderate to severe hepatic dysfunction. This suggests the possibility that the concomitant use of lorlatinib with a CYP3A inducer other than rifampicin may also cause hepatic dysfunction. Therefore, data collection on the occurrence of hepatic dysfunction during the concomitant use of lorlatinib with a CYP3A inducer is encouraged.

In response to the comments from the Expert Discussion, PMDA instructed the applicant to re-consider the plan of the post-marketing surveillance.

The applicant's explanation:

- The safety specifications will include (a) identification of risk factors for CNS disorders and (b) investigation of the effect of the combination of lorlatinib with a CYP3A inducer on hepatic dysfunction.

- The planned sample size is 651. This sample size will suffice to identify risk factors for CNS disorders [see Review Report (1) Section 7.R.6]. Based on the occurrence of hepatic dysfunction and the percentage of patients receiving lorlatinib with a CYP3A inducer in Study 1001, data of 651 patients enable to investigate the effect of lorlatinib with a CYP3A inducer on hepatic dysfunction.

- The follow-up period is 52 weeks. This will suffice to identify risk factors for CNS disorders [see Review Report (1) Section 7.R.6]. A 52-week follow-up period will also accommodate the investigation of hepatic dysfunction following the concomitant use of lorlatinib with a CYP3A

inducer. In Study 1011, hepatic dysfunction occurred within 2 days after the concomitant use of lorlatinib with rifampicin, a CYP3A inducer, in all affected patients.

PMDA accepted the applicant's explanation.

Based on the discussions above, PMDA has concluded that the current risk management plan (draft) for lorlatinib should include the safety specification presented in Table 48, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 49 and 50. Whether to retain "condition setting for the use of lorlatinib," an additional risk minimization activity listed, should be re-reviewed at the evaluation of the additional risk minimization activities for conventional ALK-TKIs or any appropriate timing.

Table 48. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• CNS disorders • ILD • QT interval prolongation	• Pancreatitis • Embryo-fetal toxicity • Hepatic dysfunction	• Use in patients with hepatic impairment • Safety of concomitant use with a CYP3A inducer
Efficacy specification		
Not applicable		

Table 49. Summary of additional pharmacovigilance activities, efficacy surveillance and studies, and additional risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy surveillance and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (all-case surveillance)	Not applicable	• Information provision based on the early post-marketing phase vigilance • Condition setting for use of lorlatinib • Preparation and distribution of materials for healthcare professionals

Table 50. Outline of post-marketing surveillance plan (draft)

Objective	To identify risk factors for CNS disorders and to investigate the effect of concomitant use with a CYP3A inducer on the onset of hepatic dysfunction
Survey method	All-case surveillance
Population	All patients treated with lorlatinib
Observation period	52 weeks
Planned sample size	651
Main survey items	Safety specification: CNS disorders and safety in concomitant use with a CYP3A inducer Other main survey items: Patient characteristics (age, sex, disease stage, past illness, concurrent illness, etc.), status of treatment with lorlatinib, etc.

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

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

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

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

The new drug application data (CTD 5.3.5.2.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. PMDA concluded that the clinical studies overall were conducted in compliance with GCP and that there were no obstacles to conducting its review based on the application documents submitted. PMDA identified the following inadequacy at the sponsor. Despite no significant impact on the review of the overall clinical studies, PMDA notified the applicant (sponsor) of the matter as an area for improvement.

Area for improvement

Sponsor:

- Some information on serious and unexpected adverse drug reactions, etc. was not notified to the head of the study site in a timely manner.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that Lorbrena may be approved for the indication and dosage and administration shown below, with the following conditions. However, necessary cautionary advice must be given in the package insert and information on the proper use of the product must be disseminated appropriately in the post-marketing setting. The proper use of the product must be strictly ensured under the supervision of physicians with adequate knowledge and experience in the treatment of cancer chemotherapy at medical institutions well-prepared for emergency care. Because Lorbrena is a drug with a new active ingredient, its re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

ALK fusion gene-positive unresectable advanced and/or recurrent non-small cell lung cancer with resistance or intolerance to ALK tyrosine kinase inhibitor(s)

Dosage and Administration

The usual adult dosage is 100 mg of lorlatinib administered orally once daily. The dose may be adjusted according to the patient's condition.

Conditions of Approval

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

2. Because of limited Japanese clinical study data, the applicant is required to conduct a post-marketing use-results survey covering all Japanese patients treated with the product. The survey must be continued until data of a certain number of patients are gathered so as to understand the characteristics of patients receiving the treatment and to collect safety and efficacy data promptly. Based on data collected, necessary measures must be taken to ensure the proper use of the product.

3. The applicant is required to take necessary measures, prior to its launch, to ensure that the product is prescribed by physicians with sufficient experience in the diagnosis and chemotherapy of lung cancer and that the product is available only at medical institutions and pharmacies with adequate capability to manage and explain the risks, etc. associated with the product.

Warning

The product should be administered only to patients recognized eligible for the treatment with the product by a physician with adequate knowledge and experience in cancer chemotherapy at a medical institution well-prepared for emergency care. Prior to treatment, patients or their families should be thoroughly informed of the potential risks and benefits of the treatment and provide consent.

Contraindications

1. Patients with a history of hypersensitivity to any ingredients of Lorbrena

2. Patients on treatment with rifampicin

Precautions for Indications

1. The efficacy and safety of lorlatinib in the first-line therapy have not been established.

2. The efficacy and safety of lorlatinib in post-operative adjuvant therapy have not been established.

3. Physicians should select patients to be treated with lorlatinib based on their good understanding of the "Clinical Studies" section of the package insert, and of the efficacy and safety of lorlatinib, after due consideration of other treatment options.

Precautions for Dosage and Administration

In case of a lorlatinib-induced adverse drug reaction, treatment should be interrupted or discontinued, or the dose of lorlatinib should be reduced according to the following criteria.

Doses in case of a dose reduction/discontinuation

Dose reduction level	Dose
Normal dose	100 mg/day
1st step dose reduction	75 mg/day
2nd step dose reduction	50 mg/day
Discontinuation	Discontinue administration if the dose of 50 mg/day is intolerable.

Criteria for treatment interruption, dose reduction, and discontinuation following an adverse drug reaction

Adverse drug reactions	Severity[Note1)]	Action
Pancreatitis	Grade ≤2 amylase or lipase increased, and evidence of pancreatitis in diagnostic imaging	Withhold lorlatinib until the imaging diagnosis normalizing to baseline, while lipase and amylase increased remaining Grade ≤2. After recovery, resume lorlatinib at the next lower dose.
	Glade 3 or 4	Discontinue lorlatinib.
Interstitial lung disease	Grade 1 and symptomatic	• Withhold lorlatinib until recovery to baseline. After recovery, resume lorlatinib at the same dose. • Discontinue lorlatinib at relapse or persistence after 6-week withdrawal despite appropriate treatment.
	Grade 2	• Withhold lorlatinib until recovery to baseline. After recovery, resume lorlatinib at the next lower dose. • Discontinue lorlatinib at relapse or persistence after 6-week withdrawal despite appropriate treatment.
	Grade 3 or 4	Discontinue lorlatinib.
QT interval prolongation	Grade 3	Withhold lorlatinib until recovery to Grade ≤1. After recovery, resume lorlatinib at the next lower dose.
	Grade 4	Discontinue lorlatinib.
Left ventricular ejection fraction decreased	Grade 3 or 4	Discontinue lorlatinib.
Atrioventricular block	Atrioventricular block first degree	Symptomatic: Withhold lorlatinib until recovery to asymptomatic. After recovery, resume lorlatinib at the same dose or next lower dose.
	Atrioventricular block second degree	• Asymptomatic: Withhold lorlatinib until recovery of second degree atrioventricular block. After recovery, resume lorlatinib at the same dose or next lower dose. • Symptomatic: Withhold lorlatinib until recovery to asymptomatic and first degree or no block. After recovery, resume lorlatinib at the next lower dose.[Note2)]
	Atrioventricular block complete	Withhold lorlatinib until recovery to asymptomatic with PR interval of <200 msec. After recovery, resume lorlatinib at the next lower dose.[Note2)]
CNS disorder (including language disorder, memory impairment, sleep disorder, and cognitive disorder), visual disturbance	Grade 1	Continue lorlatinib at the same dose or withhold lorlatinib until recovery to baseline. After recovery, resume lorlatinib at the same dose or next lower dose.
	Grade 2 or 3	Withhold lorlatinib until recovery to Grade ≤1. After recovery, resume lorlatinib at the next lower dose.
	Grade 4	Discontinue lorlatinib.
Hyperlipidaemia (increased total cholesterol or triglycerides)	Grade 3	Continue lorlatinib at the same dose or withhold lorlatinib until recovery to Grade ≤2. After recovery, resume lorlatinib at the same dose.
	Grade 4	Withhold lorlatinib until recovery to Grade ≤2. After recovery, resume lorlatinib at the next lower dose.
Other nonhematological toxicity	Grade 3	Withhold lorlatinib until recovery to Grade ≤1 or baseline.[Note3)] After recovery, resume lorlatinib at the same dose or next lower dose.
	Grade 4	Withhold lorlatinib until recovery to Grade ≤1 or baseline.[Note3)] After recovery, resume lorlatinib at the next lower dose or discontinue lorlatinib.
Lymphopenia	Grade 3 or 4	Continue lorlatinib at the same dose[Note4)] or withhold lorlatinib until recovery to Grade ≤1 or baseline. After recovery, resume lorlatinib at the same dose or next lower dose.
Other hematological toxicity	Grade 3 or 4	Withhold lorlatinib until recovery to Grade ≤1 or baseline. After recovery, resume lorlatinib at the same dose or next lower dose.

Note 1): According to NCI-CTCAE ver. 4.03
Note 2): After pacemaker placement, resume lorlatinib at the same dose.
Note 3): Lorlatinib may be continued during asymptomatic Grade 4 hyperuricaemia or Grade 3 hypophosphataemia. Adjust the dose when Grade 3 or 4 nausea, vomiting, or diarrhoea persists.
Note 4): In the absence of infection or clinically serious toxic findings

Appendix

List of Abbreviations

A/G ratio	albumin/globulin Ratio
Alectinib	alectinib hydrochloride
ALK	anaplastic lymphoma kinase
ALK-TKI	anaplastic lymphoma kinase-
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Application	application for marketing approval
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC_{ss}	area under the plasma concentration-time curve at steady state
AURKA	aurora kinase A
BA	bioavailability
BCRP	breast cancer resistance protein
BID	bis in die
BSA	bovine serum albumin
Ca	calcium
CI	confidence interval
Cl	chloride
CNS	central nervous system
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CrCL	creatinine clearance
CYP	cytochrome P450
^{14}C-lorlatinib	^{14}C-labeled lorlatinib
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EML4	echinoderm microtubule-associated protein-like 4
ERK	extracellular signal-regulated kinase
FER	FER tyrosine kinase
FES	FES proto-oncogene, tyrosine kinase
FIG	fused in glioblastoma
F_{rel}	relative bioavailability
FRET	fluorescence resonance energy transfer
FRK	fyn related Src family tyrosine kinase
GC	gas chromatography
GGT	gamma-glutamyltransferase
GLDH	glutamate dehydrogenase
HCl	hydrochloric acid
hERG	human *ether-a-go-go* related gene
HSP90	heat shock protein 90
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q1E Guideline	"Guideline on the Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3 2003).
ILD	interstitial lung disease
IR	infrared absorption spectrum

Japanese Clinical Practice Guidelines	Clinical Practice Guidelines for Lung Cancer, 2017 edition, Drug therapy for stage IV non-small-cell lung cancer, Edited by the Japan Lung Cancer Society,
K_a	absorption rate constant
K_I	inhibitor concentration at 50% of maximum inhibition rate
Ki	inhibition constant
KIF5B	kinesin family member 5B
k_{inact}	maximum inactivation rate constant
LC	liquid chromatography
LCK	lymphocyte-specific protein tyrosine kinase
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LIC	lead-in cohort
Lorlatinib	Lorlatinib
Lorlatinib/itraconazole	concomitant use of lorlatinib with itraconazole
Lorlatinib/rifampicin	concomitant use of lorlatinib with rifampicin
LTK	leukocyte receptor tyrosine kinase
LVEF	left ventricular ejection fraction
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
Na	sodium
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NE	not evaluable
NMR	nuclear magnetic resonance spectrum
NSCLC	non-small cell lung cancer
NTRK	neurotrophic receptor tyrosine kinase
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
$P_{app\ A\rightarrow B}$	apparent permeability in apical to basolateral direction
$P_{app\ B\rightarrow A}$	apparent permeability in basolateral to apical direction
PAR	proven acceptable range
PD	progressive disease
PEG	polyethylene glycol
PFS	progression free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPI	proton pump inhibitor
PPK	population pharmacokinetics
PPK/PD	population pharmacokinetics/pharmacodynamics
PR	partial response
PS	performance status
PT	preferred term
PTK2	protein tyrosine kinase 2
PTK2B	protein tyrosine kinase 2 beta
PTP	press through packaging

PXR	pregnane X receptor
QbD	quality by design
QD	quaque die
(Q)SAR	(quantitative) structure-activity relationship
QTcF	QT interval adjusted by Fridericia correction formula
Rabeprazole	rabeprazole sodium
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	c-ros oncogene 1
RP2D	recommended Phase II dose
SD	stable disease
SLC34A2	solute carrier family 34 member 2
SOC	system organ class
STAT3	signal transducer and activator of transcription 3
Study 1001	Study B7461001
Study 1004	Study B7461004
Study 1005	Study B7461005
Study 1006	Study B7461006
Study 1007	Study B7461007
Study 1008	Study B7461008
Study 1009	Study B7461009
Study 1010	Study B7461010
Study 1011	Study B7461011
Study 1012	Study B7461012
Study 1016	Study B7461016
TNK2	tyrosine kinase non receptor 2
UGT	uridine diphosphate glucuronosyl transferase
ULN	upper limit of normal
UV/VIS	ultraviolet/visible spectrum
UV-A	ultraviolet A
UV-B	ultraviolet B
V_2	volume of distribution of the central compartment
ΔQTcF	difference from placebo in changes from baseline in QTcF