Report on the Deliberation Results

June 3, 2019

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Rozlytrek Capsules 100 mg, Rozlytrek Capsules 200 mg
Non-proprietary Name	Entrectinib (JAN*)
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	December 19, 2018

Results of Deliberation

In its meeting held on May 30, 2019, 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, and the re-examination period is 10 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 the number of patients participating in clinical trials in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

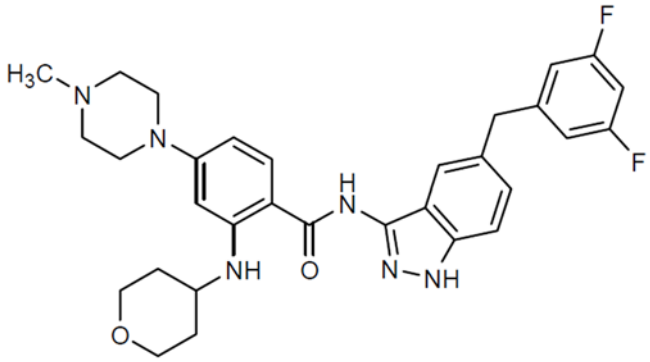
**Japanese Accepted Name (modified INN)*

Review Report

May 21, 2019
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	Rozlytrek Capsules 100 mg, Rozlytrek Capsules 200 mg
Non-proprietary Name	Entrectinib
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	December 19, 2018
Dosage Form/Strength	Capsules: Each capsule contains 100 or 200 mg of entrectinib.
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Chemical Structure	



Molecular formula: $C_{31}H_{34}F_2N_6O_2$
Molecular weight: 560.64
Chemical name:

N-{5-[(3,5-Difluorophenyl)methyl]-1*H*-indazol-3-yl}-4-(4-methylpiperazin-1-yl)-2-[(oxan-4-yl)amino]benzamide

Items Warranting Special Mention

SAKIGAKE designation drug (SAKIGAKE Drug Designation No. 6 of 2018 [*30 yaku*]; PSEHB/PED Notification No. 0903-2 dated September 3, 2018, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Orphan drug (Orphan Drug Designation No. 422 of 2018 [*30 yaku*]; PSEHB/PED Notification No. 1206-1 dated December 6, 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 a certain level of efficacy in the treatment of *NTRK* fusion-positive, advanced/recurrent solid tumors, 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 incidences of cardiac disorders (excluding QT interval prolongation), cognitive impairment/ataxia, QT interval prolongation, syncope, interstitial lung disease, and delayed growth and development, and the efficacy of the product in the treatment of *NTRK* fusion-positive, advanced/recurrent solid tumors should be further investigated.

Indication

NTRK fusion-positive, advanced/recurrent solid tumors

Dosage and Administration

The usual adult dosage is 600 mg of entrectinib administered orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition.

The usual pediatric dosage is 300 mg/m^2 (body surface area) of entrectinib administered orally once daily. The dose should not exceed 600 mg. The dosage should be reduced, as appropriate, according to the patient's condition.

Dosing in pediatric patients (300 mg/m^2 administered orally once daily)

Body surface area (m^2)	Dosage (once daily)
0.43-0.50	100 mg
0.51-0.80	200 mg
0.81-1.10	300 mg
1.11-1.50	400 mg
≥1.51	600 mg

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients participating in clinical trials in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

Attachment

Review Report (1)

April 11, 2019

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

Product Submitted for Approval

Brand Name	RO7102122 Capsules 100 mg, RO7102122 Capsules 200 mg
Non-proprietary Name	Entrectinib
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	December 19, 2018
Dosage Form/Strength	Capsules: Each capsule contains 100 or 200 mg of entrectinib.
Proposed Indication	*NTRK* fusion-positive, locally advanced or metastatic solid tumors

Proposed Dosage and Administration

The usual dosage in patients aged ≥18 years is 600 mg of entrectinib administered orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition.

The usual dosage in patients aged <18 years is 300 mg/m^2 (body surface area) of entrectinib administered orally once daily. The dose should not exceed 600 mg. The dosage should be reduced, as appropriate, according to the patient's condition.

Dosing in patients aged <18 years (300 mg/m^2 administered orally once daily)

Body surface area (m^2)	Dosage (once daily)
0.43-0.50	100 mg
0.51-0.80	200 mg
0.81-1.10	300 mg
1.11-1.50	400 mg
≥1.51	600 mg

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

The neurotrophic tyrosine receptor kinase (*NTRK*) genes[1)] that encode the receptor tyrosine kinases tropomyosin receptor kinases (TRK) fuse with other genes, producing TRK fusion proteins. The resulting fusion proteins constitutively activate downstream signaling pathways such as the mitogen-activated protein kinase (MAPK) pathway. These fusion proteins are one of the principal causes of oncogenesis etc., and have been reported to contribute to the proliferation/survival of tumor cells and the tumorigenesis of normal cells (*Nat Rev Clin Oncol*. 2018;15:731-47, *Cancers*. 2018;10;105, etc.).

Entrectinib is a small molecule inhibitor of tyrosine kinases including TRK, discovered by Nerviano Medical Sciences (Italy). It is considered to inhibit tumor growth by inhibiting the phosphorylation of TRK (TRKA, TRKB, TRKC) etc. and their downstream signal transducers.

1.2 Development history etc.

Outside Japan, Nerviano Medical Sciences (Italy) initiated a phase I study in patients with advanced/recurrent malignant solid tumors positive for *NTRK*, anaplastic lymphoma kinase (*ALK*), or c-ros oncogene 1 (*ROS1*) fusions etc. (ALKA study) in October 2012. Then, Ignyta (the US) and Roche (Switzerland) initiated a global phase II study in patients with *NTRK* fusion-positive, advanced solid tumors etc. (STARTRK-2 study) in November 2015.

In the US and the EU, a new drug application for entrectinib was filed based mainly on the results from the STARTRK-2 study in December 2018 and January 2019, respectively, and is currently under review.

As of March 2019, entrectinib has not been approved in any country or region.

In Japan, the STARTRK-2 study initiated patient enrollment in [redacted].

The applicant has submitted a marketing application for entrectinib based mainly on the results from the STARTRK-2 study.

Entrectinib received a SAKIGAKE designation (SAKIGAKE Drug Designation No. 6 of 2018 [*30 yaku*]) with the intended indication of "the treatment of adult and pediatric patients with NTRK gene fusion-positive, locally advanced or metastatic solid tumors who have progressed following prior therapies or have no acceptable standard therapies" in September 2018 and an orphan drug designation (Orphan Drug Designation No. 422 of 2018 [*30 yaku*]) with the intended indication of "*NTRK* fusion-positive, locally advanced or metastatic solid tumors" in December 2018.

[1)] TRKA, TRKB, and TRKC proteins are encoded by the genes *NTRK1*, *NTRK2*, and *NTRK3*, respectively.

The proposed brand name is to be changed from "RO7102122 Capsules 100 mg, RO7102122 Capsules 200 mg" to "Rozlytrek Capsules 100 mg, Rozlytrek Capsules 200 mg," at the applicant's request.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to pale pink powder or masses, and its description, solubility, hygroscopicity, melting point, dissociation constant, and partition coefficient have been determined. Four crystalline forms (, , , and), 2 forms of (and), and 1 hydrate ( ) of the drug substance occur, but ( ) only is formed at production scale and has been demonstrated to be stable at room temperature.

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

2.1.2 Manufacturing process

The drug substance is synthesized using as starting materials.

Quality by design (QbD) approaches were used, and a quality control strategy was established based on the following studies etc. (Table 1)

- Identification of critical quality attributes (CQAs)
- Identification of critical material attributes and critical process parameters (CPPs) through quality risk assessment, and determination of proven acceptable ranges

Table 1. Overview of drug substance control strategy

CQA	Method of control

and have been defined as critical steps, and process control items and values have been established for each step.

2.1.3 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identification (IR, high performance liquid chromatography [HPLC], and X-ray powder diffraction), purity ([redacted] [inductively coupled plasma mass spectrometry], related substances [HPLC], residual solvents [gas chromatography (GC)]), water content, residue on ignition, particle size, and assay (HPLC).

2.1.4 Stability of drug substance

Primary stability studies on the drug substance are shown in Table 2. The photostability data show that the drug substance is photostable.

Table 2. Stability studies on drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	4 production batches	25°C	60%RH	LDPE bag	12 months
Accelerated	4 production batches	40°C	75%RH		6 months

Based on the above, in accordance with the ICH Q1E guideline, a re-test period of [redacted] months has been proposed for the drug substance when packaged in [redacted] low-density polyethylene (LDPE) bag within [redacted] and stored at room temperature. The 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 an immediate-release hard capsule containing 100 or 200 mg of drug substance and the following excipients: anhydrous lactose, tartaric acid, crospovidone, hypromellose, microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of premixing, [redacted], mixing, and capsule filling. [redacted] has been defined as a critical step, and process control items and values have been established.

QbD approaches were used, and a quality control strategy was established based on the following studies etc. (Table 3)

- Identification of CQAs
- Determination of CPPs through quality risk assessment and design of experiments

Table 3. Overview of drug product control strategy

CQA	Method of control
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

2.2.3 Control of drug product

The proposed specifications for the drug product consist of strength, description (appearance), identification (UV and HPLC), purity (related substances [HPLC]), water content, uniformity of dosage units (mass variation test), microbial limits, dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

Primary stability studies on the drug product are shown in Table 4. The photostability data show that the drug product is photostable.

Table 4. Stability studies on drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term	3 production batches	30°C	65%RH	HDPE bottle (with desiccant) with a polypropylene cap	12 months
Accelerated	3 production batches	40°C	75%RH		6 months

Based on the above, in accordance with the ICH Q1E guideline, a shelf life of 24 months has been proposed for the drug product when packaged in a high-density polyethylene (HDPE) bottle (with desiccant) with a polypropylene/polyethylene cap and stored at room temperature. The long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

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

2.R.1 Proposed shelf-life for drug product

According to the ICH Q1A guideline, long-term and accelerated studies should be conducted on the dosage form packaged in the same container closure system as proposed for marketing. However, a shelf-life of 24 months has been proposed for the drug product, based on the data from stability studies (Table 4) conducted on the primary batches packaged in a container closure system that is different from the packaging proposed for marketing (Table 5).

Table 5. Differences in packaging for drug product

Drug product		Bottle size	Quantity of desiccant	Material of cap
Stability studies	100-mg capsule	[redacted] mL	[redacted] g	Polypropylene
	200-mg capsule	[redacted] mL	[redacted] g	
Proposed for marketing	100-mg capsule	[redacted] mL	[redacted] g	Polypropylene/ Polyethylene
	200-mg capsule	[redacted] mL	[redacted] g	

PMDA asked the applicant to explain the appropriateness of the proposed shelf-life for the drug product.

The applicant's response:
Although there is a concern about [redacted] for the drug product during the storage period due to [redacted], [redacted], etc. of the container attributable to differences in the packaging, given the following points, the effect of differences in the packaging on the stability of the drug product is considered small. Thus, the proposed shelf-life of 24 months based on the data from stability studies conducted on the primary batches packaged in a container closure system that is different from the packaging proposed for marketing (Table 4) should be acceptable.

- Since the quantity of desiccant used was determined, taking account of differences in the moisture permeability of packaging for stability studies and marketing at 40°C/75%RH, the possibility of [redacted] for the drug product should be low.
- A 3-month stability study of the to-be-marketed drug product stored in an uncapped bottle at 30°C/75%RH showed no changes over time for all attributes tested, including purity (related substances). Thus, the effect of differences in the packaging on the stability of the drug product should be small.
- There were no changes over time for all attributes tested up to [redacted] months in long-term and accelerated studies of the to-be-marketed drug product, which showed no different trend from the results of the studies on the primary stability batches.

PMDA's discussion:
As a general principle, the shelf-life of the drug product should be based on the data from long-term and accelerated studies conducted on the dosage form packaged in the same container closure system as proposed for marketing. However, given the above explanation by the applicant and the fact that the quantity of desiccant for the to-be-marketed drug product was determined conservatively based on the moisture permeability of packaging at 40°C/75%RH, the applicant's explanation (the effect of differences in the packaging on the stability of the drug product is small) and the proposed shelf-life of 24 months for the drug product based on the data from stability studies (Table 4) are acceptable.

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

3.1 Primary pharmacodynamics

3.1.1 Inhibition of phosphorylation of various kinases (CTD 4.2.1.1-1, 4.2.1.1-2, 4.2.1.1-3)

Inhibition of the phosphorylation of TRKA, TRKB, TRKC, ROS1, or ALK (recombinant proteins) by entrectinib or M5 (a metabolite of entrectinib) was determined by monitoring the incorporation of ^{33}P-ATP

into the substrate. The IC_{50} values of entrectinib and M5 for the inhibition of various kinases are shown in Table 6.

Table 6. Inhibition of phosphorylation of TRKA, TRKB, TRKC, ROS1, or ALK by entrectinib or M5

Kinase	IC_{50} value (nmol/L)	
	Entrectinib	M5
TRKA	1.7	2.5
TRKB	0.1	0.1
TRKC	0.1	0.2
ROS1	0.2	0.2
ALK	1.6	1.9

n = 1

Inhibition of the phosphorylation of 51 different kinases (recombinant proteins) by entrectinib was determined by monitoring the incorporation of ^{33}P-ATP into the substrate. The IC_{50} values of entrectinib were <100 nmol/L for the following kinases presented in Table 7.

Table 7. Inhibition of phosphorylation of different kinases by entrectinib

Kinase	IC_{50} value (nmol/L)
TRKA	2 ± 1
ROS1	7 ± 3
ALK	19 ± 9
JAK2	38 ± 27
ACK1	68 ± 14

Mean ± standard deviation (SD), n = 6

3.1.2 Inhibition of phosphorylation of TRK signal transducers (CTD 4.2.1.1-9, 4.2.1.1-14)

Using the human colorectal cancer (CRC) cell line KM12 harboring a *TPM3-NTRK1* gene fusion,[2)] inhibition of the phosphorylation of TRKA and downstream signal transducers (PLC-γ, AKT, ERK1/2) by entrectinib 10 nmol/L was determined by Western blotting. Entrectinib inhibited the phosphorylation of TRKA, PLC-γ, AKT, and ERK1/2.

Using SCID mice (3/group) subcutaneously xenografted with the human acute myeloid leukemia (AML) cell line (1) IMS-M2 or (2) M0-91 harboring an *ETV6-NTRK3* gene fusion,[3)] inhibition of the phosphorylation of TRKC and downstream signal transducers (PLC-γ, ERK1/2, STAT3) by entrectinib was determined by Western blotting. Mice were treated with a single oral dose of entrectinib 3 or 30 mg/kg when their tumor volume reached (1) 120 mm^3 or (2) 140 mm^3. In tumors at 4 hours post-dose, entrectinib at either dose level inhibited the phosphorylation of TRKC, PLC-γ, ERK1/2, and STAT3.

3.1.3 Inhibition of ROS1 phosphorylation (CTD 4.2.1.1-21)

Using the mouse pro-B cell line Ba/F3 transformed with an *ETV6-ROS1* gene fusion,[4)] inhibition of ROS1 phosphorylation by entrectinib was determined by Western blotting. Entrectinib inhibited ROS1 phosphorylation.

[2)] Exon 7 of *TPM3* fused to exon 10 of *NTRK1*
[3)] Exon 4 of *ETV6* fused to exon 15 of *NTRK3*
[4)] Exon 5 of *ETV6* fused to exon 34 of *ROS1*

3.1.4 Cell cycle arrest (CTD 4.2.1.1-7, 4.2.1.1-9)

Using the KM12 cell line, cell cycle distribution was analyzed by propidium iodide staining. Entrectinib increased the percentage of cells in the G_1 phase of the cell cycle.

3.1.5 Induction of apoptosis (CTD 4.2.1.1-7)

Using the KM12 cell line, the apoptotic effects of entrectinib were determined by measuring caspase 3/7 activity. Entrectinib induced apoptosis.

3.1.6 Anti-proliferative activity against malignant tumor cell lines

3.1.6.1 *In vitro* (CTD 4.2.1.1-4, 4.2.1.1-8, 4.2.1.1-13, 4.2.1.1-14, 4.2.1.1-21)

Entrectinib was tested for anti-proliferative activity against human malignant tumor cell lines harboring an *NTRK* or *ALK* fusion based on the amount of ATP from viable cells. The IC_{50} values of entrectinib are shown in Table 8.

Table 8. Anti-proliferative activity of entrectinib against cel lines harboring an *NTRK* or *ALK* fusion

Cell line	Fusion gene	Tumor type	n	IC_{50} value (nmol/L)
IMS-M2	*ETV6-NTRK3*	AML	4	0.47 ± 0.11
M0-91			4	0.65 ± 0.09
CUTO-3	*MPRIP-NTRK1*[*1]	NSCLC	1	1.255
KM12	*TPM3-NTRK1*	CRC	7	17 ± 4
SU-DHL-1	*NPM1-ALK*[*2]	Anaplastic large cell lymphoma (ALCL)	1	20
KARPAS-299			54	31 ± 17
SUP-M2			5	41 ± 20
SR-786			43	81 ± 33
NCI-H2228	*EML4-ALK*[*3]	NSCLC	6	68 ± 30

Mean ± SD; Individual values are listed for n = 1.
*1, Exon 22 of *MPRIP* fused to exon 12 of *NTRK1*; *2, Exon 4 of *NPM1* fused to exon 20 of *ALK*; *3, Exon 6 of *EML4* fused to exon 20 of *ALK*.

Entrectinib was tested for anti-proliferative activity against the Ba/F3 cell lines transformed with *NTRK* fusions based on the amount of ATP from viable cells. The IC_{50} values of entrectinib are shown in Table 9.

Table 9. Anti-proliferative activity of entrectinib against Ba/F3 cell lines transformed with *NTRK* fusions

Fusion gene	n	IC_{50} value (nmol/L)	Fusion gene	n	IC_{50} value (nmol/L)
TPM3-NTRK1	3	2.52 ± 0.11	*VCL-NTRK2*[*6]	2	6.50, 4.28
LMNA-NTRK1[*1]	2	1.31, 1.25	*AFAP1-NTRK2*[*7]	2	2.76, 2.94
ETV6-NTRK1	2	2.58, 2.41	*TRIP13-NTRK2*[*8]	2	0.74, 0.66
BCAN-NTRK1[*2]	2	0.49, 0.52	*ETV6-NTRK2*[*9]	2	4.04, 4.19
SQSTM1-NTRK1[*3]	2	0.83, 0.86	*ETV6(e5)-NTRK3(e15)*[*10]	2	3.50, 5.43
SCYL3-NTRK1[*4]	4	1.42 ± 0.17	*ETV6(e4)-NTRK3(e14)*[*11]	2	0.27, 0.47
PLEKHA6-NTRK1[*5]	4	1.05 ± 0.40			

Mean ± SD; Individual values are listed for n = 2.
*1, Exon 11 of *LMNA* fused to exon 11 of *NTRK1*; *2, Exon 13 of *BCAN* fused to exon 11 of *NTRK1*; *3, Exon 3 of *SQSTM1* fused to exon 10 of *NTRK1*; *4, Exon 11 of *SCYL3* fused to exon 12 of *NTRK1*; *5, Exon 14 of *PLEKHA6* fused to exon 10 of *NTRK1*; *6, Exon 16 of *VCL* fused to exon 12 of *NTRK2*; *7, Exon 13 of *AFAP1* fused to exon 12 of *NTRK2*; *8, Exon 3 of *TRIP13* fused to exon 13 of *NTRK2*; *9, Exon 5 of *ETV6* fused to exon 16 of *NTRK2*; *10, Exon 5 of *ETV6* fused to exon 15 of *NTRK3*; *11, Exon 4 of *ETV6* fused to exon 14 of *NTRK3*.

Entrectinib and crizotinib were tested for anti-proliferative activity against the Ba/F3 cell line transformed with an *ETV6-ROS1* gene fusion based on the amount of ATP from viable cells. The IC_{50} values of entrectinib and crizotinib (n = 1) were 5 and 180 nmol/L, respectively.

3.1.6.2 *In vivo*

3.1.6.2.1 Cell lines or tumor fragments derived from solid tumors harboring *NTRK1* fusions (CTD 4.2.1.1-10, 4.2.1.1-13, 4.2.1.1-17, 4.2.1.1-18, 4.2.1.1-20, 4.2.1.1-25)

The anti-tumor activity of entrectinib was assessed in nude mice (10/group) subcutaneously xenografted with the KM12 cell line. Treatment was initiated 7 days after xenografting (Day 7). Mice were treated orally with entrectinib 0.3, 1.5, 3, 15, or 30 mg/kg QD for 14 days, and tumor volumes were calculated. On Day 20, statistically significant tumor growth inhibition was seen in the entrectinib 15 and 30 mg/kg groups compared with the vehicle control[5)] group (Figure 1).

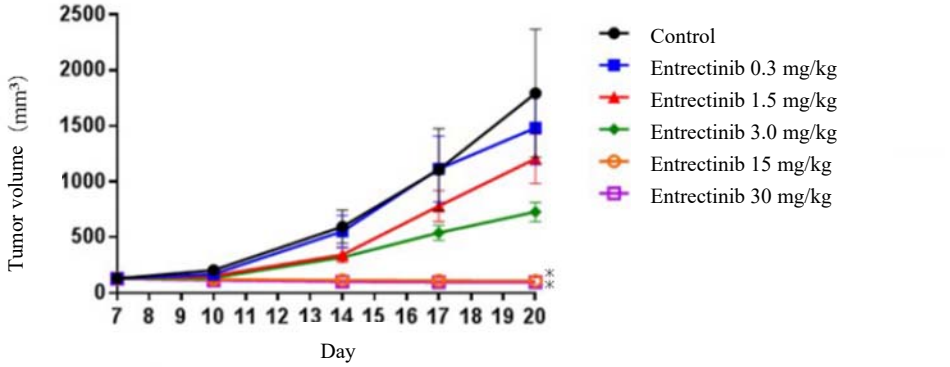


Figure 1. Anti-tumor activity of entrectinib in nude mice subcutaneously xenografted with KM12 cell line
n = 10; Mean ± standard error (SE); *, $P < 0.05$, entrectinib 15 mg/kg and 30 mg/kg vs. control (two-way ANOVA)

The anti-tumor activity of entrectinib was assessed in nude mice (10/group) subcutaneously xenografted with the human non-small cell lung cancer (NSCLC) cell line CUTO-3 harboring an *MPRIP-NTRK1* gene fusion. Treatment was initiated on Day 9. Mice were treated orally with entrectinib 0.1, 0.3, 1, 3, 10, or 30 mg/kg QD for 39 days, and tumor volumes were calculated. Statistically significant tumor growth inhibition was seen in the entrectinib 3, 10, and 30 mg/kg groups compared with the vehicle control[5)] group (Figure 2).

[5)] 0.5% methylcellulose containing 1% v/v polysorbate 80

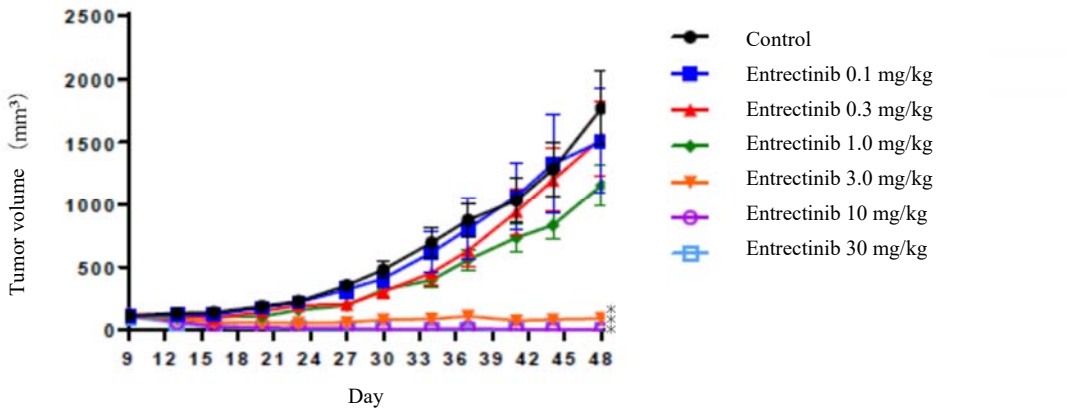


Figure 2. Anti-tumor activity of entrectinib in nude mice subcutaneously xenografted with CUTO-3 cell line
n = 10; Mean ± SE; *, $P < 0.05$, entrectinib 3.0 mg/kg, 10 mg/kg, and 30 mg/kg vs. control (two-way ANOVA)

The anti-tumor activity of entrectinib was assessed in nude mice (10/group) subcutaneously xenografted with head and neck cancer patient-derived CTG-0798 tumor fragments harboring an *ETV6-NTRK3* gene fusion.[6)] Treatment was initiated when their tumor volume reached 100 to 300 mm^3. Mice were treated orally with entrectinib 15 or 60 mg/kg BID for 21 days, and tumor volumes were calculated. Statistically significant tumor growth inhibition was observed in all entrectinib groups compared with the vehicle control[5)] group ($P \leq 0.0001$, Dunnett's multiple comparison test).

The anti-tumor activity of entrectinib was assessed in SCID mice (10/group) subcutaneously xenografted with sarcoma patient-derived G002 tumor fragments harboring a *TPM3-NTRK1* gene fusion.[7)] Treatment was initiated on Day 26. Mice were treated orally with entrectinib 0.1, 0.3, 1, 3, 10, or 30 mg/kg QD for 20 days, and tumor volumes were calculated. Statistically significant tumor growth inhibition was observed in the entrectinib 3, 10, and 30 mg/kg groups compared with the vehicle control[5)] group ($P < 0.05$, two-way ANOVA).

The anti-tumor activity of entrectinib was assessed in nude mice (9/group) intracranially injected with the KM12-Luc cell line.[8)] Treatment was initiated on Day 6. Mice were treated orally with entrectinib 10 or 30 mg/kg QD for 28 days, and survival time was determined. There was a statistically significant increase in survival time in all entrectinib groups compared with the vehicle control[5)] group ($P < 0.05$, one-way ANOVA).

3.1.6.2.2 Malignant tumor fragments harboring a *ROS1* fusion (CTD 4.2.1.1-22, 4.2.1.1-23)

The anti-tumor activity of entrectinib was assessed in nude mice (8/group) subcutaneously xenografted with NSCLC patient-derived CTG-0848 tumor fragments harboring a *CD74-ROS1* gene fusion.[9)] Treatment was initiated when their tumor volume reached 150 to 300 mm^3. Mice were treated orally with entrectinib 30 or 60 mg/kg BID for 29 days, and tumor volumes were calculated. Statistically significant tumor growth inhibition

[6)] Exon 5 of *ETV6* fused to exon 14 of *NTRK3*
[7)] Exon 7 of *TPM3* fused to exon 9 of *NTRK1*
[8)] Luciferase-expressing KM12 cell line
[9)] Exon 6 of *CD74* fused to exon 34 of *ROS1*

was seen in all entrectinib groups compared with the vehicle control[5] group ($P < 0.001$, Newman-Keuls multiple comparison test).

The anti-tumor activity of entrectinib was assessed in nude mice (10/group) subcutaneously xenografted with NSCLC patient-derived LU-01-0414 tumor fragments harboring a *SDC4-ROS1* gene fusion.[10] Treatment was initiated when their tumor volume reached 100 to 200 mm^3. Mice were treated orally with entrectinib 1.5 or 5 mg/kg BID for 21 days, or entrectinib 15 or 45 mg/kg BID for 49 days, and tumor volumes were calculated. Statistically significant tumor growth inhibition was seen in all entrectinib groups compared with the vehicle control[5] group ($P < 0.05$, Dunnett's multiple comparison test).

3.1.6.2.3 Cell lines derived from non-solid malignant tumors harboring an *NTRK3* fusion (CTD 4.2.1.1-15, 4.2.1.1-16)

The anti-tumor activity of entrectinib was assessed in SCID mice subcutaneously xenografted with the IMS-M2 or M0-91 cell line, and entrectinib displayed anti-tumor activity against both xenograft tumors.

3.2 Secondary pharmacodynamics

3.2.1 Effects on various receptors, ion channels, transporters, and enzymes (CTD 4.2.1.2-2, 4.2.1.2-3, 4.2.1.2-4, 4.2.1.2-5)

The effects of entrectinib and M5 on 89 receptors, ion channels, transporters, and enzymes were investigated. Entrectinib or M5 10 μmol/L caused ≥50% inhibition of the following receptors etc.: α_{1A}, α_{2A}, α_{2C}, CB2, D1, $D2_S$, D3, D5, δ (DOP), GR, sigma2, OX_1, H_1, H_2, kappa (KOP), M_1, M_4, M_5, μ (MOP), PPAR-γ, 5-HT_{1B}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{5A}, 5-HT_6, 5-HT_7, sst_4, L-type calcium channels (dihydropyridine and verapamil sites), potassium channel (human *ether-a-go-go* [hERG]), sodium channel (site 2), norepinephrine, dopamine, choline, serotonin transporter, and COX2.

The applicant's explanation about the above results:

Given that the entrectinib and M5 concentrations tested were ≥500-fold higher than the unbound entrectinib concentration at the recommended human dose (0.0157 μmol/L[11]), these effects are unlikely to cause safety issues in the clinical use of entrectinib, but binding to hERG-related gene channels may be associated with QT interval prolongation observed in clinical studies. The package insert will caution about QT interval prolongation [see Section 7.R.3.7].

3.3 Safety pharmacology

3.3.1 Effects on central nervous system (CTD 4.2.1.3-1)

Rats (5/group) received single or repeated oral doses of entrectinib 50, 100, or 200 mg/kg for 14 days, and the effects of entrectinib on clinical signs and body temperature were assessed by modified Irwin's test. Abnormal gait was observed in the entrectinib 200 mg/kg group on Day 14.

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[10] Exon 2 of *SDC4* fused to exon 32 of *ROS1*

[11] In the STARTRK-1 study, the C_{max} was 3.13 μmol/L on Day 14 of Cycle 1 in patients with solid tumors treated with entrectinib 600 mg QD [see Section 6.2.1.1]. The plasma protein binding was assumed to be 99.5% [see Section 4.2.2].

The applicant's explanation about the above finding:
Since the findings suggestive of ataxia such as balance disorder and gait disturbance were observed also in clinical studies [see Section 7.R.3.3] etc., the package insert will caution about ataxia.

3.3.2 Effects on cardiovascular system

3.3.2.1 Effects on hERG potassium current (CTD 4.2.1.3-2)

The effects of entrectinib 0.05, 0.5, 1.5, and 15 μmol/L on the hERG potassium current were assessed using the human embryonic kidney HEK293 cell line transfected with hERG. Entrectinib inhibited the hERG potassium current with an IC_{50} value of 0.6 μmol/L.

3.3.2.2 Effects on blood pressure, heart rate, and ECG (CTD 4.2.1.3-4)

Single oral doses of entrectinib 60 and 120 mg/kg were administered sequentially to dogs (n = 4) at an interval of 7 days to assess the effects of entrectinib on blood pressure, heart rate, ECG (RR interval, PR interval, QRS interval, QT interval, QTc interval), and body temperature. There were no entrectinib-related effects.

3.3.3 Effects on respiratory system (CTD 4.2.1.3-5)

Single oral doses of entrectinib 50, 100, and 200 mg/kg were administered to rats (8/group) to assess the effects of entrectinib on tidal volume, minute volume of ventilation, respiratory rate, peak inspiratory flow, peak expiratory flow rate, inspiratory time, expiratory time, time of pause, and pulmonary flow resistance. There were no entrectinib-related effects.

3.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the non-clinical pharmacology of entrectinib is acceptable, except for the considerations in the following section.

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

The applicant's explanation about the mechanism of action and efficacy of entrectinib in the treatment of *NTRK* fusion-positive solid tumors:
Gene fusions are one of the principal causes of oncogenesis (transformation) etc. The breakpoint cluster region-Abelson (BCR-ABL) fusion gene has been reported to act as an oncogenic driver in chronic myeloid leukemia, and *ALK* and *ROS1* fusions, etc. have been reported to act as oncogenic drivers in NSCLC (*Nature*. 2007;448:561-6, *Nat Med*. 2012;18:378-81). Likewise, given the following points etc., *NTRK* fusions are considered to act as an oncogenic driver in *NTRK* fusion-positive solid tumors across multiple tumor types.

- Transgenic mice encoding the *TRK-T1* fusion gene expressed in the murine thyroid follicular cells under the control of the thyroglobulin promoter, developed thyroid hyperplasia and papillary thyroid carcinoma (*Oncogene*. 2000;19:5729-35).

- In conditional knockin mice in which the expression of the *ETV6-NTRK3* fusion gene is activated by Cre recombinase, the whey acidic protein (WAP) gene promoter-driven expression of Cre recombinase led to breast cancer (*Cancer Cell*. 2007;12:542-58).

Moreover, the mechanism by which *NTRK* fusions drive oncogenesis (transformation) etc. is as follows. When the *NTRK* genes fuse with other genes, the resulting TRK (TRKA, TRKB, TRKC) fusion proteins drive ligand-independent activation of signaling pathways such as the MAPK pathway, causing increased cell proliferation, etc. (*Nat Rev Clin Oncol*. 2018;15:731-47, etc.)

Based on the above, entrectinib, which is a small molecule that binds to the TRK kinase domain (*Mol Cancer Ther*. 2016;15: 628-39), is considered to exhibit anti-tumor activity against *NTRK* fusion-positive solid tumors by inhibiting the phosphorylation of TRK (TRKA, TRKB, TRKC) fusion proteins etc. [see Section 3.1.1] and downstream signal transducers (PLC-γ, AKT, ERK1/2, etc.) [see Section 3.1.2]. Taking account of the mechanism by which *NTRK* fusions drive oncogenesis etc. and the following points, the efficacy of entrectinib in the treatment of *NTRK* fusion-positive solid tumors is expected across multiple tumor types.

- Irrespective of the identity of the fusion partner (the partner gene that fuses with the *NTRK* gene), entrectinib was bound to TRK fusion proteins and inhibited the kinase activities of these fusion proteins [see Section 3.1.2].
- Entrectinib exhibited anti-tumor activity against human solid tumor cell lines harboring multiple *NTRK* fusions [see Section 3.1.6].

PMDA asked the applicant to explain the latest findings on entrectinib resistance mutations.

The applicant's response:
Entrectinib has been reported to show similar TRKA inhibitory activity in *NTRK1* fusion-positive cell line with F589L[12)] mutation, which is considered a point mutation at the gatekeeper position in TRKA protein, and wild-type cell line (*Nat Rev Clin Oncol*. 2018;15:731-47). It has been reported that also in (1) *NTRK1* fusion-positive cell lines with G667S[13)] or V573M[14)] mutation, which are known to be responsible for larotrectinib (a TRK inhibitor, like entrectinib) (unapproved in Japan) resistance and (2) *NTRK1* fusion-positive cell lines with L564H,[15)] D679G,[16)] or F646I[17)] mutation, which are known to confer resistance to other TRK inhibitors, entrectinib largely retained TRKA inhibitory activity (*JCO Precis Oncol*. 2018;2:doi:10.1200/PO.18.00183, *Mol Cancer Ther*. 2017;16:2130-43).

12) phenylalanine at position 589 of TRKA substituted with leucine
13) glycine at position 667 of TRKA substituted with serine
14) valine at position 573 of TRKA substituted with methionine
15) leucine at position 564 of TRKA substituted with histidine
16) aspartic acid at position 679 of TRKA substituted with glycine
17) phenylalanine at position 646 of TRKA substituted with isoleucine

On the other hand, low kinase inhibitory activity of entrectinib has been reported in *NTRK1* fusion-positive cell lines with G595R,[18] G595L,[19] or G667C[20] mutation and *NTRK3* fusion-positive cell line with G623R[21] mutation (*Nat Rev Clin Oncol*. 2018;15:731-47, *Mol Cancer Ther*. 2017;16:2130-43). Though the number of cases was limited, 1 patient with *NTRK1* fusion-positive CRC and 1 patient with *NTRK3* fusion-positive mammary analog secretory carcinoma who progressed during treatment with entrectinib have been reported to have G595R and G667C mutations and G623R mutation, respectively, etc. (*Cancer Discov*. 2016;6:36-44, *Ann Oncol*. 2016;27:920-6)

PMDA's discussion:
PMDA largely accepted the above explanation by the applicant. However, the relationship between the presence of *NTRK* fusions and oncogenesis in each solid tumor type, and the detailed mechanism of acquiring resistance to entrectinib are not fully understood at present. As these issues may be important in the clinical use of entrectinib in terms of predicting efficacy and selecting appropriate patients, the applicant should continue to investigate them and appropriately inform healthcare professionals about new findings as they become available.

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

The non-clinical pharmacokinetics (PK) of entrectinib were studied in rats, dogs, etc. Studies on the plasma protein binding, drug metabolizing enzymes, transporters, etc. of entrectinib were conducted using human or animal biomaterials.

4.1 Absorption

4.1.1 Single-dose studies

Following a single intravenous (IV) dose of ^{14}C-entrectinib 2 mg/kg or a single oral dose of ^{14}C-entrectinib 20 mg/kg in male and female rats, plasma concentrations etc. of entrectinib and M5 (formed via demethylation) were determined (Table 10). There were no evident gender-related differences in the PK of entrectinib or M5. The bioavailability (BA) of entrectinib after oral administration was 36.9% in males and 39.5% in females. The applicant explained that since the V_{ss} of entrectinib is larger than the total body water in the rat (0.67 L/kg) (*Pharm Res.* 1993;10:1093-5) etc., entrectinib is considered to have high tissue distribution.

Table 10. PK parameters* of entrectinib and M5 (male and female rats, single IV or oral administration)

Dose (Route of administration)	Analyte	C_{max} (nmol/L)		t_{max} (h)		AUC_{inf} (nmol·h/L)		$t_{1/2}$ (h)		CL (L/h/kg)		V_{ss} (L/kg)	
		M	F	M	F	M	F	M	F	M	F	M	F
2 mg/kg (IV)	Entrectinib	1344	1369	0.083	0.083	2656	3529	3.28	3.70	1.34	1.01	6.34	5.40
	M5	6.01	3.93	1	4	96.3	—	10.8	—	—	—	—	—
20 mg/kg (Oral)	Entrectinib	795	1077	8	4	9340	13,333	5.24	4.18	—	—	—	—
	M5	25.6	26.7	8	4	—	249	—	7.23	—	—	—	—

*, PK parameters were calculated based on the mean plasma concentration at each time point (n = 3). —, Not calculated

[18] glycine at position 595 of TRKA substituted with arginine
[19] glycine at position 595 of TRKA substituted with leucine
[20] glycine at position 667 of TRKA substituted with cysteine
[21] glycine at position 623 of TRKC substituted with arginine

4.1.2 Repeated-dose studies

Male and female dogs were dosed orally with entrectinib 7.5, 15, or 30 mg/kg QD for 13 weeks, and plasma concentrations of entrectinib and M5 were determined (Table 11). The C_{max} and AUC_{24h} of entrectinib and M5 increased almost dose-proportionally over the dose range tested. The C_{max} and AUC_{24h} of entrectinib and M5 on Day 91 were higher than those on Day 1. There were no evident gender-related differences in the PK of entrectinib or M5.

Table 11. PK parameters of entrectinib and M5 (male and female dogs, 13-week oral administration)

Day	Dose (mg/kg)	Analyte	n	C_{max} (μmol/L)		t_{max}*1 (h)		AUC_{24h} (μmol·h/L)	
				M	F	M	F	M	F
1	7.5	Entrectinib	4	0.195 ± 0.110	0.136 ± 0.0282	2 (2, 2)	2 (2, 2)	1.06 ± 0.699	0.773 ± 0.212
		M5	4	0.203 ± 0.147	0.158 ± 0.0302	4 (4, 4)	4 (2, 4)	2.00 ± 1.46	1.52 ± 0.314
	15	Entrectinib	4	0.274 ± 0.0965	0.299 ± 0.198	1.5 (1, 2)	1.5 (1, 2)	1.52 ± 0.565	1.92 ± 1.52
		M5	4	0.262 ± 0.109	0.261 ± 0.157	3 (2, 4)	4 (4, 4)	2.53 ± 1.19	3.12 ± 2.28
	30	Entrectinib	6	0.528 ± 0.271	0.564 ± 0.450	2 (1, 2)	2 (1, 2)	3.31 ± 1.84	4.17 ± 2.97
		M5	6	0.403 ± 0.187	0.451 ± 0.250	4 (2, 4)	4 (1, 4)	4.73 ± 2.88	5.77 ± 4.42
91	7.5	Entrectinib	4	0.276 ± 0.0404	0.226 ± 0.148	3 (2, 4)	2 (1, 2)	1.93 ± 0.289	1.81 ± 1.69
		M5	4	0.239 ± 0.0565	0.204 ± 0.130	4 (2, 4)	4 (2, 4)	2.66 ± 0.893	2.44 ± 1.67
	15	Entrectinib	4	0.476 ± 0.232*2	0.673 ± 0.398	2 (1, 4)*2	2 (2, 2)	3.39 ± 1.42*2	5.04 ± 2.18
		M5	4	0.350 ± 0.122*2	0.488 ± 0.160	4 (2, 4)*2	4 (2, 4)	4.46 ± 1.76*2	6.45 ± 1.85
	30	Entrectinib	6	0.912 ± 0.482	0.839 ± 0.672	2 (2, 4)	2 (2, 2)	8.04 ± 4.94	7.09 ± 5.98
		M5	6	0.699 ± 0.419	0.605 ± 0.467	4 (4, 4)	4 (4, 4)	9.06 ± 5.65	8.06 ± 7.45

Arithmetic mean ± SD; *1, Median (Range); *2, n = 3

4.1.3 *In vitro* cell permeability

The cell permeability of entrectinib was evaluated in the human CRC Caco-2 cell line. The apparent permeability in apical to basolateral direction ($P_{app\ A\rightarrow B}$) of entrectinib 0.1 μmol/L was 1.07×10^{-6} cm/sec in the presence of cyclosporin (a P-gp inhibitor) 10 μmol/L. The applicant explained that entrectinib is moderately permeable, given that the $P_{app\ A\rightarrow B}$ values of poorly permeable atenolol 100 μmol/L and highly permeable minoxidil 10 μmol/L were 0.191×10^{-6} and 5.25×10^{-6} cm/sec, respectively.

4.2 Distribution

4.2.1 Tissue distribution

Male pigmented and albino rats received a single oral dose of ^{14}C-entrectinib 20 mg/kg, and the tissue distribution of radioactivity was studied using quantitative whole-body autoradiography. In pigmented rats, extensive tissue distribution of radioactivity was observed, and radioactivity concentrations peaked by 8 hours post-dose in most tissues including blood. In pigmented rats, the maximum concentrations of radioactivity in the bile, lung, pituitary gland, and liver (66,200, 44,900, 31,500, and 29,800 ng Eq./g, respectively) were particularly higher than the maximum concentration of radioactivity in blood (2370 ng Eq./g). The tissue distribution of radioactivity in albino rats was similar to that in pigmented rats, except for the uvea and eyeball. The maximum concentrations of radioactivity in the uvea and eyeball of pigmented rats (24,100 and 4160 ng Eq./g, respectively) were markedly higher than those of albino rats (3590 and 523 ng Eq./g, respectively). The radioactivity concentrations in the uvea and eyeball of pigmented rats at 24 hours post-dose (23,200 and 4000 ng Eq./g, respectively) were higher than those of albino rats (608 ng Eq./g and below the detection limit

[179 ng Eq./g], respectively), and the elimination of radioactivity tended to be slow in pigmented rats. The applicant explained that the above results indicated that entrectinib or its metabolites bind to melanin.

4.2.2 Plasma protein binding

The plasma from mouse, rat, dog, monkey, or human was incubated with (1) entrectinib (5 and 50 μmol/L) or (2) M5 (0.5, 2.5, and 10 μmol/L) at 37℃ for (1) 6 or (2) 5 hours, and the plasma protein binding of entrectinib and M5 was determined using an equilibrium dialysis method. The plasma protein binding of entrectinib and M5 was almost constant, regardless of concentration, across all animal species. The plasma protein binding of (1) entrectinib (50 μmol/L) and (2) M5 (10 μmol/L) in mouse, rat, dog, monkey, and human plasma was (1) 98.35%, 99.32%, >99.98%, 99.17%, and 99.39%, respectively, and (2) 99.8%, 99.8%, 99.8%, 99.7%, and 99.9%, respectively.

Human serum albumin (45 g/L) or human α1-acid glycoprotein (0.7 g/L) was incubated with entrectinib (1 μmol/L) at 37℃ for 5 hours, and the binding of entrectinib to human serum albumin and human α1-acid glycoprotein was determined using an equilibrium dialysis method. The binding of entrectinib to human serum albumin and human α1-acid glycoprotein was 98.7% and 98.2%, respectively. The applicant explained that the above results indicated that entrectinib binds to both serum albumin and α1-acid glycoprotein in human plasma.

4.2.3 Distribution in blood cells

The blood from mouse, rat, or human was incubated with entrectinib (3 μmol/L) or M5 (3 μmol/L) at 37℃ for 30 minutes, and the distribution of entrectinib and M5 in blood cells was determined. The blood to plasma concentration ratios of (1) entrectinib and (2) M5 in mouse, rat, and human blood were (1) 1.8, 2.0, and 1.3, respectively, and (2) 1.2, 1.5, and 1.0, respectively. The applicant explained that the above results indicated that entrectinib and M5 are distributed in blood cells in all animal species tested.

4.2.4 Placental transfer to fetus

Placental and fetal transfer of entrectinib or M5 has not been studied. The applicant explained that since a rat embryo-fetal development study showed toxicities such as fetal external and skeletal abnormalities [see Section 5.5], entrectinib or its metabolites may cross the placenta into the fetus.

4.3 Metabolism

4.3.1 *In vitro*

Mouse, rat, dog, monkey, and human hepatocytes were incubated with entrectinib (10 μmol/L) at 37℃ for 1 hour, and the metabolites of entrectinib were identified. In all of mouse, rat, dog, monkey, and human hepatocytes, M2, M3, M7, and M14 (all formed via oxidization), in addition to M5, were detected. M1 (formed via oxidization) and M11 (formed via *N*-glucuronidation) were also detected in monkey and human hepatocytes. The applicant explained that the above results etc. indicated that the major metabolic pathways of entrectinib are demethylation, oxidization, and glucuronidation.

The applicant explained that the following study results (1) (2) indicated that (1) entrectinib is metabolized primarily by CYP3A4, and that (2) UGT1A4 is involved in the glucuronidation of entrectinib. Pharmacokinetic interactions of entrectinib with a CYP3A inhibitor or a CYP3A inducer are described in Section "6.2.2.1 Drug interaction study with itraconazole or rifampicin."

(1) Recombinant human CYP isoforms (CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2D6, CYP2E1, CYP3A4, or CYP3A5) were incubated with entrectinib (10 μmol/L) in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37°C for 1 hour, and CYP isoforms involved in the metabolism of entrectinib were identified. In the presence of CYP3A4, the percentage of entrectinib that remained intact was reduced to 56%. In the presence of other CYP isoforms tested, 79% to 102% of entrectinib remained intact, and there were no clear reductions in this percentage.

(2) Recombinant human uridine diphosphate glucuronsyl transferase (UGT) isoforms (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2 B7, UGT2B10, UGT2B15, or UGT2B17) were incubated with ^{14}C-entrectinib (2 μmol/L) in the presence of uridine diphosphate glucuronic acid (UDPGA) at 37°C for 1 hour, and UGT isoforms involved in the glucuronidation of entrectinib were identified. In the presence of UGT1A4, M11 was detected.

4.3.2 *In vivo*

Male and female rats received (1) a single intravenous dose of ^{14}C-entrectinib 2 mg/kg or (2) a single oral dose of ^{14}C-entrectinib 20 mg/kg, and its metabolites in plasma and feces were identified. The following results were obtained.

- In the plasma collected at 4 hours post-dose, the unchanged drug was mainly detected (In males and females, the unchanged drug accounted for (1) 100% and 100%, respectively, and (2) 94.0% and 100%, respectively, of the total radioactivity in plasma).
- In the feces collected up to 24 hours post-dose, the unchanged drug and M5 were mainly detected (representing (1) 49.6% and 40.6%, respectively, and (2) 72.7% and 25.6%, respectively, of the administered radioactivity, in males, and (1) 50.6% and 36.7%, respectively, and (2) 79.6% and 20.4%, respectively, of the administered radioactivity, in females).

Male dogs received (1) a single intravenous dose of ^{14}C-entrectinib 1 mg/kg or (2) a single oral dose of ^{14}C-entrectinib 10 mg/kg, and its metabolites in plasma and feces were identified. The following results were obtained.

- In the plasma collected up to 6 hours post-dose, the unchanged drug and M5 were mainly detected (accounting for (1) 53.5% and 46.5%, respectively, and (2) 30.1% and 69.9%, respectively, of the total radioactivity in plasma).
- In the feces collected up to 12 to 24 hours post-dose, M5 was mainly detected (representing (1) 91.8% and (2) 93.7% of the administered radioactivity).

4.4 Excretion

4.4.1 Urinary and fecal excretion

The applicant explained that the following study results indicated that entrectinib and its metabolites are excreted predominantly in feces.

- Male and female rats received (1) a single intravenous dose of ^{14}C-entrectinib 2 mg/kg or (2) a single oral dose of ^{14}C-entrectinib 20 mg/kg. The recoveries of radioactivity in urine and feces over 168 hours (the percentage of the administered radioactivity) were determined. In males, (1) 1.64% and 102% and (2) 0.849% and 97.4% of the administered radioactivity were recovered in urine and feces, respectively. In females, (1) 1.28% and 99.5% and (2) 0.686% and 97.7% of the administered radioactivity were recovered in urine and feces, respectively.
- Male dogs received (1) a single intravenous dose of ^{14}C-entrectinib 1 mg/kg or (2) a single oral dose of ^{14}C-entrectinib 10 mg/kg, and (1) 0.612% and 78.0% and (2) 0.401% and 84.6% of the administered radioactivity were recovered in urine and feces, respectively, over 120 hours.

When male and female dogs were dosed orally with entrectinib 7.5, 15, or 30 mg/kg QD for 13 weeks, a multiphasic decline in plasma concentrations of entrectinib and M5, suggestive of enterohepatic circulation, did not occur following the first dose, etc. Thus, the applicant explained that enterohepatic circulation is considered to contribute little to the PK of entrectinib and M5.

4.4.2 Excretion into milk

Entrectinib or M5 excretion in milk has not been studied. The applicant explained that given that (1) the plasma protein binding of entrectinib and M5 is high [>99%, see Section 4.2.2], and that (2) M5 has been shown to be a substrate of breast cancer resistant protein (BCRP) [see Section 4.5.3], etc., M5 may be excreted in milk.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation about pharmacokinetic interactions via inhibition of metabolizing enzymes by entrectinib and M5:

Given the following study results, and the $C_{max,ss}$ values of entrectinib and M5 following the proposed dosing regimen (2.48 and 0.997 μmol/L,[22)] respectively), entrectinib is unlikely to cause pharmacokinetic interactions via inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 by entrectinib or M5, or inhibition of CYP3A by M5 in clinical use. On the other hand, entrectinib has the potential to cause pharmacokinetic interactions via inhibition of CYP3A.

- Human liver microsomes were incubated with entrectinib (0.00729-10 μmol/L) or M5 (0.025-25 μmol/L) in the presence of the substrates for CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19,

[22)] The C_{max} values on Day 1 of Cycle 2 in Japanese patients treated orally with entrectinib 600 mg QD in a global phase II study (STARTRK-2 study)

CYP2D6, or CYP3A)[23] and NADPH, and the potential of entrectinib and M5 to inhibit the CYP isoforms was assessed. Entrectinib inhibited the metabolism of a CYP3A substrate (testosterone) with an IC_{50} value of 2.04 μmol/L. M5 inhibited the metabolism of a CYP2C8 substrate with an IC_{50} value of 4.9 μmol/L. On the other hand, entrectinib or M5 did not cause evident inhibition of the metabolism of the substrates for other CYP isoforms tested.

- Human liver microsomes were preincubated with entrectinib (0.00729-10 μmol/L) or M5 (0.025-25 μmol/L) in the presence of NADPH, and then incubated with the substrates for CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A),[23] and entrectinib and M5 were evaluated as time-dependent inhibitors of these CYP isoforms. Entrectinib caused time-dependent inhibition of the metabolism of a CYP3A substrate (testosterone), with an IC_{50} value of 1.28 μmol/L. On the other hand, entrectinib did not cause evident time-dependent inhibition of the metabolism of the substrates for other CYP isoforms tested. M5 did not cause evident time-dependent inhibition of the metabolism of any of the substrates for the CYP isoforms tested.

4.5.2 Enzyme induction

The applicant's explanation about pharmacokinetic interactions via induction of metabolizing enzymes by entrectinib:

Given (1) the following study results and (2) the $C_{max,ss}$ values of entrectinib and M5 following the proposed dosing regimen (2.48 and 0.997 μmol/L,[22] respectively) etc., entrectinib is unlikely to cause pharmacokinetic interactions via induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP3A, or induction of CYP1A2, CYP2B6, CYP2C19, or CYP3A by M5 in clinical use.

- Human hepatocytes were incubated with entrectinib (1 and 10 μmol/L) for 24 hours, and the mRNA expression levels of CYP isoforms (CYP1A2, CYP2B6, CYP3A4) were determined. Positive controls[24] caused 87-, 5-, and 78-fold increases in the mRNA expression levels of CYP1A2, CYP2B6, and CYP3A4, respectively, compared with vehicle (0.1% dimethyl sulfoxide [DMSO]). Entrectinib (10 μmol/L) induced the mRNA expression of CYP1A2 and CYP3A4, and caused 7- and 29-fold increases in the mRNA expression levels of CYP1A2 and CYP3A4, respectively, compared with vehicle (0.1% DMSO). On the other hand, entrectinib (10 μmol/L) caused no evident increases in the mRNA expression level of CYP2B6.
- Human hepatocytes were incubated with entrectinib (1-10 μmol/L) for 3 days, and the mRNA expression levels or activities of CYP isoforms (CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A) were determined.[25] The increases in the mRNA expression of CYP2C8, CYP2C9, and CYP3A4 caused by entrectinib [(1) 3 μmol/L and (2) 10 μmol/L] were (1) 30.8%, 38.3%, and 12.5%, respectively, and (2) 90.2%, 109%, and 47.9%, respectively, of those caused by positive control.[26] On the other hand,

[23] For the assessment of the potential of entrectinib to inhibit CYP isoforms, phenacetin, efavirenz, amodiaquine, diclofenac, *S*-mephenytoin, and *R*-bufuralol were used as the substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, respectively, and midazolam and testosterone were used as CYP3A substrates. For the assessment of the potential of M5 to inhibit CYP isoforms, the same drugs as used for entrectinib were used as CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A substrates, and dextromethorphan was used as CYP2D6 substrate.

[24] Omeprazole (50 μmol/L), phenobarbital (1000 μmol/L), and rifampicin (25 μmol/L) were used as positive controls for CYP1A2, CYP2B6, and CYP3A4, respectively.

[25] The potential of entrectinib to induce CYP1A2 mRNA expression and activity, the mRNA expression of CYP2C8 and CYP2C9, CYP2C19 activity, CYP3A4 mRNA expression, and CYP3A activity was assessed.

[26] Rifampicin (20 μmol/L) was used as positive control for CYP2C8, CYP2C9, and CYP3A4.

entrectinib (3 and 10 μmol/L) caused no evident increases in CYP1A2 mRNA expression and activity, CYP2C19 activity, or CYP3A activity.

- Human hepatocytes were incubated with M5 (0.1-10 μmol/L) for 3 days, and the mRNA expression levels or activities of CYP isoforms (CYP1A2, CYP2B6, CYP2C19, and CYP3A) were determined.[27] The increases in the mRNA expression levels of CYP1A2, CYP2B6, and CYP3A4 caused by M5 (10 μmol/L) were 1.7%, 26.5%, and 16.5%, respectively, of those caused by positive controls.[28] On the other hand, M5 (10 μmol/L) caused no evident increases in the activities of CYP1A2, CYP2B6, CYP2C19 and CYP3A.

4.5.3 Transporters

The applicant's explanation about transporter-mediated pharmacokinetic interactions of entrectinib or M5:

The following study results etc. showed that entrectinib is not a substrate of BCRP, organic anion transporting polypeptide (OATP) 1B1, or OATP1B3, but is a substrate of p-glycoprotein (P-gp), and that M5 is not a substrate of OATP1B1, OATP1B3, or organic cation transporter (OCT) 1, but is a substrate of P-gp and BCRP.

- P-gp-mediated transport of entrectinib (3 μmol/L) or M5 (1.5 μmol/L) was investigated using the canine kidney MDCKII cell line expressing human P-gp. The efflux ratios of entrectinib were 13.8 and 1.25 in the absence and presence of a P-gp inhibitor (valspodar, 10 μmol/L), respectively. The efflux ratios of M5 were 108 and 28.0 in the absence and presence of a P-gp inhibitor (elacridar, 3 μmol/L), respectively.
- BCRP-mediated transport of entrectinib (3 μmol/L) or M5 (1.5 μmol/L) was investigated using the MDCKII cell line expressing human BCRP. In the absence and presence of a BCRP inhibitor (Ko143, 1 μmol/L), the efflux ratios of entrectinib were 1.72 and 1.18, respectively, and the efflux ratios of M5 were 33.2 and 8.77, respectively.
- OATP1B1- or OATP1B3-mediated transport of entrectinib (1-25 μmol/L) was investigated using the HEK293 cell lines expressing human OATP1B1 or OATP1B3. An OATP1B1 and OATP1B3 inhibitor[29] did not show a clear inhibitory effect on the uptake of entrectinib in the cells.
- OATP1B1-, OATP1B3-, or OCT1-mediated transport of M5 (0.15-15 μmol/L) was investigated using the MDCKII cell lines expressing human OATP1B1, OATP1B3, or OCT1. The ratios of the uptake of M5 in the OATP1B1-, OATP1B3-, or OCT1-expressing cell lines to the uptake in the parental cell line were all <2.

Given (1) the following study results, (2) the $C_{max,ss}$ values of entrectinib and M5 following the proposed dosing regimen (2.48 and 0.997 μmol/L,[22] respectively), and (3) the estimated entrectinib concentration in the gastrointestinal tract after administration of entrectinib 600 mg (4280 μmol/L), entrectinib is unlikely to cause pharmacokinetic interactions via inhibition of OAT1, OAT3, OATP1B3, OCT1, OCT2, multidrug and toxin extrusion (MATE) 2-K, or bile salt export pump (BSEP), or inhibition of P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE2-K, or BSEP by M5. On the other hand, entrectinib has the potential to cause pharmacokinetic interactions via inhibition of P-gp, BCRP, OATP1B1, or MATE1, or

[27] The potential of M5 to induce the mRNA expression and activities of CYP1A2 and CYP2B6, CYP2C19 activity, CYP3A4 mRNA expression, and CYP3A activity was assessed.
[28] Omeprazole (50 μmol/L), phenobarbital (750 μmol/L), and rifampicin (20 μmol/L) were used as positive controls for CYP1A2, CYP2B6, and CYP3A4, respectively.
[29] Rifampicin (10 μmol/L) was used as an OATP1B1 and OATP1B3 inhibitor.

inhibition of MATE1 by M5 in clinical use.

- Using the Caco-2 cell line, the MDCKII cell lines expressing human BCRP, OCT1, MATE1, or MATE2-K, the HEK293 cell lines expressing human OAT1, OAT3, OATP1B1, OATP1B3, or OCT2, and the membrane vesicles from the Sf9 insect cell line expressing human BSEP, the potential of entrectinib (0.1-30 μmol/L[30)]) to inhibit P-gp-, BCRP-, OAT1-, OAT3-, OATP1B1-, OATP1B3-, OCT1-, OCT2-, MATE1-, MATE2-K-, or BSEP-mediated transport of their substrates[31)] was assessed. Entrectinib inhibited the transport of the substrates of P-gp, BCRP, OATP1B1, MATE1, MATE2-K, and BSEP, with IC_{50} values of 1.33, 3.02, 6.46, 1.10, 19.4, and 13.3 μmol/L, respectively. On the other hand, entrectinib caused no evident inhibition of the transport of the substrates of OAT1, OAT3, OATP1B3, OCT1, and OCT2.
- Using the MDCKII cell lines expressing human P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, MATE1, or MATE2-K, and the membrane vesicles from the Sf9 insect cell line expressing human BSEP, the potential of M5 (0.1-30 μmol/L) to inhibit P-gp-, BCRP-, OAT1-, OAT3-, OATP1B1-, OATP1B3-, OCT1-, OCT2-, MATE1-, MATE2-K-, or BSEP-mediated transport of their substrates[32)] was assessed. M5 inhibited the transport of the substrates of P-gp, BCRP, MATE1, and MATE2-K, with IC_{50} values of 10.1, 8.35, 0.642, and 3.14 μmol/L, respectively. On the other hand, M5 caused no evident inhibition of the transport of the substrates of OAT1, OAT3, OATP1B1, OATP1B3, OCT1, OCT2, and BSEP.

4.R Outline of the review conducted by PMDA

Based on the submitted data and the considerations in the following sections, PMDA concluded that the applicant's explanation about the non-clinical pharmacokinetics of entrectinib is acceptable.

4.R.1 Tissue distribution

Since the study results indicated that entrectinib or its metabolites bind to melanin [see Section 4.2.1], PMDA asked the applicant to explain the safety of entrectinib in melanin-containing tissues.

The applicant's response:

According to an integrated analysis of a global phase II study (STARTRK-2 study), foreign phase I studies (ALKA study and STARTRK-1 study), and a foreign phase I/Ib study (STARTRK-NG study), vision blurred (8.7%, 31 of 355 subjects), pruritus (8.2%, 29 of 355 subjects), etc. were reported as adverse events related to skin and subcutaneous tissue disorders or eye disorders, but most of the adverse events were of Grade 2 or lower in severity, and there were no particular clinical concerns. The above results etc. indicated that the

30) The concentrations tested for OATP1B1, OATP1B3, OCT2, OAT1, and OAT3 were 0.03 to 30 μmol/L.

31) Digoxin (10 μmol/L), prazosin (1 μmol/L), *p*-aminohippuric acid (1 μmol/L), estrone-3-sulfate (0.05 μmol/L), ^{3}H-1-methyl-4-phenylpyridinium iodide (2 μmol/L), metformin (10 μmol/L), and ^{3}H-taurocholic acid (1 μmol/L) were used as the substrates of P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, and BSEP, respectively, estradiol-17β-glucuronide (0.05 μmol/L) was used as a substrate of OATP1B1 and OATP1B3, and ^{14}C-metformin (10 μmol/L) was used as a substrate of MATE1 and MATE2-K.

32) ^{3}H-quinidine (0.1 μmol/L), ^{3}H-prazosin (2 μmol/L), ^{3}H-*p*-aminohippuric acid (2 μmol/L), ^{3}H-*p*-aminohippuric acid (10 μmol/L), ^{3}H-estradiol-17β-glucuronide (2 μmol/L), ^{3}H-cholecystokinin 8 (2 μmol/L), ^{3}H-1-methyl-4-phenylpyridinium iodide (2 μmol/L), and ^{3}H-taurocholic acid (1 μmol/L) were used as the substrates of P-gp, BCRP, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and BSEP, respectively, and ^{14}C-metformin (10 μmol/L) was used as a substrate of OCT2, MATE1, and MATE2-K.

distribution of entrectinib or its metabolites in melanin-containing tissues is unlikely to cause safety issues in the clinical use of entrectinib.

PMDA accepted the applicant's explanation.

4.R.2 Pharmacokinetic interactions

In vitro studies indicated that entrectinib has the potential to cause pharmacokinetic interactions mediated by the following transporters in clinical use [see Section 4.5.3].

- Entrectinib inhibits BCRP, OATP1B1, and MATE1, and M5 inhibits MATE1.
- Entrectinib is a substrate of P-gp, and M5 is a substrate of P-gp and BCRP.

The applicant's explanation:
According to an integrated analysis of a global phase II study (STARTRK-2 study), foreign phase I studies (ALKA study and STARTRK-1 study), and a foreign phase I/Ib study (STARTRK-NG study), coadministration of entrectinib with a substrate of BCRP, OATP1B1, or MATE1, or a P-gp or BCRP inhibitor raised no particular safety concerns, etc. Thus, coadministration of entrectinib with the above substrates or inhibitors is unlikely to cause a problem in clinical use.

PMDA's discussion:
PMDA largely accepted the applicant's explanation. However, as the information on entrectinib pharmacokinetic interactions mediated by P-gp, BCRP, OATP1B1, or MATE1 is important for the proper use of entrectinib, the applicant should continue to collect relevant information and appropriately provide any beneficial information to healthcare professionals in clinical practice.

The study results indicated that entrectinib inhibits CYP3A and P-gp [see Sections 4.5.1 and 4.5.3], and this information is described in Section "6.2.2 Drug interaction studies."

5. Toxicity and Outline of the Review Conducted by PMDA

In this section, unless otherwise specified, 0.5% methylcellulose aqueous solution was used as vehicle.

5.1 Single-dose toxicity

The acute toxicity of entrectinib was assessed based on the findings after the first dose in a 2-week repeated-dose toxicity study in mice and the findings from single-dose toxicity studies in rats and dogs (Table 12).

Table 12. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Principal findings	Approximate lethal dose (mg/kg)	CTD
Female mice (CD-1)	Oral	0, 120, 240	Acute toxicity was assessed in a 2-week repeated oral dose toxicity study. No toxic changes in clinical signs	>240	4.2.3.2-1 Reference data
Male and female rats (Sprague Dawley)	Oral	0, 60, 120, 240	≥120: decreased body weight 240: increases in neutrophil count/platelet count, increases in serum phosphorus/total bilirubin, decreased extramedullary hematopoiesis in the spleen	>240	4.2.3.1-1 Reference data
Male and female dogs (Beagle)	Oral	0, 300	300: increases in serum lactate dehydrogenase/creatine kinase	>300	4.2.3.1-2 Reference data

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies in mice (2 weeks), rats (4 and 13 weeks), and dogs (4 and 13 weeks) were conducted (Table 13). The primary target organ toxicities of entrectinib were observed in the central nervous system (CNS), skin, liver, and hematologic system in rats and dogs, and the gastrointestinal tract and ECG (QT/QTc interval) in dogs. In rats, there were effects on the cornea, incisor, submandibular gland, and kidney.[33)] Entrectinib exposures (C_{max} and $AUC_{0\text{-}24h}$) at the no observed adverse effect level (NOAEL) (7.5 mg/kg/day in rats, <7.5 mg/kg/day in dogs) in 13-week repeated-dose toxicity studies in rats and dogs were 0.630 μmol/L and 6.34 μmol/L·h, respectively, in rats and 0.251 μmol/L and <1.87 μmol/L·h, respectively, in dogs, which were 0.20- and 0.13-fold the human exposure,[34)] respectively, in rats, and 0.08- and <0.04-fold the human exposure, respectively, in dogs.

Table 13. Repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	CTD
Female mice (CD-1)	Oral	2 weeks (QD)	0, 120, 240	240: decreased activity (transient), dyspnea (transient), increases in serum creatinine/urea/sodium/chloride, decreases in serum amylase/lipase, etc.	240	4.2.3.2-1 Reference data
Male and female rats Sprague Dawley)	Oral	2 weeks (QD) + 2-week rest period + 2 weeks (QD) + 4-week recovery period	0, 50, 100, 200	Deaths: 200 (3 of 15 females)[b)] ≥50: skin scabs, reddish material around the nose, decreases in red blood cell count/hemoglobin/hematocrit, increases in MCV/reticulocyte count, increases in serum AST/ALT/total bilirubin/inorganic phosphorus, increased spleen weights, red pulp congestion/extramedullary hematopoiesis/lymphoid depletion in the spleen, etc. ≥100: skin ulceration, discoloration of incisors, increased platelet count, corneal opacity, foamy macrophages in mesenteric lymph nodes,[c)] acinar hypertrophy/increased acinar apoptosis of the submandibular gland, etc. ≥200: CNS symptoms such as incoordination and abnormal gait, increased serum amylase,	NOAEL was not assessed.	4.2.3.2-3

33) In a 2-week repeated-dose toxicity study in rats (CTD 4.2.3.2-2), which was conducted as a dose-finding study, vacuolation of cortical tubular epithelial cells in the kidney was observed at 400 mg/kg/day. The applicant discussed that the finding may be suggestive of phospholipidosis.

34) In the STARTRK-1 study, the C_{max} was 3.13 μmol/L and the $AUC_{0\text{-}24h}$ was 48.0 μmol/L·h on Day 14 of Cycle 1 in patients with solid tumors treated with entrectinib 600 mg QD (calculated from the Formulation F2A group) [see Section 6.2.1.1].

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	CTD
				foamy macrophages in the spleen/mandibular lymph nodes/liver/periodontal tissue,[c] increased apoptosis in the parotid gland, vacuolation of bile duct epithelium[c]/bile duct epithelial hyperplasia in the liver, etc. These findings were reversible.		
Male and female rats (Sprague Dawley)	Oral	4 weeks (QD) + 2-week recovery period	0, 25, 50, 100	Deaths or moribund sacrifices: 100 (all animals)[d] ≥25: skin scabs, decreases in red blood cell count/hemoglobin, increases in MCV/MCH/platelet count/reticulocyte count/white blood cell count/neutrophil count/monocyte count/basophil count, increased fibrinogen, increased serum globulin, decreased serum A/G ratio, increased spleen weights, decreased submandibular gland weights, congestion/extramedullary hematopoiesis/lymphoid depletion in the spleen, erosion or ulcers/acanthosis/exudate on epidermal surface/hemorrhage/mixed cell inflammation in the skin or subcutis, etc. ≥50: skin ulcerative wet lesions, decreased hematocrit, increased lymphocyte count, decreased serum ALB, decreased seminal vesicle weights, etc. These findings were reversible.	<25	4.2.3.2-4
Male and female rats (Sprague Dawley)	Oral	13 weeks (QD) + 8-week recovery period	0, 7.5, 15, 30	Deaths or moribund sacrifices: ≥15 (15 [1 of 15 males,[e] 2 of 15 females]; 30 [2 of 15 males, 1 of 15 females]) ≥7.5 [f]: skin scabs, increased body weight, increased food consumption, serocellular crusts/mixed cell inflammation/acanthosis in the skin or subcutis, etc. ≥15 [g]: skin inflammation, decreases in red blood cell count/hemoglobin/hematocrit/MCHC, increases in MCV/MCH/reticulocyte count/white blood cell count/neutrophil count/monocyte count/platelet count, increased serum globulin, decreased serum A/G ratio, increased spleen weights, erosion or ulcers/hemorrhage in the skin or subctutis, extramedullary hematopoiesis in the spleen, hypercellular bone marrow, etc. 30: increased fibrinogen These findings were reversible.	7.5	4.2.3.2-5
Male and female dogs (Beagle)	Oral	2 weeks (QD) + 2-week rest period + 2 weeks (QD) + 4-week recovery period	0, 30, 60, 120	Deaths or moribund sacrifices: 120 (4 of 5 females) [h] ≥30: diarrhea, soft stool, decreased body weight, decreases in red blood cell count/hemoglobin/hematocrit/reticulocyte count, increased serum urea, decreased serum ALB, congestion/pigmented macrophages in the spleen, aspiration pneumonia, etc. ≥60: CNS symptoms such as abnormal gait, incoordination, decreased/increased activity, and stereotypy, emesis, crust formation/ulcers in the skin, decreased food consumption, increases in white blood cell count/neutrophil count/monocyte count/platelet count, increases	NOAEL was not assessed.	4.2.3.2-7 4.2.3.2-8

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	CTD
				in activated partial thromboplastin time/fibrinogen, increased serum ALT/AST, skin ulcers, subcutaneous inflammation, hepatocellular necrosis, extramedullary hematopoiesis in the liver, etc. 120: staggering, tremors, depression, recumbency, unresponsive, prolonged ventricular repolarization (QT/QTc interval prolongation), increases in serum ALP/GGT/total bilirubin, etc. These findings were reversible.		
Male and female dogs (Beagle)	Oral	4 weeks (QD) + 2-week recovery period	0, 15, 30, 60/45[a)]	Death: 60 (1 of 5 females),[i)] fecal abnormalities, erosion or ulcers in the transition zone between rectal mucosa and skin, etc. ≥15: increases in white blood cell count/neutrophil count/platelet count, increased fibrinogen, decreased serum A/G ratio, skin lesions (broken skin/discolored skin/scabs/inflammation, skin ulcers/acanthosis/hyperkeratosis/dermal fibrosis/mononuclear cell infiltrates/neutrophil infiltrates, etc.) ≥30: decreased red blood cell count, increases in monocyte count/large unstained cell count, decreased serum ALB, increases in serum globulin/cholesterol, increased liver weights, erosion or ulcers in the rectum, aspiration-related changes (mixed cell infiltrates/granulomatous inflammation/bronchiolar or alveolar epithelial hyperplasia in the lung), etc. 60/45: emesis, liquid feces, increased serum total protein, decreased serum calcium, etc. Except for increased serum globulin and decreases in serum A/G ratio/calcium, these findings were reversible.	<15	4.2.3.2-9
Male and female dogs (Beagle)	Oral	13 weeks (QD) + 8-week recovery period	0, 7.5, 15, 30	Moribund sacrifice: 15 (1 of 4 males) [j)] ≥7.5: skin lesions (inflammation, scabs, raised area, discolored skin, etc.), increases in white blood cell count/neutrophil count/monocyte count/fibrinogen, increases in serum total protein/globulin, decreases in serum A/G ratio/calcium, increased liver weights, decreased prostate gland weights, lung inflammation following aspiration, etc. ≥15: decreases in red blood cell count/hemoglobin/hematocrit, squamous epithelial erosion or ulcers/neutrophil infiltrates in the transition zone between mucosa and skin of rectal section including the anus and perianal skin, etc. 30: abnormal feces (red/black liquid feces, mucoid feces, muddy feces), decreases in body weight/food consumption, etc. These findings were reversible.	<7.5	4.2.3.2-10

a) Due to serious toxicity associated with entrectinib (vomitus, liquid feces, decreases in body weight/food consumption, death, etc.), dosing was stopped from Day 9 until Day 14 and resumed at a reduced dose level of 45 mg/kg/day on Day 15. b) The cause of death was considered to be deep anesthesia because deterioration in clinical signs occurred (the animals died under anesthesia during blood collection for laboratory tests on Day 15). c) The applicant discussed that the findings may be suggestive of phospholipidosis. d) The applicant discussed that the cause of death was entrectinib-related skin lesions. All animals surviving on Day 24 in the main study and TK group

were sacrificed, and recovery of animals continued until the end of the recovery period. In animals that died or were sacrificed moribund, decreased body weight gain, decreased food consumption, increases in serum urea nitrogen/triglycerides/calcium/inorganic phosphorus/ALT/ALP/GGT, decreased serum chloride, etc. were noted, in addition to the changes observed in surviving animals. e) Since there were no entrectinib-related changes in clinical observations or histopathological examinations, the death was not considered related to entrectinib. f) Since skin lesions observed at 7.5 mg/kg/day occurred at a low incidence and were of minimal severity, these findings were considered to be nonadverse. g) In 3 males and 1 female in the 15 mg/kg/day group and 11 males and 3 females in the 30 mg/kg/day group, dosing was interrupted (6-22 days) and resumed on Day 49 to 64. h) The cause of death or moribund sacrifice was considered to be CNS effects such as decreased activity and incoordination. i) The cause of death was undetermined. j) The animal had symptoms suggestive of aspiration, such as white foamy vomitus, recumbency, decreased activity, abnormal respiratory sounds, and increased respiratory rate after dosing on Day 25, and then exhibited abnormal behavior. Thus, the animal was sacrificed moribund on Day 33.

5.3 Genotoxicity

As *in vitro* studies, (1) bacterial reverse mutation assay and (2) micronucleus assay in human peripheral blood lymphocytes (including fluorescence *in situ* hybridization [FISH] analysis) were performed. As an *in vivo* study, (3) rodent bone marrow micronucleus and comet assay was performed. Entrectinib tested (1) negative, (2) positive (15 μg/mL in the absence of metabolic activation), and (3) negative (Table 14). Entrectinib tested positive in the micronucleus assay in human peripheral blood lymphocytes, and the results of FISH analysis indicated an aneugenic mechanism, not a clastogenic mechanism. The maximum entrectinib exposures (C_{max} and $AUC_{0\text{-}24h}$) in the *in vivo* micronucleus and comet assay were 11.6 μmol/L and 242 μmol/L·h, respectively, which were 3.7- and 5.0-fold the human exposure,[34)] respectively.

Table 14. Genotoxicity studies

Type of study		Test system	Metabolic activation (Treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Test result	CTD
In vitro	Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2 uvrA	S9−/+	0,[c)] 2.44, 4.88, 9.76, 19.5, 39, 78.1, 156.25, 312.5,[d)] 625,[d)] 1250 [d)]	Negative	4.2.3.3.1-1
	Chromosomal aberration assay in human peripheral blood lymphocytes (including FISH analysis)	Human peripheral blood lymphocytes	S9− (4 hours)	0,[c)] 7.5, 15, 25	Negative	4.2.3.3.1-3
			S9+ (4 hours)	0,[c)] 7.5, 15, 20	Negative	
			S9− (24 hours)	0,[c)] 3, 7.5, 15	15: Positive [f)]	
In vivo	Rodent micronucleus and comet assay	Male rats (Sprague Dawley) bone marrow, [a)] liver [b)]		0,[e)] 250, 1000, 2000 (oral, 3 days)	Negative	4.2.3.3.2-1

a) Evaluated in the micronucleus assay. b) Evaluated in the comet assay. c) Vehicle (DMSO) only was administered. d) Precipitate was seen. e) Vehicle (0.5% methylcellulose and 1% polysorbate 80 in deionized water) only was administered. f) Since micronuclei were induced at 15 μg/mL, the control and 15 μg/mL groups were subjected to FISH analysis. The percentage of micronuclei with centromeres was 81% in the 15 μg/mL group vs. 45% in the control group.

5.4 Carcinogenicity

The applicant did not conduct a carcinogenicity study because entrectinib is an anti-neoplastic drug intended to treat patients with advanced cancer.

5.5 Reproductive and developmental toxicity

The applicant did not conduct a study of fertility and early embryonic development to implantation or a study for effects on pre- and postnatal development, including maternal function, for entrectinib, because the drug is an anti-neoplastic agent intended to treat patients with advanced cancer.

The applicant explained that the possibility that entrectinib affects male and female fertility cannot be ruled out for the following reasons etc.

- Although there were no effects on male and female reproductive organs in repeated-dose toxicity studies in rats and dogs [see Section 5.2], entrectinib exposure at the highest dose (24.5 μmol/L·h in rats, 7.57 μmol/L·h in dogs) was lower than the human exposure ($AUC_{0\text{-}24h}$)[34)] and the effects of entrectinib on male and female reproductive organs could not fully be evaluated.
- Dysmorphic sperm, decreased sperm motility, infertility, etc. in mice lacking *ROS1*, one of the molecular targets of entrectinib, have been reported (*Endocrinology*. 2014;155:3661-73, *Genes Dev*. 1996;10:1184-93).

An embryo-fetal developmental toxicity study in rats was conducted (Table 15), which showed fetal toxicity (lower fetal body weight, etc.) at ≥50 mg/kg/day and teratogenicity (external and skeletal abnormalities) at 200 mg/kg/day. Entrectinib exposures (C_{max} and $AUC_{0\text{-}24h}$) at the NOAEL for embryo-fetal developmental toxicity in rats (12.5 mg/kg/day) were 0.82 μmol/L and 10.2 μmol/L·h, respectively, which were 0.26- and 0.21-fold the human exposure,[34)] respectively.

Table 15. Reproductive and developmental toxicity study

Type of study	Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	CTD
Embryo-fetal development	Female rats (Sprague Dawley)	Oral	Gestation days 6-17 (QD)	0, 12.5, 50, 200	Dams: 200: red material around the nose, decreased body weight, decreased food consumption, decreased gravid uterine weights Fetuses: ≥12.5: lower body weight [a)] ≥50: increased percentage per litter of skeletal variations (bent ribs, reduced ossification of the skull, unossified 5th/6th sternebrae, reduced ossification of the vertebral arches, reduced ossification of the ribs, misaligned sternebrae, unossified 1st/2nd/3rd/4th sternebrae, unossified ischium, unossified pubis, bent scapulae, etc.) 200: external/skeletal abnormalities (omphalocele, gastroschisis, micromelia, adactyly, filamentous tail, localized fetal edema, bent limb bones, vertebral anomaly associated with rib anomaly), etc.	Maternal general and reproductive toxicity: 50 Embryo-fetal developmental toxicity: 12.5	4.2.3.5.2-2

a) Decreased fetal body weights (5.1% to 5.4% decreases) were observed at 12.5 mg/kg/day, which were considered to be nonadverse because the decreases were within the historical control ranges of the laboratory ([redacted] g), etc.

5.6 Local tolerance

Local tolerance studies to examine the effects of entrectinib on the ocular mucosa and skin of rabbits were conducted (Table 16). Entrectinib was considered to be a mild irritant to the ocular mucosa of rabbit.

Table 16. Local tolerance studies

Test system	Application site	Test method	Principal findings	CTD
Female rabbits (NZW)	Skin	The skin was evaluated at 1, 24, 48, and 72 hours after a single application (4 hours) of entrectinib 500 mg.	No irritating effects	4.2.3.6-1
Female rabbits (NZW)	Eye	The eyes were evaluated at 1, 24, 48, and 72 hours after a single application (1 hour) of entrectinib 100 mg to the right eye (the left eye served as untreated control).	Entrectinib induced transient irritant reactions, which resolved within 3-7 days after application.	4.2.3.6-2

5.7 Other toxicity studies

5.7.1 Juvenile animal study

A 13-week repeated-dose toxicity study in rats on postnatal day 7 was conducted (Table 17).

The applicant explained that the following findings etc. indicated that juvenile rats are more susceptible to the toxicity of entrectinib than adult rats.

- In addition to toxicological findings similar to those observed in adult rats (including CNS toxicity and effects on the skin and hemolymphopoietic system), changes related to delayed growth and development (decreased body weight gain, decreased food consumption, decreased femur length, delayed sexual maturation, an increased reaction time in neurobehavioral test, etc.) occurred in juvenile rats.
- Entrectinib exposures (C_{max} and $AUC_{0\text{-}24h}$) at the NOAEL (<4 mg/kg/day) in a 13-week repeated-dose toxicity study in juvenile rats were 0.343 μmol/L and 2.66 μmol/L·h, respectively (0.11- and <0.06-fold the human exposure,[34)] respectively), which were lower than entrectinib exposures at the NOAEL in a 13-week repeated-dose toxicity study in adult rats [see Section 5.2].
- CNS toxicity occurred at 200 mg/kg/day, resulting in exposures 1.9- and 2.3-fold the human exposures (C_{max} and $AUC_{0\text{-}24h}$),[34)] in adult rats, while at 8 mg/kg/day, resulting in exposures 0.22- and 0.12-fold the human exposures (C_{max} and $AUC_{0\text{-}24h}$),[34)] in juvenile rats.

The applicant's explanation about the possible reasons that juvenile rats are more susceptible to the toxicity of entrectinib:

The TRK signal transduction system is critical for the growth/development of CNS (*Annu Rev Neurosci*. 2003;26:299-330), and the nervous system is functionally immature at birth in rodents compared to humans (*Reprod Toxicol*. 2017;72:129-35).

Table 17. Juvenile animal study

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	CTD
Male and female rats (Sprague Dawley)	Oral	13 weeks (postnatal days 7-97) + 4-week recovery period	0, 4, 8, 16	Deaths or moribund sacrifices: 16 (2 of 59 [a)] males, 1 of 59 [a)] females),[b)] decreased activity, abnormal gait, dehydration, etc. ≥4: partial eyelid closure, piloerection, effects on forelimb and hindlimb grip strength/landing foot splay, dehydration, skin scabs, loss of fur, staining of fur, decreased body weight gain, decreased food consumption, delayed sexual maturation, decreases in red blood cell count/hemoglobin/hematocrit, increased serum urea nitrogen, decreases in serum triglycerides/glucose/ALB/calcium, increased spleen weights, extramedullary hematopoiesis in the spleen, dermal fibrosis, epidermal hyperplasia, etc. ≥8: CNS symptoms such as non-sustained convulsions, abnormal gait, tremors, and decreased activity, hunched posture, pale skin, dyspnea, prostration, crouching, increased respiratory rate, effects on learning and memory (Morris water maze assessments), hyperkeratosis, dermal inflammatory mononuclear cell infiltration, congestion in the spleen, etc. 16: decreased femur length Except for decreased body weight gain, decreased food consumption, effects on forelimb and hindlimb grip strength/landing foot splay, effects on learning and memory (Morris water maze assessments), and changes suggestive of delayed growth and development such as decreased femur length, these findings were reversible.	<4	4.2.3.5.4-3

a) The sum of 10 animals (the main study), 5 animals (neurobehavioral assessments), 20 animals (evaluation of reversibility), and 24 animals (TK assessment). b) The cause of death was inferred to be excessive CNS effects.

5.7.2 Photosafety

Although an *in vitro* phototoxicity study using a mouse fibroblast cell line suggested that entrectinib may cause phototoxicity, based on the results of a phototoxicity study in pigmented rats, it was concluded that entrectinib has no phototoxic potential (Table 18). Either in the presence or absence of ultraviolet radiation, there were effects of entrectinib on the cornea.[35)]

Table 18. Photosafety studies

Type of study	Test system	Test method	Principal findings	CTD
In vitro	Mouse fibroblast cell line Balb/c 3T3	0.178-10.00 mg/L (in the presence of UVR [a)]) 0.178-10.00 mg/L (in the absence of UVR)	Phototoxic potential (the mean value of photo irritation factor, approximately 6.0)	4.2.3.7.7-1
In vivo	Female pigmented rats (Long-Evans)	Rats were dosed with entrectinib 0, 50, 100, or 200 mg/kg/day once daily for 3 days and then exposed to UVR.[b)] The skin of each rat was observed prior to and at 1 and 4 hours and 3 days after UVR exposure. The eyes of each rat were examined ophthalmologically and histopathologically prior to and 3 days after UVR exposure.	Not phototoxic	4.2.3.7.1-2

a) Exposed to UVR (UV-A [5 J/cm^2] and UV-B [19 mJ/cm^2]) for about 30 minutes.
b) Exposed to UVR (UV-A [9.80-10.29 J/cm^2], UV-B [138-145 mJ/cm^2], visible light) for 40 to 42 minutes at about 5 hours and

[35)] Increased incidence and/or severity of neutrophil infiltrates in the corneal stroma, and single cell necrosis of the corneal epithelium were observed.

15 minutes after the third dose.

5.7.3 Toxicity studies on impurities

Although no impurities need to be assessed for safety as per the ICH Q3A and Q3B guidelines, 6 different impurities (Impurity A, Impurity B, Impurity C, Impurity D, Impurity E, Impurity F) tested negative in bacterial reverse mutation assays (Table 19).

Table 19. Genotoxicity studies

Impurity	Type of study	Test system	Metabolic activation (Treatment)	Concentration (μg/plate or μg/well)	Test result	CTD
Impurity A Impurity B Impurity C	Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium*: TA98, TA100, TA1535, TA97a *Escherichia coli*: WP2 uvrA	S9−/+	0,[a] 0.3, 1, 3, 10, 30, 100, 300, 1000 μg/well	Negative	4.2.3.7.6-2 4.2.3.7.6-3 4.2.3.7.6-4
Impurity D Impurity E Impurity F	Bacterial reverse mutation assay (Ames)	*Salmonella typhimurium*: TA97, TA98, TA100, TA1535, TA102	S9−/+	0,[a] 5, 16, 50, 160, 500, 1600, 5000 μg/plate	Negative	4.2.3.7.6-5 4.2.3.7.6-6 4.2.3.7.6-7

a) Vehicle (DMSO) only was administered.

A rat 4-week repeated-dose toxicity study on Impurity G was conducted, which raised no safety concerns (Table 20).

Table 20. Repeated-dose toxicity study on Impurity G

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	NOAEL (mg/kg/day)	CTD
Male and female rats (Sprague Dawley)	Oral	4 weeks (QD)	0, 0.33, 1.0	No toxic signs	1.0	4.2.3.7.6-1

5.7.4 Study for CNS symptoms and QT interval prolongation in dogs

A study for CNS symptoms and QT interval prolongation, which were observed in a repeated-dose toxicity study of entrectinib [see Section 5.2], was conducted. The study results suggested the relationship of CNS symptoms and QT interval prolongation with the dose/duration of exposure and entrectinib exposure (Table 21).

Table 21. Study for CNS and QT interval prolongation in dogs

Test system	Route of administration	Duration of dosing	Dose (mg/kg/day)	Principal findings	CTD
Female dogs (Beagle)	Oral	7 days (QD)	80, 120	120: CNS symptoms occurred in 2 of 4 animals treated for 7 days (C_{max}, ≥4.2 μmol/L; $AUC_{0\text{-}24h}$, ≥90 μmol/L·h). QT interval prolongation occurred in 1 of 4 animals treated for 7 days (C_{max}, 7.08 μmol/L; $AUC_{0\text{-}24h}$, 144 μmol/L·h). (Although entrectinib exposure on Day 4 was similar to that after 7 days of dosing, CNS symptoms or QT interval prolongation did not occur.)	4.2.3.7.7-1 Reference data

5.R Outline of the review conducted by PMDA

Based on the submitted data and the considerations in the following sections, PMDA concluded that the applicant's explanation about the toxicity of entrectinib is acceptable.

5.R.1 Use of entrectinib in pediatric patients

The applicant's explanation:
Delayed growth and development and CNS toxicity occurred at a lower dose in juvenile rats than in adult rats, etc., indicating that juvenile rats are more susceptible to the toxicity of entrectinib than adult rats [see Section 5.7.1]. Thus, the package insert etc. will caution about these findings.

PMDA accepted the applicant's explanation.

The safety of entrectinib in pediatric patients is described in Section 7.R.5.2.

5.R.2 Use of entrectinib in pregnant women or women who may be pregnant

PMDA asked the applicant to explain the use of entrectinib in pregnant women or women who may be pregnant.

The applicant's response:
Given that a reproductive and developmental toxicity study in rats showed the teratogenic effects of entrectinib [see Section 5.4], entrectinib can cause fetal harm when administered to pregnant women or women who may be pregnant. Thus, the use of entrectinib in pregnant women or women who may be pregnant is not recommended.

However, taking into account that the prognosis of *NTRK* fusion-positive solid tumors is very poor, etc., entrectinib may be administered with caution to pregnant women or women who may be pregnant if the expected therapeutic benefits outweigh the possible risks, on the premise that patients are fully informed of the potential risks to the fetus associated with entrectinib. The package insert will include the results from the embryo-fetal developmental toxicity study in rats, and advise that entrectinib may adversely affect the fetus.

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

As the oral formulations of entrectinib, granules and capsules are available. The PK etc. of entrectinib were studied using the granule and capsule formulations (Table 22). The proposed commercial formulation (F06), i.e. the 100-mg capsule and the 200-mg capsule, share the same qualitative and quantitative composition, and the results obtained from performing the proposed dissolution test showed no clear differences in dissolution profile between the 100-mg and 200-mg capsules.

Table 22. Formulations used in clinical studies

Formulation		Study ID
Granules	F400 (400 mg/g)	foreign phase I study (Study 101-06)
Capsules	^{14}C-entrectinib-containing formulation (200 mg)	foreign phase I study (Study 101-05)
	F1 (50, 100, and 200 mg)	global phase II study (STARTRK-2 study[*1, *2]), foreign phase I studies (ALKA study, Study CA14707,[*1] STARTRK-1 study, Study 101-06[*1]), foreign phase I/Ib study (STARTRK-NG study[*3])
	F2 (200 mg)	foreign phase I study (Study CA14707)
	F2A (200 mg)	global phase II study (STARTRK-2 study), foreign phase I studies (Study CA14707, STARTRK-1 study, Study 101-04, Study 101-07, Study 101-13, and Study 101-15)
	F2B (100 and 200 mg)	foreign phase I study (Study CA14707[*1]), foreign phase I/Ib study (STARTRK-NG study)
	F05 (200 mg)	foreign phase I study (Study 101-07)
	F06 (100 and 200 mg)	foreign phase I studies (Study 101-07,[*1] Study 101-08,[*1] Study 101-09,[*1] Study 101-12, Study 101-14,[*1] Study 101-15[*1])
	F07 (200 mg)	foreign phase I study (Study 101-07)

*1, The 200-mg capsules were used. *2, Formulation F2A was mainly used. *3, The 100- and 200-mg capsules were used.

6.1.1 Analytical method

For *NTRK* fusion testing, next-generation sequencing (NGS) assay etc. were used in the STARTRK-1 study and the STARTRK-NG study, and Ignyta's NGS assay, the "Trailblaze Pharos" assay, in addition to NGS assay etc., were used in the STARTRK-2 study. The applicant submitted a partial change approval application for its *in vitro* diagnostic NGS assay, "FoundationOne CDx Cancer Genomic Profile," as an aid in identifying patients eligible for treatment with entrectinib, as of January 18, 2019.

6.1.2 Assay

Entrectinib and M5 (formed via demethylation) in human plasma were quantified by liquid chromatography/tandem mass spectrometry (LC-MS/MS), and the lower limit of quantification was 2 ng/mL for both entrectinib and M5.

6.1.3 Foreign clinical studies

6.1.3.1 Foreign phase I study (CTD 5.3.1.2-2, Part 1 of Study 101-15 [February to June 2018])

A two-treatment, two-period, crossover study was conducted in 48 healthy adults (48 subjects included in PK analysis) to test for bioequivalence between Formulations F2A and F06 (200-mg capsules). A single oral dose of entrectinib 600 mg was to be administered under fasting conditions,[36] and a ≥9-day washout period was included between the treatment periods.

The entrectinib C_{max} and AUC_{last} geometric mean ratios for Formulation F06 to Formulation F2A [90% confidence interval (CI)] were 0.933 [0.883, 0.986] and 0.914 [0.853, 0.979], respectively, which both fell within the equivalence range (0.80-1.25).

The applicant explained that the above results demonstrated the bioequivalence between Formulations F2A and F06 (200-mg capsules).

6.1.3.2 Foreign phase I study (CTD 5.3.1.2-2, Part 2 of Study 101-15 [February to June 2018])

A two-treatment, two-period, crossover study was conducted in 48 healthy adults[37] (47 subjects included in PK analysis) to assess the effect of food on the PK of Formulation F06 (200-mg capsules). A single oral dose of entrectinib 600 mg was to be administered under fasting conditions[36] or 30 minutes after a high-fat meal,[38] and a ≥9-day washout period was included between the treatment periods.

The entrectinib C_{max} and AUC_{inf} geometric mean ratios for a high-fat meal vs. fasted [90% CI] were 1.06 [0.989, 1.15] and 1.15 [1.07, 1.24], respectively.

The applicant explained that the above results indicated that entrectinib can be taken without regard to meals.

6.1.3.3 Foreign phase I study (CTD 5.3.3.4-1, Study 101-09 [November 2017 to January 2018])

A two-treatment, two-period, crossover study was conducted in 20 healthy adults (19 subjects included in PK analysis) to assess the effects of a proton pump inhibitor (lansoprazole) on the PK of Formulation F06 (200-mg capsules). A single oral dose of entrectinib 600 mg was to be administered, or lansoprazole 30 mg was to be administered orally QD for 9 days, with a single oral dose of entrectinib 600 mg on Day 5. A ≥10-day washout period was included between the treatment periods.

The entrectinib C_{max} and AUC_{inf} geometric mean ratios for entrectinib + lansoprazole vs. entrectinib alone [90% CI] were 0.765 [0.676, 0.866] and 0.745 [0.647, 0.859], respectively. The applicant explained that although coadministration with lansoprazole resulted in decreased entrectinib exposure, taking account of variability in entrectinib exposure after oral administration of entrectinib (Formulation F2A) 600 mg QD [see Section 6.2.1.1] etc., this finding is unlikely to become a clinically relevant problem.

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[36] Subjects fasted for ≥10 hours (overnight) before administration and for ≥4 hours after administration.
[37] Including 13 subjects enrolled in Part 1 of Study 101-15.
[38] Approximately 800-1000 kcal with approximately 50% of total caloric content of the meal from fat

6.2 Clinical pharmacology

The PK of entrectinib alone or in combination with itraconazole or rifampicin were studied in healthy adults and patients with cancer. The effects of entrectinib on the PK of midazolam or digoxin were assessed.

6.2.1 Foreign clinical studies

6.2.1.1 Foreign phase I study (CTD 5.3.5.2-2, STARTRK-1 study [ongoing since July 2014 (data cutoff date of May 31, 2018)])

An open-label, uncontrolled study was conducted in 76 patients with advanced/recurrent solid tumors positive for *NTRK*, *ALK*, or *ROS1* fusions etc. (75 subjects included in PK analysis) to assess the PK etc. of entrectinib. In the dose escalation segment, entrectinib was to be administered orally QD at the following doses within 30 minutes after meal in 28-day cycles, and the plasma concentrations of entrectinib and M5 were determined.

- Formulation F1 100, 200, or 400 mg/m^2
- Formulation F1 600 or 800 mg
- Formulation F1 600 mg for body surface area of ≤1.85 m^2 and Formulation F1 800 mg for body surface area of >1.85 m^2
- Formulation F2A 600 mg

The PK parameters of entrectinib and M5 in Cycle 1 are shown in Table 23. Based on the obtained PK data, an analysis using a power model was performed. The applicant explained that the C_{max} and AUC_{24h} of entrectinib increased in an almost dose-proportional manner over the dose range of 100 to 400 mg/m^2. The accumulation ratios[39)] of entrectinib and M5 after oral administration of Formulation F2A 600 mg QD were 1.55 and 2.84, respectively.

[39)] The ratio of AUC_{24h} on Day 14 to AUC_{24h} on Day 1

Table 23. PK parameters of entrectinib and M5

Formulation	Dosing regimen	Sampling day (Day)	Analyte	n	C_{max} (nmol/L)	t_{max}[*1] (h)	AUC_{24h} (nmol·h/L)
F1	100 mg/m^2 QD	1	Entrectinib	5	506 (52.8)	6.00 (4.00, 8.00)	7170 (34.1)
			M5	2	200, 220	6.00, 6.00	3040, 3320
		14	Entrectinib	4	1040 (50.4)	2.00 (2.00, 6.00)	16,800 (66.0)
			M5	2	402, 1,150	6.00, 4.00	8310, 19,000
	200 mg/m^2 QD	1	Entrectinib	5	1340 (46.7)	6.00 (4.00, 8.00)	19,700 (41.6)
			M5	5	441 (54.8)	6.00 (4.00, 8.00)	6560 (60.6)
		14	Entrectinib	5	1530 (79.5)	6.00 (2.00, 8.00)	22,500 (96.8)[*3]
			M5	5	713 (42.9)	6.00 (0, 8.00)	12,800 (60.4)[*3]
	400 mg/m^2 QD	1	Entrectinib	10	2520 (45.2)	4.00 (2.00, 8.00)	38,000 (57.9)[*4]
			M5	7	930 (76.2)	4.00 (4.00, 8.00)	17,800 (80.6)[*5]
		14	Entrectinib	7	4030 (60.4)	4.00 (2.00, 6.00)	68,500 (65.3)
			M5	6	892 (36.9)	4.00 (2.00, 6.00)	16,400 (37.2)
	600 mg QD	1	Entrectinib	22	1870 (42.4)	4.00 (1.00, 8.00)	22,300 (52.1)[*6]
			M5	22	461 (94.8)	4.00 (3.00, 8.00)	6670 (90.8)[*7]
		14	Entrectinib	17	2740 (58.1)	4.00 (2.00, 8.00)	43,900 (63.9)[*8]
			M5	17	634 (76.4)	4.00 (2.00, 24.0)	11,600 (75.5)[*9]
	800 mg QD	1	Entrectinib	9	3410 (52.7)	4.00 (4.00, 8.00)	49,600 (50.1)
			M5	9	1410 (84.8)	6.00 (4.00, 24.0)	23,000 (84.6)
		14	Entrectinib	6	4720 (53.3)	6.00 (2.00, 8.00)	77,300 (72.7)[*5]
			M5	6	2910 (65.3)	7.00 (4.00, 24.0)	49,600 (62.1)[*5]
	600 or 800 mg QD[*2]	1	Entrectinib	5	3100 (4.61)	4.00 (2.00, 4.00)	41,100 (17.6)
			M5	5	525 (102)	4.00 (4.00, 6.00)	7980 (120)[*3]
		14	Entrectinib	3	3030 (27.3)	4.00 (4.00, 4.00)	50,200 (24.7)
			M5	3	845 (89.0)	6.00 (4.00, 8.00)	14,400 (96.2)
F2A	600 mg QD	1	Entrectinib	18	2250 (57.5)	4.00 (2.00, 8.00)	31,800 (47.7)[*9]
			M5	18	622 (79.2)	4.00 (2.00, 24.0)	10,200 (81.5)[*9]
		14	Entrectinib	12	3130 (80.3)	4.00 (2.00, 6.00)	48,000 (76.5)[*10]
			M5	12	1250 (89.6)	4.00 (0.580, 24.0)	24,000 (97.4)[*10]

Geometric mean (Coefficient of variation of geometric mean [%]) (Individual values are listed for n = 2)
*1, Median (Range); *2, 600 mg for body surface area of ≤1.85 m^2, 800 mg for body surface area of >1.85 m^2; *3, n = 4; *4, n = 8; *5, n = 5; *6, n = 19; *7, n = 17; *8, n = 15; *9, n = 16; *10, n = 9

6.2.1.2 Foreign phase I study (CTD 5.3.3.1-2, Study 101-05 [March to April 2016])

An open-label, uncontrolled study was conducted in 7 healthy adults (6 subjects included in PK analysis) to determine the mass balance etc. of entrectinib. A single oral dose of ^{14}C-entrectinib 600 mg was to be administered, and radioactivity concentrations in blood, plasma, urine, and feces, etc. were determined.

The AUCs (arithmetic mean) of plasma and blood radioactivity over 24 hours post-dose were 47,300 and 90,300 nmol·h/L, respectively, etc. The applicant explained that these results indicated that entrectinib and its metabolites are distributed in blood cells. In the plasma collected up to 24 hours post-dose, the unchanged drug was mainly detected (accounting for 68.6% of the total radioactivity in plasma), and the major metabolites detected were M11 (formed via *N*-glucuronidation) and M5 (accounting for 18.6% and 11.5%, respectively, of the total radioactivity in plasma).

The recoveries of radioactivity in urine and feces (% of the administered radioactivity) over 312 hours were 3.06% and 82.9%, respectively. In the urine collected up to 24 hours post-dose, M2 (formed via oxidation) was found as the primary metabolite (representing 0.782% of the administered radioactivity), and the unchanged

drug and M5 were also detected (representing 0.663% and 0.171%, respectively, of the administered radioactivity). In the feces collected up to 264 hours post-dose, the unchanged drug was mainly found (representing 35.7% of the administered radioactivity), and M5 was detected as the primary metabolite (representing 22.1% of the administered radioactivity).

6.2.2 Drug interaction studies

6.2.2.1 Drug interaction study with itraconazole or rifampicin (CTD 5.3.3.4-2, Study 101-12 [October to December 2017])

A two-treatment, two-period, open-label, uncontrolled study was conducted in 20 healthy adults (19 subjects included in PK analysis)[40] to assess the effects of itraconazole (a CYP3A inhibitor) or rifampicin (a CYP3A inducer) on the PK of entrectinib. The dosing regimens are shown below. A 9-day washout period was included between the treatment periods.

Cohort 1: A single oral dose of entrectinib 100 mg on Day 1 of Period 1, and oral itraconazole 200 mg QD on Days 10 to 19 of Period 2, with a single oral dose of entrectinib 100 mg on Day 14

Cohort 2: A single oral dose of entrectinib 600 mg on Day 1 of Period 1, and oral rifampicin 600 mg QD on Days 10 to 25 of Period 2, with a single oral dose of entrectinib 600 mg on Day 21

The entrectinib C_{max} and AUC_{inf} geometric mean ratios for (1) entrectinib + itraconazole or (2) entrectinib + rifampicin vs. entrectinib alone [90% CI] were (1) 1.73 [1.37, 2.18] and 6.04 [4.54, 8.04], respectively, and (2) 0.444 [0.353, 0.559] and 0.233 [0.184, 0.295], respectively.

The applicant's explanation:
Based on the above, coadministration with a CYP3A inhibitor or a CYP3A inducer may result in increased or decreased entrectinib exposure, respectively, and caution is needed. Thus, the relevant precautions will be provided.

6.2.2.2 Drug interaction study with digoxin (CTD 5.3.3.4-3, Study 101-13 [September to October 2017])

A two-period, open-label, uncontrolled study was conducted in 10 healthy adults (10 subjects included in PK analysis) to assess the effects of entrectinib on the PK of digoxin (a P-gp substrate). Subjects were to receive a single oral dose of digoxin 0.5 mg, or a single oral dose of entrectinib 600 mg followed 1 hour later by a single oral dose of digoxin 0.5 mg. A 10-day washout period was included between the treatment periods.

The digoxin C_{max} and AUC_{inf} geometric mean ratios for digoxin + entrectinib vs. digoxin alone [90% CI] were 1.28 [0.982, 1.67] and 1.18 [1.06, 1.32], respectively. Coadministration with entrectinib resulted in increased digoxin exposure. However, an integrated analysis of a global phase II study (STARTRK-2 study), foreign phase I studies (ALKA study and STARTRK-1 study), and a foreign phase I/Ib study (STARTRK-NG study) raised no particular concerns about the safety of coadministration of entrectinib and a P-gp substrate. The

[40] Ten subjects each in Cohorts 1 and 2 (9 and 10 subjects, respectively, included in PK analysis)

applicant explained that given this finding etc., a precaution for coadministration with P-gp substrates is unnecessary.

6.2.2.3 Drug interaction study with midazolam (CTD 5.3.3.4-4, Study 101-14 [ongoing since November 2017 (data cutoff date of July 16, 2018)])

An open-label, uncontrolled study was conducted in 15 patients with advanced/recurrent solid tumors (10 subjects included in PK analysis) to assess the effects of entrectinib on the PK of midazolam (a CYP3A substrate) etc. Entrectinib 600 mg was to be administered orally QD on Days 8 to 22, with a single oral dose of midazolam 2 mg on Days 1, 8, and 21.

The midazolam C_{max} and AUC_{inf} geometric mean ratios for midazolam + entrectinib vs. midazolam alone (Day 21) [90% CI] were 0.786 [0.659, 0.937] and 1.50 [1.29, 1.73], respectively.

The applicant's explanation:
Based on the above, coadministration of entrectinib with a CYP3A substrate resulted in increased CYP3A substrate exposure, and caution should be exercised when administering entrectinib with a CYP3A substrate. Thus, the relevant precaution will be provided.

6.2.3 Use of entrectinib in patients with renal impairment

The applicant explained that taking account of the following points etc., no dose adjustment is required in patients with renal impairment.

- The results of a foreign phase I study (Study 101-05) indicated that renal excretion contributes little to the elimination of entrectinib and M5 [see Section 6.2.1.2].
- According to an integrated analysis of a global phase II study (STARTRK-2 study), foreign phase I studies (ALKA study and STARTRK-1 study), and a foreign phase I/Ib study (STARTRK-NG study), the incidences of (1) serious adverse events, (2) Grade 3 or higher adverse events, (3) adverse events leading to dose reduction, and (4) adverse events leading to treatment discontinuation in patients with normal renal function (166 patients) and patients with mild, moderate, or severe renal impairment (108, 34, or 46 patients, respectively) were (1) 41.6%, 34.3%, 29.4%, and 45.7%, respectively, (2) 59.6%, 65.7%, 50.0%, and 65.2%, respectively, (3) 25.9%, 28.7%, 32.4%, and 32.6%, respectively, and (4) 9.0%, 6.5%, 14.7%, and 6.5%, respectively. There was no clear relationship between renal impairment and the incidence of adverse events.

6.2.4 Relationship between exposure and change in QT/QTc interval

The relationship between plasma entrectinib concentration and ΔQTcF was analyzed using a linear mixed-effects model, based on the data from 107 patients who had time-matched PK/ECG data in a global phase II study (STARTRK-2 study).

The applicant's explanation:

Since there was no clear relationship between plasma entrectinib concentration and ΔQTcF, entrectinib administered at the proposed dosing regimen is unlikely to cause changes in QT/QTc interval.

6.2.5 PPK analyses

Population pharmacokinetic (PPK) analyses of entrectinib and M5 were performed by non-linear mixed-effects model (software, NONMEM Version 7.4), based on the entrectinib and M5 PK data from a global phase II study (STARTRK-2 study), a foreign phase I study (STARTRK-1 study), and a foreign phase I/Ib study (STARTRK-NG study) (7642 PK samples from 276 subjects[41)]). The PK of entrectinib were described by a 1-compartment model with first-order elimination and with a sequential zero- and first-order absorption. Entrectinib is metabolized into M5, and the PK of M5 were described by a 1-compartment model with first-order absorption and first-order elimination.

In these analyses, (1) body weight and (2) Formulation[42)] and concomitant use of a pH modifier were tested as potential covariates on (1) the CL/F and V/F and (2) F_{rel} and k_a of entrectinib. No significant covariate was identified for k_a. (1) Body weight[43)] and (2) Formulation[44)] were identified as significant covariates for (1) CL/F and V/F and (2) F_{rel}. Body weight was tested as a potential covariate on the CL/F and V/F of M5, and identified as a significant covariate.[43)]

The applicant's explanation about the above analyses results:

- Since there was no clear relationship between body weight and the response rate/the incidence of adverse events in the global phase II study (STARTRK-2 study) etc., changes in body weight in adult patients are unlikely to have a clinically relevant effect on the PK of entrectinib. On the other hand, in pediatric patients, changes in body size during development may have a clinically relevant effect on the PK of entrectinib. In the foreign phase I/Ib study (STARTRK-NG study), when pediatric patients received body surface area (BSA)-adjusted doses of entrectinib (BSA is correlated with body weight), there were responders, and entrectinib was tolerable [see Sections 7.1.3.3 and 7.R.5.2]. Given these findings, a BSA-based dosing regimen should be employed for pediatric patients.
- Since the proposed commercial formulation is Formulation F06 only etc., there is no possibility that differences in formulation result in clinically relevant effects on the PK of entrectinib.

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41) (i) Age (years), (ii) body weight (kg), and (iii) body surface area (m^2) [mean (range)] in the analysis populations of the STARTRK-1 study, the STARTRK-2 study, and the STARTRK-NG study were (i) 55.1 (18.0, 80.0), 54.1 (15.0, 86.0), and 10.5 (4.00, 20.0), respectively, (ii) 72.4 (46.7, 127), 69.4 (31.6, 130), and 32.1 (13.3, 79.2), respectively, and (iii) 1.8 (1.43, 2.58), 1.8 (1.17, 2.54), and 1.1 (0.59, 1.94), respectively. The proportions of patients who received (iv) Formulation F1 only, (v) either Formulation F2A or F2B, and (vi) both Formulations F1 and F2A (%) in the analysis populations of the STARTRK-1 study, the STARTRK-2 study, and the STARTRK-NG study were (iv) 66.7%, 8.4%, and 81.2%, respectively, (v)33.3%, 91.1%, and 18.8%, respectively, and (vi) 0%, 0.5%, and 0%, respectively. The proportions of (vii) patients who received concomitant pH modifier and (viii) patients who did not receive concomitant pH modifier were (vii) 35.1%, 32.0%, and 0%, respectively, and (viii) 64.9%, 68.0%, and 100%, respectively.

42) (i) Formulation F1 only, (ii) either Formulation F2A or F2B, (iii) both Formulations F1 and F2A

43) CL/F and V/F were allometrically scaled by individual body weights normalized to 70 kg, with the exponents fixed to 0.75 and 1, respectively.

44) The effect of Formulation F1 on F_{rel} in the STARTRK-NG study was included in the final model, and the estimated F_{rel} of Formulation F1 to other formulations was 0.718.

6.2.6 Exposure-efficacy/safety relationship

6.2.6.1 Exposure-efficacy relationship

Based on the data from a global phase II study (STARTRK-2 study) and a foreign phase I study (STARTRK-1 study), the applicant explored the relationship between exposure[45)] (the sum of the AUC_{ss} values of entrectinib and M5) and best overall response in patients with *NTRK* fusion-positive solid tumors. There was no clear relationship between exposure and best overall response.

6.2.6.2 Exposure-safety relationship

Based on the data from a global phase II study (STARTRK-2 study), a foreign phase I study (STARTRK-1 study), and a foreign phase I/Ib study (STARTRK-NG study), the applicant explored the relationship between exposure[45)] (C_{max} and AUC on Day 1, and $C_{max,ss}$ and AUC_{ss}; the sum of entrectinib and M5) and the incidences of treatment-emergent adverse events (Grade 3, 4, or 5 and Grade 3 or higher) and serious adverse events. There was no clear relationship between exposure and the incidences of the above adverse events.

6.2.7 Differences in PK between Japanese and non-Japanese populations

The applicant explained that taking account of the following points, there should be no clear differences in the PK of entrectinib or M5 between Japanese and non-Japanese populations.

- In a foreign phase I study (Study 101-04),[46)] there were no clear differences between Japanese and Caucasian subjects in the PK parameters of entrectinib following a single oral dose of entrectinib 400 or 600 mg administered under fasting conditions[36)] or a single oral dose of entrectinib 600 mg administered 30 minutes after a high-fat meal[38)] (Table 24).
- The entrectinib and M5 $C_{max,ss}$ ranges largely overlapped between Japanese patients in a global phase II study (STARTRK-2 study) (657-1930 ng/mL and 225-1060 ng/mL, respectively) and non-Japanese patients treated orally with entrectinib (Formulation F2A) 600 mg QD in a foreign phase I study (STARTRK-1 study) (802-4620 ng/mL and 142-1080 ng/mL, respectively).

Table 24. PK parameters of entrectinib

	Dosing regimen	n	C_{max} (nmol/L)	AUC_{inf} (nmol·h/L)
Japanese	400 mg under fasting conditions	12	1740 (28.3)	32,200 (28.1)
	600 mg under fasting conditions	12	2170 (27.6)	40,800 (31.7)
	600 mg after a high-fat meal	12	2200 (19.9)	47,800 (26.4)
Caucasian	400 mg under fasting conditions	12	1520 (23.9)	32,100 (30.9)
	600 mg under fasting conditions	12	1920 (35.1)	41,500 (40.3)
	600 mg after a high-fat meal	11	1950 (19.6)	49,800 (33.1)

Geometric mean (CV %)

6.R Outline of the review conducted by PMDA

Based on the submitted data and the considerations in the following section, PMDA concluded that the applicant's explanation about the clinical pharmacology etc. of entrectinib is acceptable.

45) Estimated from PPK analyses [see Section 6.2.5].

46) An open-label, uncontrolled study in 24 Japanese and Caucasian healthy adults (24 subjects included in PK analysis) to assess the PK etc. of entrectinib

6.R.1 Use of entrectinib in patients with hepatic impairment

The applicant's explanation about the use of entrectinib in patients with hepatic impairment:

Given that (1) entrectinib is metabolized mainly by the liver and eliminated [see Section 6.2.1.2], and that (2) the information on the safety of entrectinib in patients with hepatic impairment is limited, entrectinib should be administered with care to such patients, and the relevant information should be provided. However, taking account of the following results of an integrated analysis of a global phase II study (STARTRK-2 study), foreign phase I studies (ALKA study and STARTRK-1 study), and a foreign phase I/Ib study (STARTRK-NG study),[47] etc., there is currently no information suggesting the need for dose adjustment in patients with hepatic impairment.

- In patients with normal hepatic function (294 patients) and patients with mild hepatic impairment (59 patients), the incidences of (1) serious adverse events, (2) Grade 3 or higher adverse events, (3) adverse events leading to dose reduction, and (4) adverse events leading to treatment discontinuation were (1) 37.8% and 40.7%, respectively, (2) 58.8% and 71.2%, respectively, (3) 29.6% and 22.0%, respectively, and (4) 7.5% and 11.9%, respectively. There were no clear differences in the incidence of adverse events between patients with normal hepatic function and patients with mild hepatic impairment.
- One patient with severe hepatic impairment experienced a serious adverse event and a Grade 3 or higher adverse event, but a causal relationship to entrectinib was denied for both events.

The applicant plans to conduct a clinical study to assess the PK of entrectinib in patients with hepatic impairment (Study GP41174), and will appropriately provide the information to healthcare professionals in clinical practice as soon as the results become available.

PMDA accepted the applicant's explanation.

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from 15 studies presented in Table 25: 1 global phase II study, 13 foreign phase I studies, and 1 foreign phase I/Ib study.

Table 25. Listing of efficacy and safety clinical studies

Data category	Country	Study ID	Phase	Study population	No. of subjects enrolled	Dosing regimen[*1]	Main endpoints
Evaluation data	Global	STARTRK-2	II	Patients with *NTRK, ALK*, or *ROS1* fusion-positive, advanced/recurrent solid tumors	207	Entrectinib (Formulation F1 or F2A) 600 mg QD orally	Efficacy Safety
	Foreign	STARTRK-1	I	[Dose escalation segment] Patients with advanced solid tumors	76	Entrectinib (Formulation F1) 100, 200, or 400 mg/m^2, 600 or 800 mg, or 600-800 mg based on BSA[*2] QD orally, or entrectinib (Formulation F2A) 600 mg QD orally	Safety PK

[47] Normal hepatic function was defined as total bilirubin and AST within the normal range; mild hepatic impairment was defined as total bilirubin ≤ULN and AST ≥ULN or total bilirubin >1.0 and <1.5 times ULN; moderate hepatic impairment was defined as total bilirubin ≥1.5 and <3 times ULN; and severe hepatic impairment was defined as total bilirubin ≥3 times ULN. No patients with moderate hepatic impairment were included in this integrated analysis.

Data category	Country	Study ID	Phase	Study population	No. of subjects enrolled	Dosing regimen[*1]	Main endpoints
		ALKA	I	Patients with advanced/recurrent solid tumors positive for *NTRK*, *ALK*, or *ROS1* fusions etc.	58 (1) 20 (2) 32 (3) 6	(1) Entrectinib (Formulation F1) 100, 200, 400, 800, 1200, or 1600 mg/m^2 QD orally (fasted), 4 days on and 3 days off for 3 weeks followed by 7 days of rest, in a 28-day cycle (2) Entrectinib (Formulation F1) 200, 400 mg/m^2, or 600 mg QD orally (fed) (3) Entrectinib (Formulation F1) 400 or 800 mg/m^2 QD orally (fed), 4 days on and 3 days off for 4 weeks, in a 28-day cycle	Safety PK
		CA14707	I	Healthy adults	72 (1) 24 (2) 24 (3) 24	(1) With oral lansoprazole 30 mg QD on Days 1-9, a single oral dose of entrectinib (Formulation F1 or F2) 800 mg in the fasted state or after a high-fat meal on Day 4 (2) With or without oral lansoprazole 30 mg QD on Days 1-9, a single oral dose of entrectinib (Formulation F2A) 800 mg in the fasted state or after a high-fat meal on Day 4 (3) With or without oral lansoprazole 30 mg QD on Days 1-8 or 1-9, a single oral dose of entrectinib (Formulation F2B) 800 mg in the fasted state or after a high-fat meal on Day 1	PK
		101-04	I	Healthy adults	24	A single oral dose of entrectinib (Formulation F2A) 400 mg in the fasted state on Day 1, and a single oral dose of entrectinib (Formulation F2A) 600 mg in the fasted state or after a high-fat meal on Day 10, followed by crossover to the other treatment on Day 19	PK
		101-05	I	Healthy adults	7	A single oral dose of ^{14}C-entrectinib 600 mg (fasted)	PK
		101-06	I	Healthy adults	16	Treatment periods were separated by ≥9 days. A single oral dose of entrectinib (Formulation F1) 600 mg or entrectinib (Formulation F400) 400 or 600 mg (fed) in Periods 1-3, and a single oral dose of entrectinib (Formulation F400) 600 mg (fasted) in Period 4	PK
		101-07	I	Healthy adults	48	A single oral dose of entrectinib (Formulation F05, F06, F07, or F2A) 600 mg (fasted) in Periods 1-4, and a single oral dose of entrectinib (Formulation F05, F06, F07, or F2A) 600 mg after a high-calorie meal in Period 5	PK
		101-08	I	Healthy adults	24	A single oral dose of entrectinib 600 mg (different lots of Formulation F06) (fasted) administered in a crossover fashion	PK
		101-09	I	Healthy adults	20	A single oral dose of entrectinib 600 mg (Formulation F06) (fasted) with or without oral lansoprazole 30 mg QD, followed by crossover to the other treatment on Day 10	PK
		101-12	I	Healthy adults	20 (1) 10 (2) 10	(1) A single oral dose of entrectinib 100 mg (Formulation F06) (fasted) on Day 1, and oral itraconazole 200 mg QD on Days 10-19, with a single oral dose of entrectinib 100 mg (Formulation F06) (fasted) on Day 14 (2) A single oral dose of entrectinib 600 mg (Formulation F06) (fasted) on Day 1, and oral rifampicin 600 mg QD on Days 10-25, with a single oral dose of entrectinib 600 mg (Formulation F06) (fasted) on Day 21	PK
		101-13	I	Healthy adults	10	A single oral dose of digoxin 0.5 mg on Day 1 (fasted), and a single oral dose of entrectinib 600 mg (Formulation F2A) with a single oral dose of digoxin 0.5 mg on Day 11 (fasted)	PK

Data category	Country	Study ID	Phase	Study population	No. of subjects enrolled	Dosing regimen[*1]	Main endpoints
		101-14	I	Patients with advanced/recurrent solid tumors	15	Entrectinib 600 mg (Formulation F06) QD orally (fasted) on Days 8-22 with oral midazolam hydrochloride 2 mg (fasted) on Days 1, 8, and 21	PK
		101-15	I	Healthy adults	83[*3] (1) 48 (2) 48	(1) A single oral dose of entrectinib 600 mg (Formulation F06 or F2A) (fasted) administered in a crossover fashion (2) A single oral dose of entrectinib 600 mg (Formulation F06) administered in the fasted or fed state in a crossover fashion	PK
		STARTRK-NG	I/Ib	Phase I part: Patients with advanced/recurrent solid tumors (≥2 and <22 years) Phase Ib part: *NTRK*, *ALK*, or *ROS1* fusion-positive, advanced/recurrent solid tumors (from birth to <22 years)	16 Phase I part: 16 Phase Ib part: 0	Entrectinib 250 (Formulation F2B), 400 (Formulation F1), 550 (Formulation F1), or 750 (Formulation F1) mg/m^2 QD orally	Safety PK

*1, Capsules were administered except for F400 granules in Study 101-06. *2, 600 mg QD orally for subjects with BSA ≤1.85 m^2 and 800 mg QD orally for subjects with BSA >1.85m^2. *3, Thirteen subjects from Part 1 were also enrolled in Part 2.

The clinical studies are summarized below.

The main adverse events other than deaths observed in the clinical studies are described in Section "7.2 Adverse events etc. observed in clinical studies." PK data are described in Section "6.1 Summary of biopharmaceutic studies and associated analytical methods" and Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Clinical pharmacology studies

The applicant submitted the results from the following 11 clinical pharmacology studies in healthy adults or patients with advanced/recurrent solid tumors [see Sections 6.1 and 6.2]. Death reported during the study treatment period or within 30 days of the last dose of study drug occurred in 1 subject (Study 101-14, 1 of 14 subjects). The cause of death was pneumonia, and its causal relationship to study drug was denied.

7.1.1.1 Foreign phase I study (CTD 5.3.1.1-1, Study CA14707 [February 2015 to November 2015])
7.1.1.2 Foreign phase I study (CTD 5.3.3.1-1, Study 101-04 [December 2015 to February 2016])
7.1.1.3 Foreign phase I study (CTD 5.3.3.1-2, Study 101-05 [March 2016 to April 2016])
7.1.1.4 Foreign phase I study (CTD 5.3.1.1-3, Study 101-06 [October 2017 to December 2017])
7.1.1.5 Foreign phase I study (CTD 5.3.1.1-2, Study 101-07 [February 2017 to June 2017])
7.1.1.6 Foreign phase I study (CTD 5.3.1.2-1, Study 101-08 [October 2017 to December 2017])
7.1.1.7 Foreign phase I study (CTD 5.3.3.4-1, Study 101-09 [November 2017 to January 2018])
7.1.1.8 Foreign phase I study (CTD 5.3.3.4-2, Study 101-12 [October 2017 to December 2017])
7.1.1.9 Foreign phase I study (CTD 5.3.3.4-3, Study 101-13 [September 2017 to October 2017])
7.1.1.10 Foreign phase I study (CTD 5.3.3.4-4, Study 101-14 [ongoing since November 2017])
7.1.1.11 Foreign phase I study (CTD 5.3.1.2-2, Study 101-15 [February 2018 to June 2018])

7.1.2 Global study

7.1.2.1 Global phase II study (CTD 5.3.5.2-1, STARTRK-2 study [ongoing since November 2015 (data cutoff date of May 31, 2018)])

An open-label, uncontrolled study was conducted at 84 sites in 15 countries or regions including Japan to

evaluate the efficacy and safety of entrectinib in patients with *NTRK*, *ALK*, or *ROS1* fusion-positive, advanced/recurrent solid tumors (≥18 years) [target sample size, (1) 62 subjects in the *NTRK* fusion-positive solid tumor cohort, (2) 150 subjects in the *ROS1* fusion-positive NSCLC cohort, (3) 62 subjects in the other cohort]. Patients were allowed to be enrolled in the study, regardless of prior chemotherapy status.

Entrectinib (Formulation F1 or F2A[48)]) 600 mg was to be administered QD orally. Subjects were to receive entrectinib until disease progression or any withdrawal criterion was met. Before the start of enrollment of Japanese patients, a Japanese lead-in cohort (5 patients enrolled) was treated with entrectinib to assess the tolerability and safety of entrectinib in Japanese patients with advanced solid tumors. No dose-limiting toxicities (DLTs) occurred after oral administration of entrectinib 600 mg QD, which demonstrated the tolerability of this dosing regimen of entrectinib in Japanese patients.

Among 63 patients enrolled in the *NTRK* fusion-positive solid tumor cohort, after excluding 1 patient with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of >2, 3 patients ineligible based on biomarker testing (*NTRK* fusions),[49)] 2 patients with co-morbid conditions,[50)] 5 patients with primary intracranial tumors,[51)] and 1 patient with no measurable disease at baseline, 51 patients were included in efficacy analyses[52)] (including 1 Japanese patient). Among 207 subjects enrolled in the STARTRK-2 study, 206 subjects excluding 1 subject who did not receive study drug were included in safety analyses (including 16 Japanese patients). Of the 206 subjects included in safety analyses, 1 patient received Formulation F1 only, 17 patients received Formulations F1 and F2A, and 188 patients received Formulation F2A only.

The primary endpoint for the study was the response rate as assessed by blinded independent central review (BICR) using RECIST ver1.1. The study used a 2-stage design, and the unacceptable response rate was determined to be 20%.[53)] In the first stage, up to 13 patients were to be analyzed, and if there were ≤3 responders, the enrollment was to be terminated. In the second stage, up to an additional 49 patients were to be enrolled (a total of up to 62 patients), and if there were 14 responders, then there should be sufficient evidence of efficacy.

Regarding efficacy, since 4 responders were observed in the first stage, patient enrollment was continued. Efficacy analyses were performed when all patients included in efficacy analyses were followed up for

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48) Although Formulation F1 had been used at the initiation of the study, since Formulation F1 was found to be affected by food and gastric pH, Formulation F2A was developed in order to avoid these effects. As of [redacted], Formulation F1 was switched to Formulation F2A. Among 51 patients included in efficacy analyses, 5 patients received Formulations F1 and F2A, and 46 patients received Formulation F2A only. No patient received Formulation F1 only.

49) (1) 1 patient with a concomitant driver mutation other than *NTRK* fusions, (2) 1 patient with a non-in-frame fusion of the gene, and (3) 1 patient with the above (1) and (2)

50) One patient with pericardial effusion and 1 patient with peripheral neuropathy were considered to meet the exclusion criteria.

51) Since primary brain tumors should be evaluated by the Response Assessment in Neuro-Oncology (RANO) criteria, these patients were excluded.

52) Although the protocol stated that the Efficacy Analysis Population (EA population) defined as patients with measurable disease treated with entrectinib will be used for the primary efficacy analyses, as the Efficacy Evaluable Analysis Population (EE population) (51 patients) (after excluding groups of patients that may affect efficacy evaluation to achieve uniformity in the population to be evaluated) as the primary analysis set was considered clinically meaningful, the primary analysis set was changed in the Statistical Analysis Plan Version 3.

53) Determined based on the findings that the response rates with drugs that can be used as second-line or later therapy etc. for tumor types in which *NTRK* fusions had been identified at the time of planning the study, ranged from 0% to 41.6% (median, 13.4%).

≥6 months or discontinued from treatment (data cutoff date of May 31, 2018). The primary endpoint of the response rate as assessed by BICR as per RECIST ver1.1 is shown in Table 26 (data cutoff date of May 31, 2018).

Table 26. Best overall response and response rate (*NTRK* fusion-positive solid tumor cohort) (RECIST ver.1.1, Efficacy evaluable analysis population, BICR assessments, data cutoff date of May 31, 2018)

Best overall response	n (%)	
	Overall population N = 51	Japanese subgroup N = 1
Complete response (CR)	4 (7.8)	0
Partial response (PR)	25 (49.0)	1 (100)
Stable disease (SD)	9 (17.6)	0
Progressive disease (PD)	3 (5.9)	0
Non CR/PD	3 (5.9)	0
Missing or unevaluable	7 (13.7)	0
Response (CR + PR) (Response rate [95% CI*] (%))	29 (56.9 [42.3, 70.7])	1 (100 [−, −])

−, Unable to estimate; *, Clopper-Pearson method

Regarding safety, 30 of 206 subjects (14.6%) died during the entrectinib treatment period or within 30 days of the last dose of entrectinib (8 subjects in the *NTRK* fusion-positive solid tumor cohort, 17 subjects in the *ROS1* fusion-positive NSCLC cohort, 5 subjects in the other cohort) (including 2 Japanese patients in the *ROS1* fusion-positive NSCLC cohort). The causes of deaths other than disease progression (4 subjects in the *NTRK* fusion-positive solid tumor cohort, 15 subjects [including 2 Japanese patients] in the *ROS1* fusion-positive NSCLC cohort, 4 subjects in the other cohort) were pneumonia; cardio-respiratory arrest; sepsis; and acute respiratory failure (1 subject each) in the *NTRK* fusion-positive solid tumor cohort, pneumonia; and cardiogenic shock (1 subject each) in the *ROS1* fusion-positive NSCLC cohort, and completed suicide (1 subject) in the other cohort, and a causal relationship to entrectinib was denied for all those cases.

7.1.3 Foreign clinical studies

7.1.3.1 Foreign phase I study (CTD 5.3.5.2-2, STARTRK-1 study [ongoing since July 2014 (data cutoff date of May 31, 2018)])

An open-label, uncontrolled study was conducted at 11 sites outside Japan to evaluate the safety, PK, etc. of entrectinib in patients with advanced/recurrent solid tumors positive for *NTRK*, *ALK*, or *ROS1* fusions etc. (≥18 years) (target sample size, ≥15 subjects in the dose escalation segment, approximately 50 subjects in the dose expansion segment). In the dose escalation segment, an *NTRK*, *ALK*, or *ROS1* fusion was not a requirement for patient eligibility. As of the data cutoff date (May 31, 2018), the data from dose expansion patients were not available.

In the dose escalation segment, entrectinib (Formulation F1) 100, 200, or 400 mg/m^2, 600 or 800 mg, or 600 to 800 mg based on BSA[54)] or entrectinib (Formulation F2A) 600 mg was to be administered QD orally in 28-day cycles. Subjects were to receive entrectinib until disease progression or any withdrawal criterion was met.

All of 76 subjects enrolled in the dose escalation segment received entrectinib and were included in safety

[54)] Subjects with BSA of ≤1.85 m^2 or >1.85 m^2 were treated orally with entrectinib 600 or 800 mg QD, respectively.

analyses.

The DLT evaluation period started on Cycle 1 Day 1 and ended on Cycle 1 Day 28 in the dose escalation segment. DLTs were observed in 3 of 9 subjects in the 800 mg QD group (Grade 3 fatigue [2 subjects], Grade 3 disturbance in attention [1 subject]), and the recommended Phase 2 dose (RP2D) was determined to be entrectinib (Formulation F1) 600 mg QD.

Regarding safety, 8 of 76 subjects (10.5%) died during the entrectinib treatment period or within 30 days of the last dose of entrectinib (2 in the 400 mg/m^2 group, 6 in the 600 mg group). The causes of deaths were unknown cause of death (3 in the 600 mg group), metastases to meninges (1 in the 600 mg group, 1 in the 400 mg/m^2 group), large intestine perforation (1 in the 600 mg group), respiratory failure (1 in the 400 mg/m^2 group), and tumour lysis syndrome (1 in the 600 mg group). A causal relationship to entrectinib was denied for all those cases.

7.1.3.2 Foreign phase I study (CTD 5.3.5.2-3, ALKA study [ongoing since October 2012 (data cutoff date of May 31, 2018)])

An open-label, uncontrolled study was conducted at 2 sites outside Japan to evaluate the safety, PK, etc. of entrectinib in patients with advanced/recurrent solid tumors positive for *NTRK*, *ALK*, or *ROS1* fusions etc. (≥18 years) (target sample size, 70 subjects).

The dosing regimens are shown below. Subjects were to receive entrectinib until disease progression or any withdrawal criterion was met.

- Schedule A:

Entrectinib (Formulation F1) 100, 200, 400, 800, 1200, or 1600 mg/m^2 QD orally in the fasted state, 4 days on and 3 days off for 3 weeks followed by 7 days of rest, in a 28-day cycle

- Schedule B:

Entrectinib (Formulation F1) 200 or 400 mg/m^2 or 600 mg QD orally in the fed state

- Schedule C:

Entrectinib (Formulation F1) 400 or 800 mg/m^2 QD orally in the fed state, 4 days on and 3 days off for 4 weeks, in a 28-day cycle

Among 58 subjects enrolled in the dose-escalation segment, 57 subjects who received entrectinib were included in safety analyses.

In each schedule, the DLT evaluation period started on Cycle 1 Day 1 and ended on Cycle 1 Day 28. No DLTs occurred at any dose level or schedule.

Regarding safety, 8 of 57 subjects (14.0%) died during the entrectinib treatment period or within 30 days of the last dose of entrectinib (2 in the A group, 5 in the B group, 1 in the C group). The cause of death other than

disease progression (7 subjects) (2 in the A group,[55] 4 in the B group,[56] 1 in the C group[57]) was pulmonary embolism (1 in the 400 mg/m^2 group of B group), and its causal relationship to entrectinib was denied.

7.1.3.3 Foreign phase I/Ib study (CTD 5.3.5.2-4, STARTRK-NG study [ongoing since May 2016 (data cutoff date of May 31, 2018)])

An open-label, uncontrolled study was conducted at 8 sites outside Japan to evaluate the safety, PK, etc. of entrectinib in pediatric patients with advanced/recurrent solid tumors positive for *NTRK*, *ALK*, or *ROS1* fusions etc. (target sample size, 6-30 subjects in the phase I dose escalation part [≥2 and <22 years],[58] ≤62 subjects[59] in the phase Ib expansion part [from birth to <22 years][60]). As of the data cutoff date (May 31, 2018), the data from expansion cohorts were not available.

In the phase I dose escalation part, entrectinib (Formulation F2B) 250 mg/m^2 or entrectinib (Formulation F1) 400, 550, or 750 mg/m^2 was to be administered QD orally in 28-day cycles. Subjects were to receive entrectinib until disease progression or any withdrawal criterion was met.

All of 16 subjects who were enrolled in the phase I dose escalation part and received entrectinib were included in safety analyses.

The DLT evaluation period started on Cycle 1 Day 1 and ended on Cycle 1 Day 28 in the phase I dose escalation part. DLTs were observed in 1 of 7 subjects in the entrectinib (Formulation F1) 550 mg/m^2 QD group (Grade 2 blood creatinine increased [1 subject]) and 3 of 3 subjects in the entrectinib (Formulation F1) 750 mg/m^2 QD group (Grade 3 pulmonary oedema; Grade 2 dysgeusia; and blood creatinine increased, 1 subject each), and the RP2D was determined to be entrectinib (Formulation F1) 550 mg/m^2 QD.

Regarding safety, 2 of 16 subjects (12.5%) died during the entrectinib treatment period or within 30 days of the last dose of entrectinib (2 in the 550 mg/m^2 group). The causes of deaths were both disease progression, and their causal relationship to entrectinib was denied.

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[55] One subject each in the 100 mg/m^2 and 200 mg/m^2 groups
[56] Three subjects in the 600 mg group and 1 subject in the 400 mg/m^2 group
[57] One subject in the 800 mg/m^2 group
[58] Patients with or without an *NTRK*, *ALK*, or *ROS1* fusion were enrolled.
[59] Up to 62 subjects with specific tumor types and gene mutations in Cohorts B and D, up to 20 subjects in Cohort C, and no target sample size specified for Cohorts A and E
[60] The following patients were to be enrolled in expansion cohorts (phase Ib). Eligible patients were aged ≥2 and <22 years for Cohorts A to D, and from birth to <22 years for Cohort E.
Cohort A, Pediatric patients with extracranial solid tumors with *NTRK*, *ALK*, or *ROS1* molecular alterations (non-gene fusions) (excluding neuroblastoma)
Cohort B, Pediatric patients with primary brain tumors with *NTRK*, *ALK*, or *ROS1* molecular alterations (including gene fusions)
Cohort C, Pediatric patients with relapsed/refractory neuroblastoma
Cohort D, Pediatric patients with relapsed/refractory non-neuroblastoma, extracranial solid tumors with *NTRK*, *ALK*, or *ROS1* gene fusions
Cohort E, Patients who were otherwise eligible for Cohort A, B, C or D, but unable to swallow capsules

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

PMDA review strategy:

Among the evaluation data submitted, the pivotal clinical study to evaluate the efficacy of entrectinib in patients with *NTRK* fusion-positive, advanced/recurrent solid tumors is the *NTRK* fusion-positive solid tumor cohort of a global phase II study to evaluate the efficacy and safety of entrectinib in *NTRK*, *ALK*, or *ROS1* fusion-positive, advanced/recurrent solid tumors, etc. (STARTRK-2 study). PMDA decided to focus its review on this cohort, and evaluate the safety of entrectinib based on the following 2 foreign phase I studies in addition to the STARTRK-2 study.

- The STARTRK-1 study in patients with advanced/recurrent solid tumors positive for *NTRK* fusions etc. to evaluate the safety, PK, etc. of entrectinib
- The ALKA study in patients with advanced/recurrent solid tumors positive for *NTRK* fusions etc. to evaluate the safety, PK, etc. of entrectinib

Given that the dosing regimen for pediatric patients was established based mainly on PPK and physiologically based pharmacokinetic (PBPK) modeling analyses, the efficacy and safety of entrectinib in pediatric patients are described with dosage and administration [see Section 7.R.5.2].

7.R.2 Clinical positioning and efficacy

Based on the following considerations, PMDA concluded that a certain level of efficacy of entrectinib in patients with *NTRK* fusion-positive, advanced/recurrent solid tumors was demonstrated.

7.R.2.1 Clinical positioning of entrectinib, efficacy endpoint, and results of evaluation

There is no mention of entrectinib in the latest Japanese and foreign clinical practice guidelines or the major textbooks of clinical oncology.

PMDA asked the applicant to explain the efficacy and clinical positioning of entrectinib in the treatment of patients with *NTRK* fusion-positive, advanced/recurrent solid tumors.

The applicant's response:

Gene fusions are one of the principal causes of tumorigenesis. The breakpoint cluster region-Abelson (BCR-ABL) fusion gene has been reported to act as an oncogenic driver in chronic myeloid leukemia, and *ALK* and *ROS1* fusions, etc. have been reported to act as oncogenic drivers in NSCLC (*Nature*. 2007;448:561-6, *Nat Med*. 2012;18:378-81). Likewise, when the *NTRK* genes that encode the receptor tyrosine kinases TRK fuse with the *TPM3* gene etc. on chromosome, the fusion genes are translated into TRK fusion proteins, which constitutively activate downstream signaling pathways (MAPK, PI3K, AKT, PLC-γ, etc.), and cancer cells expressing TRK fusion proteins overproliferate etc. Thus, *NTRK* fusions have also been reported to act as oncogenic drivers (*Nat Clin Pract Oncol*. 2006;3:448-57, *Cancer Res*. 2008;68:3077-80).

NTRK fusions have been identified in a variety of cancer types, including common cancers such as colorectal cancer and NSCLC, rare cancers such as mammary secretory carcinoma, ovarian cancer, mammary analogue secretory carcinoma, and soft tissue sarcoma, and pediatric cancers such as congenital fibrosarcoma. *NTRK* fusions have been reported to have the potential to be oncogenic drivers in a variety of tumor types (*Cancers.* 2018;10:105). The prevalences of *NTRK* fusions in different tumor types reported in published literature etc. are shown in Table 27. While *NTRK* fusions are found at a lower incidence in the common types of tumor, they are found in the majority of rare tumors. Thus, it is inferred that the number of patients with *NTRK* fusions is extremely limited.

Table 27. Prevalences of *NTRK* fusions in different tumor types reported in published literature etc.

Tumor type	Prevalence of *NTRK* fusions	Tumor type	Prevalence of *NTRK* fusions
Congenital fibrosarcoma	90%-100%	Thyroid cancer (papillary, anaplastic carcinoma)	2%
Mammary secretory carcinoma	80%-100%	Colorectal cancer	1%
Salivary gland cancer: Mammary analogue secretory carcinoma	80%-100%	Glioblastoma	1%
Mesoblastic nephroma	83%	Sarcoma	1%
Malignant melanoma (Spitzoid melanoma)	16%	Head and neck cancer	<1%
Pediatric glioma	7%	NSCLC	<1%
Cholangiocarcinoma	4%	Pediatric sarcoma	<1%
Astrocytoma	3%	Pancreatic cancer	<1%
Inflammatory myofibroblastic tumor	3%	Invasive breast carcinoma	<1%

Given the above context of cancer biology and reports that the improvement of clinical symptoms associated with disease progression is expected in patients with advanced/recurrent unresectable solid tumors who have achieved responses (*J Clin Oncol.* 2006;24:3831-7, *JAMA.* 2003;290:2149-58, etc.), the achievement of responses in these patients was considered clinically meaningful. Thus, the STARTRK-2 study with the primary endpoint of the response rate was conducted.

The response rate in the *NTRK* fusion-positive solid tumor cohort [95% CI] (%) was 56.9 [42.3, 70.7] [see Section 7.1.2.1]. The response rate as assessed by BICR as per RECIST ver1.1 by tumor type in the EE population of the STARTRK-2 study is shown in Table 28 (including 1 Japanese patient [NSCLC] with PR). In addition, all of 3 Japanese patients enrolled in the *NTRK* fusion-positive solid tumor cohort of the STARTRK-2 study (all had mammary analogue secretory carcinoma) also had PR, though they had been followed-up for <6 months as of the data cutoff date and were not included in efficacy analyses.

Table 28. Response rate by tumor type in STARTRK-2 study (*NTRK* fusion-positive solid tumor cohort) (RECIST ver.1.1, EE population, BICR assessments, data cutoff date of May 31, 2018)

Tumor type	n (%) N = 51	Response (CR + PR) (Response rate (%))
Sarcoma	13 (25.5)	6 (46.2)
NSCLC	9 (17.6)	6 (66.7)
Breast cancer	6 (11.8)	5 (83.3)
Mammary analogue secretory carcinoma	6 (11.8)	5 (83.3)
Thyroid cancer	5 (9.8)	1 (20.0)
Colorectal cancer	3 (5.9)	1 (33.3)
Neuroendocrine tumor	3 (5.9)	1 (33.3)
Pancreatic cancer	3 (5.9)	2 (66.7)
Gynecological cancer *	2 (3.9)	1 (50.0)
Cholangiocarcinoma	1 (2.0)	1 (100)

*: Ovarian cancer and endometrial cancer (1 subject each)

As of [redacted], after the data cutoff date, the statistical analysis plan for the STARTRK-2 study was revised (Statistical analysis plan Version 3), and the primary analysis set for efficacy was changed from the EA population (at the initiation of the study) to the EE population.[52)] The response rate as assessed by BICR as per RECIST ver1.1 in the EA population is shown in Table 29 (data cutoff date of May 31, 2018).

Table 29. Best overall response and response rate in STARTRK-2 study (*NTRK* fusion-positive solid tumor cohort) (RECIST ver.1.1, EA population, BICR assessments, data cutoff date of May 31, 2018)

Best overall response	n (%) N = 62
CR	4 (6.5)
PR	27 (43.5)
SD	10 (16.1)
PD	7 (11.3)
Non CR/PD	3 (4.6)
Missing or unevaluable	11 (17.7)
Response (CR + PR) (Response rate [95% CI] (%))	31 (50.0 [37.6, 62.5])

Based on the above, since entrectinib, which is a drug targeting the oncogenic drivers, *NTRK* fusions, is expected to be effective in patients with *NTRK* fusion-positive, advanced/recurrent solid tumors, across multiple tumor types, taking also account of the safety profile of entrectinib in the STARTRK-2 study etc. [see Section 7.R.3], entrectinib is positioned as a treatment option for patients with *NTRK* fusion-positive, advanced/recurrent solid tumors.

PMDA's discussion:

Although the primary analysis set for efficacy was changed from the EA population to the EE population after the data cutoff date, this should have been specified in the protocol before the data cutoff date.

In terms of the following points, there are limitations to evaluation of entrectinib in patients with *NTRK* fusion-positive, advanced/recurrent solid tumors based on the pivotal STARTRK-2 study/interpretation of the study results.

- The relationship between the true endpoint, overall survival (OS), and the response rate, is unclear, and it is difficult to evaluate the survival benefit of entrectinib in these patients based on the results of the primary endpoint for the STARTRK-2 study, i.e. the response rate.

- The number of Japanese patients evaluated for the efficacy of entrectinib was limited.

However, taking also account of the above explanation by the applicant about the efficacy of entrectinib targeting the oncogenic drivers, *NTRK* fusions, and the finding that there are no clear differences in the response rate between the EA and EE populations of the STARTRK-2 study, etc., a certain level of efficacy of entrectinib was demonstrated in patients with *NTRK* fusion-positive, advanced/recurrent solid tumors, including Japanese patients. Thus, entrectinib is positioned as a treatment option for patients with *NTRK* fusion-positive, advanced/recurrent solid tumors.

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events etc. observed in clinical studies"]

PMDA's conclusion:

Based on the following considerations, adverse events that require particular attention following administration of entrectinib in patients with *NTRK* fusion-positive, advanced/recurrent solid tumors are ataxia, cognitive impairment, syncope, interstitial lung disease (ILD), QT interval prolongation, and cardiac disorders (excluding QT interval prolongation). Particular attention should be paid to the possible occurrence of these adverse events during treatment with entrectinib.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with entrectinib, entrectinib is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring for and management of adverse events and entrectinib dosage modifications etc.

7.R.3.1 Safety profile of entrectinib

The applicant's explanation about the safety profile of entrectinib based on entrectinib safety information from the STARTRK-2 study, the STARTRK-1 study, and the ALKA study:

Safety data from the STARTRK-2 study, the STARTRK-1 study, and the ALKA study are summarized in Table 30.

Table 30. Summary of safety data (STARTRK-2 study, STARTRK-1 study, ALKA study)

	n (%)		
	STARTRK-2 N = 206	STARTRK-1 N = 76	ALKA N = 57
All adverse events	205 (99.5)	75 (98.7)	57 (100)
Grade 3 or higher adverse events	131 (63.6)	51 (67.1)	27 (47.4)
Adverse events leading to death	13 (6.3)	6 (7.9)	1 (1.8)
Serious adverse events	81 (39.3)	30 (39.5)	24 (42.1)
Adverse events leading to treatment discontinuation	21 (10.2)	6 (7.9)	2 (3.5)
Adverse events leading to dose interruption	93 (45.1)	39 (51.3)	25 (43.9)
Adverse events leading to dose reduction	72 (35.0)	19 (25.0)	5 (8.8)

In the STARTRK-2 study, adverse events of any grade reported by ≥10% of subjects were constipation (110 subjects [53.4%]); dysgeusia (95 subjects [46.1%]); diarrhoea (80 subjects [38.8%]); dizziness (78 subjects [37.9%]); oedema peripheral (67 subjects [32.5%]); fatigue; and weight increased (63 subjects each [30.6%]); anaemia (61 subjects [29.6%]); dyspnoea (60 subjects [29.1%]); blood creatinine increased (59 subjects

[28.6%]); nausea (55 subjects [26.7%]); arthralgia (47 subjects [22.8%]); cough (46 subjects [22.3%]); pyrexia (42 subjects [20.4%]); AST increased (41 subjects [19.9%]); vomiting (40 subjects [19.4%]); ALT increased (37 subjects [18.0%]); headache; and myalgia (35 subjects each [17.0%]); urinary tract infection (34 subjects [16.5%]); hypotension (33 subjects [16.0%]); paraesthesia (30 subjects [14.6%]); hyperuricaemia (27 subjects [13.1%]); muscular weakness; and fall (25 subjects each [12.1%]); upper respiratory tract infection (23 subjects [11.2%]); abdominal pain (22 subjects [10.7%]); and neuropathy peripheral; pleural effusion; pain in extremity; dehydration; and decreased appetite (21 subjects each [10.2%]). Grade 3 or higher adverse events reported by ≥2% of subjects were anaemia (22 subjects [10.7%]); weight increased (20 subjects [9.7%]); dyspnoea (12 subjects [5.8%]); pneumonia (11 subjects [5.3%]); pleural effusion (10 subjects [4.9%]); ALT increased; and fatigue (9 subjects each [4.4%]); urinary tract infection; AST increased; and hypoxia (8 subjects each [3.9%]); pulmonary embolism (7 subjects [3.4%]); syncope; hypotension; and sepsis (6 subjects each [2.9%]); and diarrhoea; hypertension; hyperuricaemia; neutropenia; hypokalaemia; hyperglycaemia; and hypoalbuminaemia (5 subjects each [2.4%]). Serious adverse events reported by ≥2% of subjects were pneumonia (10 subjects [4.9%]); pleural effusion (9 subjects [4.4%]); dyspnoea (6 subjects [2.9%]); and pulmonary embolism; hypoxia; and sepsis (5 subjects each [2.4%]). Adverse events leading to dose interruption reported by ≥2% of subjects were blood creatinine increased (10 subjects [4.9%]); dizziness (8 subjects [3.9%]); dyspnoea; diarrhoea; fatigue; and anaemia (6 subjects each [2.9%]); and pleural effusion; pyrexia; pneumonia; nausea; and ALT increased (5 subjects each [2.4%]). Adverse events leading to dose reduction reported by ≥2% of subjects were dizziness (12 subjects [5.8%]); blood creatinine increased (9 subjects [4.4%]); and anaemia (5 subjects [2.4%]). There were no adverse events leading to death or treatment discontinuation reported by ≥2% of subjects.

In the STARTRK-1 study, adverse events of any grade reported by ≥10% of subjects were fatigue (47 subjects [61.8%]); dysgeusia (34 subjects [44.7%]); nausea; and constipation (28 subjects each [36.8%]); dizziness (27 subjects [35.5%]); oedema peripheral (21 subjects [27.6%]); diarrhoea; anaemia; and dyspnoea (19 subjects each [25.0%]); vomiting; myalgia; and weight increased (18 subjects each [23.7%]); cough (16 subjects [21.1%]); paraesthesia; and arthralgia (15 subjects each [19.7%]); blood creatinine increased (14 subjects [18.4%]); decreased appetite; and back pain (12 subjects each [15.8%]); peripheral sensory neuropathy; cognitive disorder; and hypotension (11 subjects each [14.5%]); hypophosphataemia; headache; pyrexia; and muscular weakness (10 subjects each [13.2%]); dehydration; and vision blurred (9 subjects each [11.8%]); and asthenia (8 subjects [10.5%]). Grade 3 or higher adverse events reported by ≥2% of subjects were anaemia (9 subjects [11.8%]); hypophosphataemia (8 subjects [10.5%]); fatigue (6 subjects [7.9%]); back pain; and pulmonary embolism (4 subjects each [5.3%]); neutropenia; mental status changes; AST increased; and hyponatraemia (3 subjects each [3.9%]); and metastases to meninges; weight increased; amylase increased; lipase increased; localised infection; dyspnoea; neutrophil count decreased; osteonecrosis; hydrocephalus; wound dehiscence; hypokalaemia; hypoxia; cognitive disorder; peripheral sensory neuropathy; vomiting; ataxia; and generalised oedema (2 subjects each [2.6%]). Adverse events leading to death reported by ≥2% of subjects were metastases to meninges (2 subjects [2.6%]). Serious adverse events reported by ≥2% of subjects were mental status changes (3 subjects [3.9%]); and metastases to meninges; osteonecrosis; hydrocephalus;

cognitive disorder; back pain; fatigue; pneumonia; and pleural effusion (2 subjects each [2.6%]). Adverse events leading to dose interruption reported by ≥2% of subjects were fatigue (5 subjects [6.6%]); ataxia (4 subjects [5.3%]); cognitive disorder; and confusional state (3 subjects each [3.9%]); and neutrophil count decreased; mental status changes; wound dehiscence; AST increased; blood creatinine increased; weight increased; back pain; anaemia; and dysphagia (2 subjects each [2.6%]). Adverse events leading to dose reduction reported by ≥2% of subjects were fatigue (3 subjects [3.9%]); and peripheral sensory neuropathy; and generalised oedema (2 subjects each [2.6%]). There were no adverse events leading to treatment discontinuation reported by ≥2% of subjects.

In the ALKA study, adverse events of any grade reported by ≥10% of subjects were nausea (31 subjects [54.4%]); paraesthesia (26 subjects [45.6%]); asthenia (24 subjects [42.1%]); vomiting; and dyspnoea (23 subjects each [40.4%]); dysgeusia (21 subjects [36.8%]); myalgia (20 subjects [35.1 %]); diarrhoea (19 subjects [33.3%]); constipation (18 subjects [31.6%]); pyrexia (17 subjects [29.8%]); fatigue (16 subjects [28.1%]); abdominal pain; dizziness; and cough (14 subjects each [24.6%]); headache (13 subjects [22.8%]); arthralgia (12 subjects [21.1%]); oedema peripheral; and back pain (11 subjects each [19.3%]); hypotension; and anaemia (10 subjects each [17.5%]); somnolence (9 subjects [15.8%]); pain in extremity; and balance disorder (8 subjects each [14.0%]); abdominal pain upper; dysphagia; decreased appetite; and confusional state (7 subjects each [12.3%]); and chest pain; muscular weakness; rash; and oropharyngeal pain (6 subjects each [10.5%]). Grade 3 or higher adverse events reported by ≥2% of subjects were dyspnoea (5 subjects [8.8%]); lipase increased; and anaemia (4 subjects each [7.0%]); amylase increased (3 subjects [5.3%]); and pulmonary embolism; respiratory failure; confusional state; general physical condition decreased; pneumonia; and asthenia (2 subjects each [3.5%]). Serious adverse events reported by ≥2% of subjects were dyspnoea (6 subjects [10.5%]); general physical condition decreased (3 subjects [5.3%]); and pulmonary embolism; abdominal pain; respiratory failure; confusional state; pneumonia; pyrexia; and vomiting (2 subjects each [3.5%]). Adverse events leading to dose interruption reported by ≥2% of subjects were pyrexia; and lipase increased (4 subjects each [7.0%]); nausea; anaemia; and vomiting (3 subjects each [5.3%]); and diarrhoea; abdominal pain; amylase increased; abdominal pain upper; and pneumonia (2 subjects each [3.5%]). Adverse events leading to dose reduction reported by ≥2% of subjects were fatigue (2 subjects [3.5%]). There were no adverse events leading to death or treatment discontinuation reported by ≥2% of subjects.

In the STARTRK-2 study, the STARTRK-1 study, and the ALKA study, a total of 6 patients with *NTRK* fusion-positive primary brain tumors (5 in the STARTRK-2 study, 1 in the STARTRK-1 study) were enrolled. Serious adverse events occurred in 4 of the 6 subjects (66.7%) (wrist fracture; pneumonia aspiration; mental status changes; depression; influenza; and generalised tonic-clonic seizure [1 subject each] [some subjects had more than 1 event]), and a causal relationship to entrectinib was denied for all those events. Grade 3 or higher adverse events occurred in 3 of the 6 subjects (50.0%) (pneumonia aspiration; AST increased; ALT increased; mental status changes; depression; and generalised tonic-clonic seizure [1 subject each] [some subjects had more than 1 event]). Adverse events leading to dose interruption occurred in 4 of the 6 subjects

(66.7%) (ataxia; diplopia; pneumonia aspiration; mental status changes; and influenza [1 subject each] [some subjects had more than 1 event]).

PMDA's discussion:
Since adverse events with a high incidence, serious adverse events, and Grade 3 or higher adverse events observed in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study, are likely to occur following administration of entrectinib, patients on entrectinib treatment should be monitored carefully for the occurrence of these events, considering their possible relationship to entrectinib. However, most of these events were manageable with dose interruption/reduction of entrectinib, etc. Given the above points, entrectinib is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. management of and monitoring for adverse events, and dose interruption/reduction of entrectinib.

7.R.3.2 Differences in safety between Japanese and non-Japanese populations

The applicant's explanation about differences in the safety of entrectinib between Japanese and non-Japanese populations based on entrectinib safety information from the STARTRK-2 study:
Safety data from Japanese and non-Japanese patients in the STARTRK-2 study are summarized in Table 31.

Table 31. Summary of safety data (STARTRK-2 study)

	n (%)	
	Japanese patients N = 16	Non-Japanese patients N = 190
All adverse events	16 (100)	189 (99.5)
Grade 3 or higher adverse events	8 (50.0)	123 (64.7)
Adverse events leading to death	1 (6.3)	12 (6.3)
Serious adverse events	4 (25.0)	77 (40.5)
Adverse events leading to treatment discontinuation	2 (12.5)	19 (10.0)
Adverse events leading to dose interruption	9 (56.3)	84 (44.2)
Adverse events leading to dose reduction	5 (31.3)	67 (35.3)

In the STARTRK-2 study, adverse events of any grade reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were blood creatinine increased (11 subjects [68.8%] in the Japanese subgroup, 48 subjects (25.3%) in the non-Japanese subgroup), diarrhoea (9 subjects [56.3%], 71 subjects [37.4%]), AST increased (9 subjects [56.3%], 32 subjects [16.8%]), dizziness (8 subjects [50.0%], 70 subjects [36.8%]), ALT increased (8 subjects [50.0%], 29 subjects [15.3%]), pyrexia (7 subjects [43.8%], 35 subjects [18.4%]), hyperuricaemia (6 subjects [37.5%], 21 subjects [11.1%]), stomatitis (5 subjects [31.3%], 2 subjects [1.1%]), white blood cell count decreased (4 subjects [25.0%], 9 subjects [4.7%]), neutrophil count decreased (3 subjects [18.8%], 13 subjects [6.8%]), oedema (3 subjects [18.8%], 11 subjects [5.8%]), lung infection (2 subjects [12.5%], 3 subjects [1.6%]), oesophagitis (2 subjects [12.5%], 2 subjects [1.1%]), blood creatine phosphokinase increased (2 subjects [12.5%], 2 subjects [1.1%]), electrocardiogram QT prolonged (2 subjects [12.5%], 1 subject [0.5%]), and haemoglobin decreased (2 subjects [12.5%], 0 subjects).

There were no Grade 3 or higher adverse events reported at a ≥20% higher incidence in the Japanese subgroup than in the non-Japanese subgroup, adverse events leading to death, treatment discontinuation, or dose interruption or reduction, or serious adverse events.

PMDA's discussion:
Although the number of Japanese patients treated with entrectinib was limited, and there are limitations to comparison of its safety profile between Japanese and non-Japanese populations, the incidences of serious adverse events and adverse events leading to treatment discontinuation or dose reduction were low with respect to diarrhoea, hepatic dysfunction, etc. that were reported at a higher incidence in Japanese patients than in non-Japanese patients. Given that entrectinib is used by physicians with adequate knowledge of and experience in cancer chemotherapy, entrectinib is tolerable also in Japanese patients.

In the following sections, based on the safety results from the STARTRK-2 study, the STARTRK-1 study, and the ALKA study, PMDA conducted its safety review, focusing on adverse events predicted by the mechanism of action of entrectinib, and adverse events that require attention following administration of other ALK/ROS1 tyrosine kinase inhibitors (alectinib, crizotinib, ceritinib, lorlatinib), etc.

7.R.3.3 Ataxia

The applicant's explanation about ataxia associated with entrectinib:
As adverse events of ataxia, MedDRA PTs "ataxia," "balance disorder," "gait disturbance," and "cerebellar ataxia" were counted.

The incidences of ataxia in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study are shown in Table 32.

Table 32. Incidence of ataxia (STARTRK-2 study, STARTRK-1 study, ALKA study)

PT (MedDRA ver.21.0)	n (%)					
	STARTRK-2 N = 206		STARTRK-1 N = 76		ALKA N = 57	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Ataxia	37 (18.0)	1 (0.5)	13 (17.1)	2 (2.6)	8 (14.0)	0
Gait disturbance	17 (8.3)	0	6 (7.9)	0	0	0
Balance disorder	14 (6.8)	0	3 (3.9)	0	8 (14.0)	0
Ataxia	11 (5.3)	1 (0.5)	5 (6.6)	2 (2.6)	0	0
Cerebellar ataxia	1 (0.5)	0	0	0	0	0

In the STARTRK-2 study, serious ataxia occurred in 3 of 206 subjects (1.5%) (ataxia; cerebellar ataxia; and gait disturbance [1 subject each]), and a causal relationship to entrectinib could not be ruled out for cerebellar ataxia; and ataxia (1 subject each). Ataxia leading to dose interruption occurred in 4 of 206 subjects (1.9%) (gait disturbance [2 subjects]; and cerebellar ataxia; and balance disorder [1 subject each]). Ataxia leading to dose reduction occurred in 6 of 206 subjects (2.9%) (gait disturbance; and ataxia [3 subjects each]; and balance disorder [1 subject] [some subjects had more than 1 event]). There was no ataxia leading to death or treatment discontinuation.

In the STARTRK-1 study, serious ataxia occurred in 1 of 76 subjects (1.3%) (ataxia), and its causal relationship to entrectinib could not be ruled out. Ataxia leading to dose interruption occurred in 5 of 76 subjects (6.6%) (ataxia [4 subjects]; and gait disturbance [1 subject]). Ataxia leading to dose reduction occurred in 2 of 76 subjects (2.6%) (ataxia; and gait disturbance [1 subject each]). There was no ataxia leading to death or treatment discontinuation.

In the ALKA study, there was no ataxia leading to death, treatment discontinuation, or dose interruption or reduction, or no serious ataxia.

The median times to the first onset of ataxia (range) in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study were 15.0 days (1-267 days), 10.0 days (2-519 days), and 13.0 days (1-858 days), respectively.

The details of patients with serious ataxia in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study are shown in Table 33.

Table 33. Listing of patients with serious ataxia (STARTRK-2 study, STARTRK-1 study)

Study ID	Sex	Age	Tumor type	PT (MedDRA ver.21.0)	Grade	Time to onset (days)	Duration (days)	Action taken with entrectinib	Causality	Outcome
STARTRK-2*	F	6[redacted]	Secretory breast carcinoma	Cerebellar ataxia	1	29	7	Interrupted	Yes	Resolved
	F	6[redacted]	NSCLC	Ataxia	3	5	4	Dose reduced	Yes	Resolved
	M	3[redacted]	NSCLC	Gait disturbance	2	318	7	Interrupted	No	Resolved
STARTRK-1	F	6[redacted]	NSCLC	Ataxia	3	8	3	Interrupted	Yes	Resolved

*: One patient experienced serious dysarthria for which a causal relationship to entrectinib could not be ruled out in the STARTRK-2 study.

PMDA's discussion:
In the clinical studies submitted, although most of the events of ataxia associated with entrectinib were of Grade 2 or lower severity, as ataxia occurred at a certain frequency following administration of entrectinib, and Grade 3 or serious ataxia for which a causal relationship to entrectinib could not be ruled out were reported, attention should be paid to the possible occurrence of ataxia during treatment with entrectinib. However, since all serious events resolved following dose interruption or reduction of entrectinib, ataxia can be managed by appropriately advising healthcare professionals in clinical practice about the incidence and management of ataxia in the clinical studies, using the package insert etc.

7.R.3.4 Cognitive impairment

The applicant's explanation about cognitive impairment associated with entrectinib:
As adverse events of cognitive impairment, MedDRA PTs "altered state of consciousness," "disturbance in attention," "mental impairment," "incoherent," "confusional state," "memory impairment," "delirium," "visual hallucination," "hallucination," "cognitive disorder," "amnestic disorder," "judgement impaired,"

"disorientation," "auditory hallucination," "mixed hallucinations," "mental status changes," "mental disorder," "amnesia," and "impaired reasoning" were counted.

The incidences of cognitive impairment in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study are shown in Table 34.

Table 34. Incidence of cognitive impairment (STARTRK-2 study, STARTRK-1 study, ALKA study)

PT (MedDRA ver.21.0)	n (%)					
	STARTRK-2 N = 206		STARTRK-1 N = 76		ALKA N = 57	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Cognitive impairment	49 (23.8)	6 (2.9)	30 (39.5)	8 (10.5)	12 (21.1)	2 (3.5)
Cognitive disorder	17 (8.3)	3 (1.5)	11 (14.5)	2 (2.6)	0	0
Confusional state	12 (5.8)	1 (0.5)	7 (9.2)	1 (1.3)	7 (12.3)	2 (3.5)
Memory impairment	9 (4.4)	0	3 (3.9)	0	1 (1.8)	0
Disturbance in attention	6 (2.9)	0	6 (7.9)	1 (1.3)	4 (7.0)	0
Hallucination	4 (1.9)	0	0	0	0	0
Mental status changes	3 (1.5)	2 (1.0)	3 (3.9)	3 (3.9)	0	0
Amnesia	3 (1.5)	0	3 (3.9)	0	3 (5.3)	0
Delirium	3 (1.5)	1 (0.5)	0	0	0	0
Visual hallucination	1 (0.5)	0	0	0	0	0
Mental disorder	0	0	1 (1.3)	1 (1.3)	0	0

In the STARTRK-2 study, no cognitive impairment leading to death was reported. Serious cognitive impairment occurred in 5 of 206 subjects (2.4%) (cognitive disorder [3 subjects]; and mental status changes [2 subjects]), and a causal relationship to entrectinib could not be ruled out for cognitive disorder (2 subjects); and mental status changes (1 subject). Cognitive impairment leading to treatment discontinuation occurred in 1 of 206 subjects (0.5%) (cognitive disorder). Cognitive impairment leading to dose interruption occurred in 6 of 206 subjects (2.9%) (cognitive disorder [4 subjects]; and memory impairment; and mental status changes [1 subject each]). Cognitive impairment leading to dose reduction occurred in 8 of 206 subjects (3.9%) (cognitive disorder [3 subjects]; confusional state [2 subjects]; and memory impairment; disturbance in attention; delirium; and mental status changes [1 subject each] [some subjects had more than 1 event]).

In the STARTRK-1 study, serious cognitive impairment occurred in 7 of 76 subjects (9.2%) (mental status changes [3 subjects]; cognitive disorder [2 subjects]; and confusional state; and mental disorder [1 subject each]), and a causal relationship to entrectinib could not be ruled out for cognitive disorder (3 subjects); and mental status changes (1 subject). Cognitive impairment leading to dose interruption occurred in 10 of 76 subjects (13.2%) (confusional state; and cognitive disorder [3 subjects each]; mental status changes [2 subjects]; and mental disorder; memory impairment; and disturbance in attention [1 subject each] [some subjects had more than 1 event]). Cognitive impairment leading to dose reduction occurred in 2 of 76 subjects (2.6%) (cognitive disorder; and confusional state [1 subject each]). There was no cognitive impairment leading to death or treatment discontinuation.

In the ALKA study, serious cognitive impairment occurred in 2 of 57 subjects (3.5%) (confusional state [2 subjects]), and a causal relationship to entrectinib was denied for both cases. Cognitive impairment leading to dose interruption occurred in 1 of 57 subjects (1.8%) (confusional state). Cognitive impairment leading to dose reduction occurred in 1 of 57 subjects (1.8%) (confusional state). There was no cognitive impairment leading to death or treatment discontinuation.

The median times to the first onset of cognitive impairment (range) in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study were 31.0 days (1-419 days), 13.5 days (1-858 days), and 13.5 days (1-341 days), respectively.

The details of patients with serious cognitive impairment in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study are shown in Table 35.

Table 35. Listing of patients with serious cognitive impairment (STARTRK-2 study, STARTRK-1 study, ALKA study)

Study ID	Sex	Age	Tumor type	PT (MedDRA ver.21.0)	Grade	Time to onset (days)	Duration (days)	Action taken with entrectinib	Causality	Outcome
STARTRK-2	F	5[redacted]	Glioma	Mental status changes	3	14	Unknown	Interrupted	No	Unresolved
	F	6[redacted]	NSCLC	Mental status changes	3	40	6	Dose reduced	Yes	Resolved
	M	6[redacted]	Glioma	Cognitive disorder	3	9	20	Discontinued	Yes	Resolved
	F	5[redacted]	GIST	Cognitive disorder	3	31	12	Dose reduced	Yes	Resolved
	M	3[redacted]	NSCLC	Cognitive disorder	2	71	4	Interrupted	No	Resolved
STARTRK-1	F	5[redacted]	Breast cancer	Mental status changes	3	7	7	Not applicable	No	Resolved
	M	6[redacted]	NSCLC	Confusional state	3	13	2	Interrupted	No	Resolved
	F	6[redacted]	NSCLC	Mental status changes	3	8	3	Interrupted	Yes	Resolved
	M	6[redacted]	Bile duct cancer	Cognitive disorder	3	27	6	Interrupted	Yes	Resolved
	F	7[redacted]	NSCLC	Mental status changes	3	29	2	Interrupted	No	Resolved
	F	5[redacted]	NSCLC	Mental disorder	3	112	2	Interrupted	No	With sequelae
	F	5[redacted]	NSCLC	Cognitive disorder	3	489	9	Interrupted	Yes	Resolved
				Cognitive disorder	2	498	15	Interrupted	Yes	Resolved
ALKA	M	6[redacted]	NSCLC	Confusional state	3	365	6	Interrupted	No	Resolved
	F	6[redacted]	NSCLC	Confusional state	3	12	3	Continued	No	Resolved

PMDA asked the applicant to explain the mechanism of development of cognitive impairment associated with entrectinib and its risk factors.

The applicant's response:
TRK blockade resulted in the loss of cholinergic neurons in the cerebral cortex of rats (*Proc Natl Acad Sci USA*. 1999;96:4067-72). Given this finding etc., entrectinib is considered to cross the blood-brain barrier into the brain, which may lead to cognitive impairment.

The risk factors for cognitive impairment associated with entrectinib may include aging, organic disease of the brain, and concurrent chronic disease, but no definitive factors have been identified.

PMDA's discussion:

Given that in the clinical studies submitted, cognitive impairment associated with entrectinib, including Grade 3 or higher events, occurred with a certain incidence, and serious cognitive impairment for which a causal relationship to entrectinib could not be ruled out was reported, etc., attention should be paid to the possible occurrence of cognitive impairment during treatment with entrectinib. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management of cognitive impairment in the clinical studies, using the package insert etc.

7.R.3.5 Syncope

The applicant's explanation about syncope associated with entrectinib:
As adverse events of syncope, MedDRA PTs "syncope" and "presyncope" were counted.

The incidences of syncope in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study are shown in Table 36.

Table 36. Incidence of syncope (STARTRK-2 study, STARTRK-1 study, ALKA study)

PT (MedDRA ver.21.0)	n (%)					
	STARTRK-2 N = 206		STARTRK-1 N = 76		ALKA N = 57	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Syncope	10 (4.9)	6 (2.9)	2 (2.6)	1 (1.3)	5 (8.8)	1 (1.8)
Syncope	7 (3.4)	6 (2.9)	2 (2.6)	1 (1.3)	4 (7.0)	1 (1.8)
Presyncope	4 (1.9)	1 (0.5)	0	0	1 (1.8)	0

In the STARTRK-2 study, serious syncope occurred in 1 of 206 subjects (0.5%) (syncope; and presyncope [1 subject each] [1 subject had more than 1 event]), and their causal relationship to entrectinib was denied. There was no syncope leading to death, treatment discontinuation, or dose interruption or reduction.

In the STARTRK-1 study, serious syncope occurred in 1 of 76 subjects (1.3%) (syncope [1 subject]), and its causal relationship to entrectinib was denied. Syncope leading to dose interruption occurred in 1 of 76 subjects (1.3%) (syncope [1 subject]). There was no syncope leading to death, treatment discontinuation, or dose reduction.

In the ALKA study, serious syncope occurred in 1 of 57 subjects (1.8%) (syncope [1 subject]), and its causal relationship to entrectinib was denied. Syncope leading to dose interruption occurred in 1 of 57 subjects (1.8%) (presyncope [1 subject]). There was no syncope leading to death, treatment discontinuation, or dose reduction.

The median times to the first onset of syncope (range) in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study were 164.5 days (13-697 days), 261.5 days (29-494 days), and 65.0 days (1-384 days), respectively.

The details of patients with serious syncope in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study are shown in Table 37.

Table 37. Listing of patients with serious syncope (STARTRK-2 study, STARTRK-1 study, ALKA study)

Study ID	Sex	Age	Tumor type	PT (MedDRA ver.21.0)	Grade	Time to onset (days)	Duration (days)	Action taken with entrectinib	Causality	Outcome
STARTRK-2	M	5[redacted]	NSCLC	Syncope	3	427	2	Continued	No	Resolved
				Presyncope	3	435	1	Continued	No	Resolved
STARTRK-1	F	6[redacted]	NSCLC	Syncope	3	494	1	Interrupted	No	Resolved
ALKA	M	6[redacted]	NSCLC	Syncope	3	384	1	Continued	No	Resolved

PMDA asked the applicant to explain the mechanism of development of syncope associated with entrectinib and its risk factors.

The applicant's response:
Given that a TRK tyrosine kinase inhibitor, entrectinib, has been reported to cause decreased heart rate by baroreceptor reflex activation, vagal activation, sympatho-inhibition, etc. (*J Neurotrauma*. 2002;19:1531-41), patients treated with entrectinib may develop syncope due to the baroreceptor reflex, but the mechanism of development is unclear.

No definitive risk factors for syncope associated with entrectinib have been identified.

PMDA's discussion:
Since in the clinical studies submitted, the limited number of subjects experienced syncope, and no serious events for which a causal relationship to entrectinib could not be ruled out were reported, it is difficult at present to draw a definitive conclusion on the risk of syncope associated with entrectinib. As CNS adverse reactions to entrectinib have been reported, and the possibility of the occurrence of syncope cannot be ruled out, it is necessary to continue to watch for the possible relationship between entrectinib and the risk of syncope, and if entrectinib is considered associated with the risk of syncope, appropriate warning/precaution etc. should be provided.

7.R.3.6 ILD

The applicant's explanation about ILD associated with entrectinib:
As adverse events of ILD, events in the MedDRA SMQ "interstitial lung disease (narrow)" were counted.

The incidences of ILD in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study are shown in Table 38.

Table 38. Incidence of ILD (STARTRK-2 study, STARTRK-1 study, ALKA study)

PT (MedDRA ver.21.0)	n (%)					
	STARTRK-2 N = 206		STARTRK-1 N = 76		ALKA N = 57	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
ILD	5 (2.4)	1 (0.5)	1 (1.3)	0	2 (3.5)	0
Pneumonitis	4 (1.9)	1 (0.5)	0	0	0	0
Radiation pneumonitis	2 (1.0)	0	1 (1.3)	0	0	0
Interstitial lung disease	0	0	0	0	1 (1.8)	0
Alveolitis	0	0	0	0	1 (1.8)	0

In the STARTRK-2 study, there was no ILD leading to death or dose reduction. Serious ILD occurred in 2 of 206 subjects (1.0%) (pneumonitis [2 subjects]), and a causal relationship to entrectinib was denied for both cases. ILD leading to treatment discontinuation occurred in 1 of 206 subjects (0.5%) (pneumonitis [1 subject]). ILD leading to dose interruption occurred in 2 of 206 subjects (1.0%) (pneumonitis [2 subjects]).

In the STARTRK-1 study and the ALKA study, there was no ILD leading to death, treatment discontinuation, or dose interruption or reduction, or no serious ILD.

The median times to the first onset of ILD (range) in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study were 84.0 days (43-280 days), 50.0 days, and 463.0 days (127-799 days), respectively.

The details of patients with serious ILD in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study are shown in Table 39.

Table 39. Listing of patients with serious ILD (STARTRK-2 study)

Sex	Age	Race	Tumor type	PT (MedDRA ver.21.0)	Grade	Time to onset (days)	Duration (days)	Action taken with entrectinib	Causality	Outcome
F	7[redacted]	Non-Japanese	NSCLC	Pneumonitis	2	280	14	Interrupted	No	Resolved
F	2[redacted]	Non-Japanese	Sarcoma	Pneumonitis	3	331	7	Interrupted	No	With sequelae

PMDA's discussion:
Because of the limited number of patients with ILD in the clinical studies submitted, it is difficult to draw a definitive conclusion on the risk of ILD associated with entrectinib. However, ILD is a known risk associated with other ALK/ROS1 tyrosine kinase inhibitors (alectinib, crizotinib, ceritinib, lorlatinib), and non-serious ILD for which a causal relationship to entrectinib could not be ruled out has been reported. Given these points etc., attention should be paid to the possible occurrence of ILD during treatment with entrectinib. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence of ILD in the clinical studies, etc., using the package insert etc.

7.R.3.7 QT interval prolongation

The applicant's explanation about QT interval prolongation associated with entrectinib:
As adverse events of QT interval prolongation, events in the MedDRA SMQ "torsade de pointes/QT prolongation (narrow)" were counted.

The incidences of QT interval prolongation in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study are shown in Table 40.

Table 40. Incidence of QT interval prolongation (STARTRK-2 study, STARTRK-1 study, ALKA study)

PT (MedDRA ver.21.0)	n (%)					
	STARTRK-2 N = 206		STARTRK-1 N = 76		ALKA N = 57	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
QT interval prolongation	3 (1.5)	1 (0.5)	2 (2.6)	0	0	0
Electrocardiogram QT interval prolonged	3 (1.5)	1 (0.5)	2 (2.6)	0	0	0

In the STARTRK-2 study, QT interval prolongation leading to dose reduction occurred in 1 of 206 subjects (0.5%) (electrocardiogram QT prolonged [1 subject]). There was no QT interval prolongation leading to death, treatment discontinuation, or dose interruption, or no serious QT interval prolongation.

In the STARTRK-1 study, there was no QT interval prolongation leading to death, treatment discontinuation, dose reduction or interruption, or no serious QT interval prolongation.

In the ALKA study, there was no QT interval prolongation leading to death, treatment discontinuation, or dose reduction or interruption, or no serious QT interval prolongation.

The median times to the first onset of QT interval prolongation (range) in the STARTRK-2 study and the STARTRK-1 study were 58.0 days (1-114 days) and 9.0 days (8-10 days), respectively.

QTcF changes following administration of entrectinib in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study are shown in Table 41. None of the patients with QTcF changes had serious QT interval prolongation-related symptoms.

Table 41. QTcF changes following administration of entrectinib (STARTRK-2 study, STARTRK-1 study)

	n (%)	
	STARTRK-2 N = 206	STARTRK-1 N = 76
Maximum QTcF		
>480 ms	2 (1.0)	0
>500 ms	1 (0.5)	1 (1.3)
>550 ms	0	0
Increase from baseline (maximum value)		
>30 ms	28 (13.6)	6 (7.9)
>60 ms	6 (2.9)	4 (5.3)
>100 ms	1 (0.5)	0
Mean increase from baseline (maximum value) [90% CI] (ms)	12.3 [9.4, 15.2]	12.4 [8.7, 16.2]

PMDA's discussion:

Because of the limited number of patients with QT interval prolongation in the clinical studies submitted, it is difficult to draw a definitive conclusion on the risk of QT interval prolongation associated with entrectinib. Although most of the events of QT interval prolongation associated with entrectinib were of Grade 2 or lower

severity, patients at risk of QT interval prolongation were excluded from these studies, and more than one patient had a ≥60 ms increase from baseline in QTcF following administration of entrectinib. There were entrectinib-related effects on the QT/QTc interval in a repeated-dose toxicity study in dogs [see Section 5.2]. Given these findings etc., attention should be paid to the possible occurrence of QT interval prolongation during treatment with entrectinib. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence of QT interval prolongation, using the package insert etc.

7.R.3.8 Cardiac disorders (excluding QT interval prolongation)

The applicant's explanation about cardiac disorders associated with entrectinib:

As adverse events of cardiac disorders, events in the MedDRA SOC "cardiac disorders" and events in the MedDRA HLTs "cardiac function diagnostic procedures" and "ECG investigations," excluding "QT interval prolongation,[61)]" were counted.

The incidences of cardiac disorders in the STARTRK-2, STARTRK-1 study, and ALKA study study are shown in Table 42.

Table 42. Cardiac disorders reported by ≥1% of subjects in any study (STARTRK-2 study, STARTRK-1 study, ALKA study)

PT (MedDRA ver.21.0)	n (%)					
	STARTRK-2 N = 206		STARTRK-1 N = 76		ALKA N = 57	
	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher	All Grades	Grade 3 or higher
Cardiac disorders	34 (16.5)	11 (5.3)	6 (7.9)	2 (2.6)	8 (14.0)	2 (3.5)
Tachycardia	7 (3.4)	0	0	0	3 (5.3)	0
Bradycardia	6 (2.9)	0	1 (1.3)	0	0	0
Atrial fibrillation	5 (2.4)	0	0	0	2 (3.5)	0
Pericardial effusion	3 (1.5)	3 (1.5)	0	0	0	0
Cardiac failure	3 (1.5)	2 (1.0)	0	0	0	0
Cardiac failure congestive	3 (1.5)	1 (0.5)	0	0	0	0
Sinus bradycardia	3 (1.5)	0	1 (1.3)	0	0	0
Ejection fraction decreased	3 (1.5)	2 (1.0)	0	0	0	0
Cardiomegaly	3 (1.5)	0	0	0	0	0
Cardio-respiratory arrest	2 (1.0)	2 (1.0)	0	0	0	0
Sinus tachycardia	2 (1.0)	0	0	0	0	0
Cardiac tamponade	1 (0.5)	1 (0.5)	0	0	1 (1.8)	1 (1.8)
Myocardial infarction	1 (0.5)	0	0	0	1 (1.8)	1 (1.8)
Palpitations	1 (0.5)	0	0	0	1 (1.8)	0
Angina pectoris	0	0	2 (2.6)	0	0	0
Myocarditis	0	0	1 (1.3)	1 (1.3)	0	0
Atrial flutter	0	0	1 (1.3)	1 (1.3)	0	0
Extrasystoles	0	0	1 (1.3)	0	0	0

In the STARTRK-2 study, cardiac disorders leading to death occurred in 3 of 206 subjects (1.5%) (cardio-respiratory arrest [2 subjects]; and cardiogenic shock [1 subject]), and a causal relationship to entrectinib was denied for all those cases. Serious cardiac disorders occurred in 9 of 206 subjects (4.4%) (pericardial effusion [3 subjects]; cardiac failure congestive; and cardio-respiratory arrest [2 subjects each]; and acute right

[61)] Events in the MedDRA SMQ "torsade de pointes/QT prolongation (narrow)"

ventricular failure; cardiac tamponade; cardiogenic shock; ventricular extrasystoles; cardiac failure; and sinus arrhythmia [1 subject each] [some subjects had more than 1 event]), and a causal relationship to entrectinib could not be ruled out for cardiac failure congestive; cardiac failure; ventricular extrasystoles; and sinus arrhythmia (1 subject each). Cardiac disorders leading to treatment discontinuation occurred in 4 of 206 subjects (1.9%) (cardio-respiratory arrest [2 subjects]; and cardiac failure congestive; cardiac tamponade; cardiogenic shock; and pericardial effusion [1 subject each] [some subjects had more than 1 event]). Cardiac disorders leading to dose interruption occurred in 7 of 206 subjects (3.4%) (cardiac failure congestive; and cardiac failure [2 subjects each]; and acute right ventricular failure; ventricular extrasystoles; pericardial effusion; sinus arrhythmia; and atrial fibrillation [1 subject each] [some subjects had more than 1 event]). There were no cardiac disorders leading to dose reduction.

In the STARTRK-1 study, serious cardiac disorders occurred in 2 of 76 subjects (2.6%) (myocarditis; and atrial flutter [1 subject each]), and a causal relationship to entrectinib could not be ruled out for myocarditis (1 subject). Cardiac disorders leading to treatment discontinuation occurred in 2 of 76 subjects (2.6%) (myocarditis; and extrasystoles [1 subject each]). There were no cardiac disorders leading to death or dose interruption or reduction.

In the ALKA study, serious cardiac disorders occurred in 2 of 57 subjects (3.5%) (cardiac tamponade; and myocardial infarction [1 subject each]), and a causal relationship to entrectinib was denied for both events. Cardiac disorder leading to treatment discontinuation occurred in 1 of 57 subjects (1.8%) (atrial fibrillation [1 subject]). There were no cardiac disorders leading to death. Cardiac disorders leading to dose interruption occurred in 2 of 57 subjects (3.5%) (myocardial infarction; and palpitations [1 subject each]). There were no cardiac disorders leading to dose reduction.

The median times to the first onset of cardiac disorders (range) in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study were 68.0 days (1-529 days), 36.0 days (3-995 days), and 8.5 days (1-318 days), respectively.

The details of patients with serious cardiac disorders in the STARTRK-2 study, the STARTRK-1 study, and the ALKA study are shown in Table 43.

Table 43. Listing of patients with serious cardiac disorders (STARTRK-2 study, STARTRK-1 study, ALKA study)

Study ID	Sex	Age	Tumor type	PT (MedDRA ver.21.0)	Grade	Time to onset (days)	Duration (days)	Action taken with entrectinib	Causality	Outcome
STARTRK-2	M	5[redacted]	NSCLC	Cardiac tamponade	4	2	Unknown	Discontinued	No	Unresolved
				Cardiogenic shock	5	Unknown	Unknown			Fatal
				Pericardial effusion	4	Unknown	2			Unresolved
	M	5[redacted]	NSCLC	Pericardial effusion	3	17	5	Interrupted	No	Resolved
				Cardiac failure congestive	2	18	Unknown			Unresolved
	M	5[redacted]	NSCLC	Sinus arrhythmia	1	1	2	Interrupted	Yes	Resolved
				Ventricular extrasystoles	1	Unknown	Unknown	Interrupted	Yes	Resolved
	M	7[redacted]	NSCLC	Cardio-respiratory arrest	5	43	1	Discontinued	No	Fatal
	F	5[redacted]	MASC	Cardio-respiratory arrest	5	2	1	Discontinued	No	Fatal
	F	3[redacted]	NSCLC	Cardiac failure	3	124	3	Interrupted	Yes	Resolved
	M	5[redacted]	Thyroid cancer	Acute right ventricular failure	3	217	9	Interrupted	No	Resolved
	M	6[redacted]	Pancreatic cancer	Cardiac failure congestive	3	57	10	Interrupted	No	Resolved
				Cardiac failure congestive	3	74	5	Discontinued	Yes	Resolved
	F	6[redacted]	Breast cancer	Pericardial effusion	3	145	9	Not applicable*	No	Resolved
STARTRK-1	M	4[redacted]	NSCLC	Myocarditis	4	3	5	Discontinued	Yes	Resolved
	M	7[redacted]	Sarcoma	Atrial flutter	3	21	2	Not applicable	No	Resolved
ALKA	F	7[redacted]	NSCLC	Myocardial infarction	3	50	17	Interrupted	No	Resolved
	F	5[redacted]	NSCLC	Cardiac tamponade	3	69	4	None	No	Resolved

*, Entrectinib had been interrupted due to Grade 3 pleural effusion on Day 141.

PMDA's discussion:

Since in the clinical studies submitted, cardiac disorders associated with entrectinib occurred at a certain frequency, and serious cardiac disorders for which a causal relationship to entrectinib could not be ruled out were reported, attention should be paid to the possible occurrence of cardiac disorders during treatment with entrectinib. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence of cardiac disorders in the clinical studies, etc., using the package insert etc.

7.R.4 Indication

The proposed indication for entrectinib was "*NTRK* fusion-positive, locally advanced or metastatic solid tumors." The following statements were included in the PRECAUTIONS CONCERNING INDICATION section of the proposed package insert.

- Entrectinib should be used in patients with an *NTRK* fusion as detected by testing with the approved *in vitro* diagnostic etc.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section and of the efficacy and safety of entrectinib.

Based on Sections "7.R.2 Clinical positioning and efficacy," "7.R.3 Safety," and "7.R.5.2 Dosage and administration for pediatric patients," and the considerations in the following sections, PMDA concluded as follows: The types of tumors etc. of patients enrolled in the STARTRK-2 study etc. should be listed in the CLINICAL STUDIES section of the package insert, and the following statements should be included in the

PRECAUTIONS CONCERNING INDICATION section. Then, the proposed indication should be modified to "*NTRK* fusion-positive, advanced/recurrent solid tumors."

- The efficacy and safety of entrectinib as adjuvant therapy following surgery have not been established.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the types of tumors etc. of patients enrolled in clinical studies, and of the efficacy and safety of entrectinib, after carefully considering the use of other treatments as well.
- Entrectinib should be used in patients with an *NTRK* fusion as detected by testing performed by a pathologist or laboratory with adequate experience. The approved *in vitro* diagnostic etc. should be used for testing.
- The use of entrectinib in pediatric patients should be determined carefully by physicians with a full understanding of the information presented in the Pediatric Use and CLINICAL STUDIES sections concerning the age of patients enrolled in clinical studies [see Section 7.R.5.2].

7.R.4.1 Target population and indication

The applicant's explanation about the target population and indication for entrectinib:

The types of tumors of patients enrolled in the STARTRK-2 study were colorectal cancer, biliary tract carcinoma, neuroendocrine tumors, breast cancer, mammary secretory carcinoma, mammary analogue secretory carcinoma, endometrial cancer, ovarian cancer, NSCLC, thyroid cancer, pancreatic cancer, and sarcoma. Standard chemotherapy etc. exist for these tumor types except for mammary secretory carcinoma and mammary analogue secretory carcinoma. However, based on the results of the STARTRK-2 study [see Sections 7.1.2.1 and 7.R.2] and given that entrectinib is a drug targeting drivers of cancer cell growth (oncogenic drivers), it is recommended that patients should first be treated with entrectinib also when standard treatments are available for their tumor types.

In the STARTRK-2 study, (1) the number of prior therapies differed among the enrolled patients, (2) no data from patients treated with entrectinib as adjuvant therapy following surgery were obtained, and (3) patients with primary brain tumors were excluded from the efficacy evaluable population.

The applicant's view on the target population, taking account of the above (1)(2)(3):

(1) In the STARTRK-2 study, the response rates in the subgroups of patients who had received no prior therapies, 1 prior therapy, 2 prior therapies, and ≥3 prior therapies were 65.0%, 45.5%, 64.3%, and 33.3%, respectively, showing no clear differences among the subgroups. Thus, the efficacy of entrectinib in patients with *NTRK* fusion-positive, advanced/recurrent solid tumors is expected, regardless of the number of prior therapies.

(2) Although there are no clinical data on the efficacy and safety of entrectinib as adjuvant therapy following surgery, it is envisaged that entrectinib will be used also in patients with unresectable solid tumors such as sarcomas for which adjuvant therapy following surgery is the standard of care. If the package insert cautions against the use of entrectinib as adjuvant therapy following surgery, these patients may miss the

opportunity to receive a standard of care treatment. Thus, a precautionary statement regarding the use of entrectinib as adjuvant therapy following surgery is unnecessary.

(3) In the STARTRK-2 study, 5 patients with *NTRK* fusion-positive primary brain tumors were enrolled. One of the 5 patients (20%) was a responder,[62)] and there were no clear differences in safety between patients with primary brain tumors and other patients [see Section 7.R.3.1] etc. Thus, the use of entrectinib is recommended also in patients with *NTRK* fusion-positive primary brain tumors.

Based on the above, the results of the STARTRK-2 study etc. have been described in the CLINICAL STUDIES section of the package insert, and the following statement has been included in the PRECAUTIONS CONCERNING INDICATION section. Then, the indication of "*NTRK* fusion-positive, locally advanced or metastatic solid tumors" has been proposed.

- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section and of the efficacy and safety of entrectinib.

PMDA's discussion:

Taking also into account that the number of patients with *NTRK* fusion-positive solid tumors is extremely limited [see Section 7.R.2.1], and that it is difficult to evaluate the efficacy of entrectinib for each and every tumor type in clinical studies, etc., PMDA largely accepted the above explanation by the applicant. Although 2 patients with "locally advanced" solid tumors in the claimed indication were enrolled in the STARTRK-2 study, as both had advanced/recurrent disease for which there is no standard treatment, the appropriate indication for entrectinib should be "*NTRK* fusion-positive, advanced/recurrent solid tumors."

Given the following (1)(2)(3), the types of tumors etc. of patients enrolled in the STARTRK-2 study etc. should be listed in the CLINICAL STUDIES section of the package insert, and then the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section.

(1) At present, there are no clinical study data on the efficacy and safety of entrectinib as adjuvant therapy following surgery.

(2) The information on the types of tumors of patients enrolled in the STARTRK-2 study is important.

(3) In the present application, the efficacy of entrectinib was evaluated based mainly on the response rates, and no information on survival benefits is available. The use of other treatments should also be considered carefully.

Precautions Concerning Indication

- The efficacy and safety of entrectinib as adjuvant therapy following surgery have not been established.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the types of tumors etc. in patients enrolled in clinical studies, and of the efficacy and safety of entrectinib, after carefully considering the use of other treatments as well.

62) Evaluated by the RANO criteria.

It is necessary to continue to collect information on the choice between entrectinib and the existing standard chemotherapy etc., and if new information becomes available, the information should appropriately be provided to healthcare professionals in clinical practice, etc.

7.R.4.2 Testing for *NTRK* fusions

The applicant's explanation:

Given the following points, "FoundationOne CDx Cancer Genomic Profile" that is marketed by the applicant should be used to identify patients who may be eligible for treatment with entrectinib, and the relevant statement will be included in the PRECAUTIONS CONCERNING INDICATION section.

- In the STARTRK-2 study that demonstrated the clinical efficacy of entrectinib, patients positive for *NTRK* fusions as detected by testing performed at the central or a local laboratory were eligible, and Ignyta's "Trailblaze Pharos" was used at the central laboratory [see Section 6.1.1]. Then, using the samples from patients who tested positive for *NTRK* fusions at local laboratories and were enrolled in the STARTRK-2 study etc., the concordance with the "Trailblaze Pharos" assay was evaluated, which showed 86.2% positive agreement.
- The concordance between the "Trailblaze Pharos" and "FoundationOne CDx Cancer Genomic Profile" assays was evaluated, which showed 85.7% positive agreement. Thus, the concordance between these diagnostic assays was demonstrated.

PMDA's discussion:

PMDA accepted the above explanation by the applicant, and concluded that the following statement should be included in the PRECAUTIONS CONCERNING INDICATION section.

- Entrectinib should be used in patients with an *NTRK* fusion as detected by testing performed by a pathologist or laboratory with adequate experience. The approved *in vitro* diagnostic etc. should be used for testing.

7.R.5 Dosage and administration

The applicant proposed the following dosage and administration of entrectinib and included the recommended dosage modifications for dose interruption, dosage reduction, discontinuation of therapy at the onset of adverse reactions in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

Dosage and Administration

The usual dosage in patients aged ≥18 years is 600 mg of entrectinib administered orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition.

The usual dosage in patients aged <18 years is 300 mg/m^2 (body surface area) of entrectinib administered orally once daily. The dose should not exceed 600 mg. The dosage should be reduced, as appropriate, according to the patient's condition.

Dosing in patients aged <18 years (300 mg/m^2 administered orally once daily)

Body surface area (m^2)	Dosage (once daily)
0.43-0.50	100 mg
0.51-0.80	200 mg
0.81-1.10	300 mg
1.11-1.50	400 mg
≥1.51	600 mg

Based on Sections "7.R.2 Clinical positioning and efficacy" and "7.R.3 Safety," and the following considerations, PMDA concluded that the following statements should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the wording for dosage and administration should be modified as shown below.

Dosage and Administration

The usual adult dosage is 600 mg of entrectinib administered orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition.

The usual pediatric dosage is 300 mg/m^2 (body surface area) of entrectinib administered orally once daily. The dose should not exceed 600 mg. The dosage should be reduced, as appropriate, according to the patient's condition.

Dosing in pediatric patients (300 mg/m^2 administered orally once daily)

Body surface area (m^2)	Dosage (once daily)
0.43-0.50	100 mg
0.51-0.80	200 mg
0.81-1.10	300 mg
1.11-1.50	400 mg
≥1.51	600 mg

Precautions Concerning Dosage and Administration

- The efficacy and safety of entrectinib in combination with other anti-neoplastic drugs have not been established.
- Recommended dosage modifications for dose interruption, dosage reduction, discontinuation of therapy at the onset of adverse reactions [see Section 7.R.5.3].

7.R.5.1 Dosage and administration for adult patients

The applicant's explanation about dosage and administration for adult patients:

The dosing regimen for the STARTRK-2 study was selected based on the following study results etc., and the STARTRK-2 study demonstrated the clinical usefulness of entrectinib in patients with *NTRK* fusion-positive, advanced/recurrent solid tumors, etc. Thus, based on the dosing regimen used in the STARTRK-2 study, the dosage and administration statement was proposed as follows: "The usual dosage in patients aged ≥18 years is 600 mg of entrectinib administered orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition." There are no clinical study data on the efficacy and safety of entrectinib in combination with other anti-neoplastic drugs, and this information will be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

- In the dose escalation cohort of a foreign phase I study (STARTRK-1 study), the RP2D of entrectinib (Formulation F1) was determined to be 600 mg QD orally, and entrectinib was well tolerated.
- In a global phase II study (STARTRK-2 study) mainly using entrectinib (Formulation F2A) 600 mg, entrectinib shrank tumors and was well tolerated.
- In the STARTRK-2 study, a Japanese lead-in cohort was treated with entrectinib to assess the tolerability of entrectinib in Japanese patients. No DLTs occurred after oral administration of entrectinib (Formulation F2A) 600 mg QD, and entrectinib (Formulation F2A) 600 mg QD orally was well tolerated also in Japanese patients.
- A foreign phase I study (Study 101-15) demonstrated the bioequivalence between Formulations F06 and F2A of entrectinib [see Section 6.1.3.1].

PMDA's discussion:
PMDA largely accepted the above explanation by the applicant. However, the CLINICAL STUDIES section of the package insert should mention that patients aged ≥18 years were enrolled in the STARTRK-2 study, and then "the usual dosage in patients aged ≥18 years" in the dosage and administration statement proposed by the applicant should be changed to "the usual adult dosage" so as to be in line with the text of the DOSAGE AND ADMINISTRATION section for other anti-neoplastic drugs.

7.R.5.2 Dosage and administration for pediatric patients

(i) Efficacy and (ii) safety results from a foreign phase I/Ib study (STARTRK-NG study) are shown below.

(i) Four of 5 pediatric patients with *NTRK* fusion-positive, advanced/recurrent solid tumors enrolled in the phase I dose escalation and phase Ib expansion parts of the STARTRK-NG study were responders (Table 44). Among these 5 patients, the AUC_{ss} of entrectinib (individual value, 62,100 nmol·h/L) in 1 patient treated orally with entrectinib (Formulation F1) QD at the RP2D of 550 mg/m^2 and the AUC_{ss} of entrectinib (range, 14,800-61,600 nmol·h/L) in 3 patients who received entrectinib (Formulation F1) 400 mg/m^2 QD orally or by enteral feeding were within the range of the AUC_{ss} of entrectinib (9530-80,300 nmol·h/L) following oral administration of entrectinib (Formulation F2A) 600 mg QD in adult patients in a foreign phase I study (STARTRK-1 study).

Table 44. Best overall response in pediatric patients with *NTRK* fusion-positive solid tumors (RECIST ver.1.1[*1], Investigator assessments, data cutoff date of October 31, 2018)

Age	Tumor type	Formulation	Dose (mg/m^2)	Best overall response
4	Infantile fibrosarcoma	F1	750	PR
3	Epidermoid glioblastoma	F1	550	CR
4	High-grade glioma	F1	400	PR
4	Malignant melanoma	F1	400	PR
0[*2]	Infantile fibrosarcoma	F1	400	SD

*1, Primary brain tumors (epidermoid glioblastoma and high-grade glioma) were evaluated by the RANO criteria. *2, 4.5 months old

(ii) In 205 adult patients (≥18 years[63]) and 17 pediatric patients (<18 years) in the STARTRK-2 study and the STARTRK-NG study, adverse events of any grade reported at a ≥20% higher incidence in pediatric patients than in adult patients were anaemia (10 pediatric patients [58.8%], 60 adult patients [29.3%]), nausea (10 pediatric patients [58.8%], 53 adult patients [25.9%]), fatigue (9 pediatric patients [52.9%], 62 adult patients [30.2%]), blood creatinine increased (9 pediatric patients [52.9%], 59 adult patients [28.8%]), cough (9 pediatric patients [52.9%], 46 adult patients [22.4%]), AST increased (9 pediatric patients [52.9%], 41 adult patients [20.0%]), pyrexia (8 pediatric patients [47.1%], 41 adult patients [20.0%]), ALT increased (8 pediatric patients [47.1%], 37 adult patients [18.0%]), pain in extremity (6 pediatric patients [35.3%], 21 adult patients [10.2%]), decreased appetite (6 pediatric patients [35.3%], 21 adult patients [10.2%]), hyperglycaemia (6 pediatric patients [35.3%], 13 adult patients [6.3%]), oropharyngeal pain (5 pediatric patients [29.4%], 17 adult patients [8.3%]), neutrophil count decreased (5 pediatric patients [29.4%], 16 adult patients [7.8%]), white blood cell count decreased (5 pediatric patients [29.4%], 12 adult patients [5.9%]), platelet count decreased (5 pediatric patients [29.4%], 7 adult patients [3.4%]), nasal congestion (5 pediatric patients [29.4%], 4 adult patients [2.0%]), sinus tachycardia (5 pediatric patients [29.4%], 2 adult patients [1.0%]), and hypernatraemia (4 pediatric patients [23.5%], 13 adult patients [6.3%]). Grade 3 or higher adverse events reported at a ≥10% higher incidence in pediatric patients than in adult patients were neutrophil count decreased (3 pediatric patients [17.6%], 4 adult patients [2.0%]), platelet count decreased (3 pediatric patients [17.6%], 1 adult patient [0.5%]), and lymphocyte count decreased (2 pediatric patients [11.8%], 3 adult patients [1.5%]). There were no serious adverse events, adverse events leading to treatment discontinuation, adverse events leading to dose interruption, adverse events leading to dose reduction, or adverse events leading to death reported at a ≥20% higher incidence in pediatric patients than in adult patients.

A serious adverse event occurring in pediatric patients only was femur fracture (1 subject), and its causal relationship to entrectinib was denied.

Although delayed growth and development and CNS toxicity occurred at a lower dose in juvenile rats than in adult rats [see Section 5.R.1], no cases of delayed growth and development have been reported at present, and there were no clear differences in the incidences of CNS adverse events (cognitive disorder, peripheral sensory neuropathy, paraesthesia, ataxia, etc.) between adult and pediatric patients in clinical studies conducted. The applicant explained that the package insert etc. will caution about the findings from the toxicity study in juvenile rats [see Section 5.R.1]

The applicant's explanation about dosage and administration for pediatric patients, based mainly on PPK and PBPK modeling analyses:
Based on the results of a foreign phase I/Ib study (STARTRK-NG study), the RP2D of entrectinib in pediatric patients was determined to be "Formulation F1 550 mg/m^2 QD orally" [see Section 7.1.3.3]. The AUC_{24h} of

[63] Age classification of pediatric patients presented in the guidance on "Clinical Investigation of Medicinal Products in the Pediatric Population" was used.

entrectinib on Day 1 of Cycle 1 in pediatric patients treated with entrectinib at this dosing regimen (the range of observed values, 26,400-53,400 nmol·h/L) was comparable to the AUC_{24h} of entrectinib on Day 1 of Cycle 1 in adult patients treated orally with entrectinib (Formulation F2A) 600 mg QD in the foreign phase I study (STARTRK-1 study) (the range of observed values, 14,900-59,300 nmol·h/L).

However, as there are no clinical study data from pediatric patients treated with the proposed commercial formulation, Formulation F06, which is bioequivalent to Formulation F2A [see Sections 6.1 and 6.1.3.1], detailed analyses were performed by age group [(1) ≥4 years, (2) <4 years], so that dosing in pediatric patients also can achieve comparable AUC_{ss} to adult patients treated orally with entrectinib (Formulation F06) 600 mg QD. The results of the analyses are shown below. Although the PK data from 3 pediatric patients aged <4 years (2 3-year-old children and 1 0-year-old [4.5-month-old] child) were obtained after regulatory submission (data cutoff date of October 31, 2018), considering that there were no clinical study data from pediatric patients aged <4 years at the time of regulatory submission (data cutoff date of May 31, 2018), pediatric patients were categorized as older or younger than "4 years."

(1) Since changes in body size during development are considered to affect the PK of entrectinib and M5, etc., the optimal dosing regimen was determined based on PPK analyses [see Section 6.2.5]. Using the PPK models, the AUC_{ss} (the sum of entrectinib and M5) following oral administration of entrectinib (Formulation F06) 600 mg QD was predicted by body weight (15-70 kg[64)]), and the relative ratios of AUC_{ss} were calculated by body weight [Table 45 (I)]. Then, based on the relative ratios of AUC_{ss}, fixed doses that can achieve comparable AUC_{ss}[65)] to that obtained with oral entrectinib (Formulation F06) 600 mg QD in a patient of 70 kg were calculated by body weight [Table 45 (II)], and the fixed doses were determined, taking account of the strengths of the proposed commercial formulation (100 or 200 mg) [Table 45 (III)]. Furthermore, these fixed doses were converted to BSA-adjusted doses, using the equation proposed by Livingston et al. (*Am J Physiol Endocrinol Metab*. 2001;281:E586-91) [Table 45 (IV)]. Entrectinib (Formulation F06) 300 mg/m^2 QD orally was predicted to achieve comparable AUC_{ss} in pediatric patients as in adult patients treated orally with entrectinib (Formulation F06) 600 mg QD.

Table 45. Dose of entrectinib by body weight

Body weight (kg)	(I)	(II)	(III)	(IV)
	Relative ratio of AUC_{ss}	Fixed dose that can achieve comparable AUC_{ss} to a patient of 70 kg (mg)	Fixed dose taking account of the strengths of the proposed commercial formulation (mg)	BSA-adjusted dose (mg/m^2)
15	3.18	188.97	200	300
20	2.56	234.48	200	300
25	2.16	277.19	300	300
30	1.89	317.81	300	300
35	1.68	356.76	400	300
40	1.52	394.34	400	300
45	1.39	430.76	400	300
50	1.29	466.18	500	300

64) Body weights of 15 and 70 kg correspond to the average body weights of 4-year-old children and ≥20-year-old adults, respectively (2016 National Health and Nutrition Survey).

65) The ratio of the AUC_{ss} following fixed dosing of oral entrectinib (Formulation F06) QD in patients of 15 to 50 kg to the AUC_{ss} following oral administration of entrectinib (Formulation F06) 600 mg QD in a patient of 70 kg was required to be within the range of 0.8 to 1.2.

70	1.00	—	—	—

—: Not applicable

(2) Considering that the expression levels of CYP3A4 (entrectinib is metabolized primarily by CYP3A4 [see Section 4.3.1]) increase at 1 to 2 years postnatal age (*J Pharmacol Exp Ther*. 2003;307:573-82), a PBPK model of entrectinib incorporating developmental changes in CYP3A4 expression (*J Clin Pharmacol*. 2016;56:266-83) was developed,[66] and the optimal dosing regimen was determined. Using the developed PBPK model, the dosing regimen that can achieve comparable AUC_{ss} in pediatric patients as in adult patients treated orally with entrectinib (Formulation F06) 600 mg QD was predicted by age group. The dosing regimens of entrectinib (Formulation F06) for (I) newborn to <1 month of age, (II) ≥1 month and <6 months of age, and (III) ≥6 months and <4 years of age were predicted to be (I) 100 to 150 mg/m^2, (II) 250 mg/m^2, and (III) 300 mg/m^2 QD orally, respectively (Table 46). Since the dose for pediatric patients (I) and (II) is <300 mg/m^2, which is equivalent to a fixed dose of <100 mg, it is difficult to administer entrectinib to these patients, in light of the lowest strength (100 mg) of the proposed commercial formulation [see Section 6.1].

Table 46. Predicted entrectinib exposure

		Dosing regimen	AUC_{ss} (nmol·h/L)
(I)	Newborn to <1 month	100 mg/m^2 QD	38,400 (15,700, 85,700)
		150 mg/m^2 QD	56,300 (22,800, 126,000)
(II)	1 to 6 months	250 mg/m^2 QD	50,900 (21,500, 88,400)
(III)	6 months to 1 year	300 mg/m^2 QD	62,700 (23,200, 89,200)
	1 year to 1 year 6 months	300 mg/m^2 QD	60,300 (22,800, 92,600)
	1 year 6 months to 2 years	300 mg/m^2 QD	49,100 (22,600, 90,500)
	2 years to 2 years 6 months	300 mg/m^2 QD	53,600 (22,500, 97,600)
	2 years 6 months to 3 years	300 mg/m^2 QD	62,700 (22,100, 93,500)
	3 years to 3 years 6 months	300 mg/m^2 QD	61,200 (22,400, 94,200)
	3 years 6 months to 4 years	300 mg/m^2 QD	58,200 (22,600, 94,900)
	Adult	600 mg QD	57,300 (27,900, 111,000)

Geometric mean (5th percentile, 95th percentile)

Taking account of the above results of analyses (1) and (2), and the recommended dosing regimen of entrectinib (Formulation F06) for adult patients (600 mg QD orally), the proposed dosing regimen of entrectinib (Formulation F06) for pediatric patients aged ≥6 months, i.e. 300 mg/m^2 (up to 600 mg) QD orally, should be appropriate.

However, given that the strengths of the proposed commercial formulation are 100 or 200 mg [see Section 6.1], it was decided to determine fixed doses that can achieve comparable AUC_{ss} to that obtained with oral entrectinib (Formulation F06) 600 mg QD in adult patients, for each BSA category, using the PPK models [see Section 6.2.5], for all age groups of children. The AUC_{ss} of entrectinib in pediatric patients with a BSA of

[66] Simcyp version 17.1 was used for PBPK analysis. The advanced dissolution absorption and metabolism (ADAM) model was selected as an absorption model, and a full PBPK model was selected as a distribution model. Based on the results of a foreign phase I study (Study 101-12) [see Section 6.2.2.1] etc., the percent contribution of CYP3A4 to metabolism was set at 78%. Simcyp default values were used for physiological parameters. A pediatric PBPK model considering CYP3A4 ontogeny (*J Clin Pharmacol.* 2016;56:266-83) was developed following the development of an adult PBPK model. The pediatric PBPK model was verified against PK data from 8 pediatric patients aged 4 to 9 years enrolled in the STARTRK-NG study.

≥0.51 m^2 treated orally with the initial dose based on BSA category of entrectinib (Formulation F06) QD was predicted to be comparable to the AUC_{ss} of entrectinib in adult patients treated orally with entrectinib (Formulation F06) 600 mg QD. On the other hand, although the AUC_{ss} of entrectinib following oral administration of entrectinib (Formulation F06) 100 mg QD in pediatric patients with a BSA of 0.43 to 0.50 m^2 was predicted to be lower than the AUC_{ss} of entrectinib following oral administration of entrectinib (Formulation F06) 600 mg QD in adult patients, given the AUC_{ss} range etc. in a global phase II study (STARTRK-2 study), the efficacy of entrectinib is expected. Body surface area in children aged 4 years to 4 years 6 months is considered to be 0.58 to 0.78 m^2 in boys and 0.57 to 0.76 m^2 in girls.[67)]

Based on the above, dosage and administration for pediatric patients was proposed as follows. With regard to the AUC_{ss} of entrectinib following oral administration of the initial dose based on BSA category of entrectinib QD, the predicted values from the PPK model [see Section 6.2.5] largely agreed with the predicted values from the PBPK model used in the above (2).

Dosage and Administration

The usual dosage in patients aged <18 years is 300 mg/m^2 (body surface area) of entrectinib administered orally once daily. The dose should not exceed 600 mg. The dosage should be reduced, as appropriate, according to the patient's condition.

Dosing in patients aged <18 years (300 mg/m^2 administered orally once daily)

Body surface area (m^2)	Dosage (once daily)
0.43-0.50	100 mg
0.51-0.80	200 mg
0.81-1.10	300 mg
1.11-1.50	400 mg
≥1.51	600 mg

PMDA's discussion:

Given the above explanation by the applicant from the clinical pharmacology standpoint, and taking also into account that (1) the number of pediatric patients with *NTRK* fusion-positive, advanced/recurrent solid tumors is extremely limited, that (2) there were responders among 5 pediatric patients with *NTRK* fusion-positive, advanced/recurrent solid tumors, and that (3) there were no clear differences in the safety profile between adult and pediatric patients, and entrectinib was tolerable also in pediatric patients, etc., the above dosage and administration of entrectinib (Formulation F06) for pediatric patients presented by the applicant is largely understandable. Based on the considerations in Section "7.R.5.1 Dosage and administration for adult patients," "the usual dosage in patients aged <18 years" in the dosage and administration statement proposed by the applicant should be changed to "the usual pediatric dosage."

Although the above explanation by the applicant about the proposed dosing regimen for pediatric patients based on the clinical pharmacological analyses is acceptable for pediatric patients aged ≥4 years, given the following

67) Calculated by the formula proposed by Du Bois et al. (*Arch Intern Med*. 1916;17:863-71), using body weight and height data reported in the Infant Physical Development Survey of MHLW (2010).

(i) and (ii) etc., this is inadequate for pediatric patients aged <4 years. Taking also into account that there are no data on the efficacy and safety of entrectinib (Formulation F06) in pediatric patients aged <4 years, the use of entrectinib (Formulation F06) in pediatric patients aged <4 years should be determined carefully.

(i) The PK data from pediatric patients aged <4 years are extremely limited, and the above PPK model was developed based on the PK data from patients aged ≥4 years.

(ii) Considering the purpose of the above PBPK modeling analysis, the model's predictive performance may not be good enough, and the PK data from pediatric patients aged <4 years are extremely limited. Thus, it cannot be concluded that the PBPK model has been verified adequately.

Based on the above, the age etc. of children enrolled in clinical studies should be mentioned in the Pediatric Use and CLINICAL STUDIES sections of the package insert, and then it should be stated in the PRECAUTIONS CONCERNING INDICATION section that the use of entrectinib should be determined carefully by physicians with a full understanding of the information presented in the Pediatric Use and CLINICAL STUDIES sections concerning the age of patients enrolled in clinical studies [see Section 7.R.4].

In addition, the PK data from pediatric patients treated with entrectinib (Formulation F06) are being collected in the ongoing STARTRK-NG study, and this information is important for confirming the appropriateness of the dosing regimen of entrectinib (Formulation F06) for pediatric patients. Thus, it is necessary to continue to collect this information, and if a new finding becomes available, appropriate action should be taken, e.g. appropriately provide the information to healthcare professionals in clinical practice. Although there were no clear differences in the safety profile between adult and pediatric patients, as the incidences of some adverse events tended to be higher in pediatric patients than in adult patients, this information should also be provided to healthcare professionals in clinical practice appropriately.

7.R.5.3 Entrectinib dosage modifications

The applicant's explanation about entrectinib dosage modifications:

Clinical studies including the STARTRK-2 study were conducted according to the specific dosage modification guidelines and demonstrated the clinical usefulness of entrectinib. Thus, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section will include a revised version of these dosage modification guidelines and specific treatments for management of adverse reactions. The details of revision are shown below.

- Although clinical studies including the STARTRK-2 study had dosage modification guidelines for ataxia and ILD, as only a few patients had serious adverse events, etc., the revised version does not include these guidelines.
- Since a certain number of serious adverse events of cardiac disorders for which a causal relationship to entrectinib could not be ruled out, such as cardiac failure and congestive cardiac failure, were reported in clinical studies including the STARTRK-2 study, the revised version states that if cardiac disorder of any grade occurs, entrectinib should be resumed at one dosage level lower upon resolution to baseline, regardless of when resolution occurs.

- Since QT interval prolongation may lead to a serious event such as sudden death, the revised version states as follows: Regardless of when resolution occurs, entrectinib should be resumed at the same dosage upon resolution to baseline if Grade 2 QT interval prolongation occurs, and entrectinib should be resumed at one dosage level lower upon resolution to baseline if Grade 3 QT interval prolongation occurs. In the event of Grade 4 QT interval prolongation, treatment should be discontinued permanently if serious symptoms are observed.
- Since cognitive impairment recurred after entrectinib was resumed at the same dosage in clinical studies including the STARTRK-2 study, etc., the revised version states that if Grade 2 or higher cognitive impairment occurs, entrectinib should be resumed at one dosage level lower upon resolution to baseline, regardless of when resolution occurs.
- Since syncope occurred regardless of the occurrence of QT interval prolongation etc. in clinical studies including the STARTRK-2 study, etc., the revised version states that if syncope of any grade occurs, entrectinib should be resumed at one dosage level lower upon resolution to baseline, regardless of when resolution occurs.
- Since 20 of 38 patients with Grade 3 or higher anaemia had no dosage modifications, and most patients recovered in clinical studies including the STARTRK-2 study, etc., the revised version states that if anaemia or neutropenia occurs, entrectinib should be resumed at the same dosage or one dosage level lower, as clinically indicated, upon resolution.

The dosage modification guidelines for pediatric patients established so as to achieve comparable AUC_{ss} of entrectinib to adult patients treated orally with entrectinib (Formulation F06) QD at reduced dose levels, based on the PPK models [see Section 6.2.5], will be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section. The dosage modification guideline for QT interval prolongation will be established based on the guideline used in the STARTRK-NG study.

PMDA's discussion:
With regard to the recommended dosage modifications for cardiac disorders (including congestive cardiac failure), cognitive impairment, and syncope, the guidelines have been made more stringent than those used in the STARTRK-2 study because serious cardiac disorders for which a causal relationship to entrectinib could not be ruled out occurred in the clinical studies submitted, etc. Taking account of this point, PMDA accepted the above explanation by the applicant. PMDA also accepted the above explanation by the applicant about the dosage modification guidelines for pediatric patients.

However, with regard to events other than cardiac disorders (including congestive cardiac failure), cognitive impairment, and syncope, since clinical studies including the STARTRK-2 study were conducted according to the specific dose interruption/reduction guidelines based on the NCI-CTCAE grades etc. and demonstrated the tolerability and safety of entrectinib, the following dosage modification guidelines[68)] based on the dose

[68)] The recommended dosage reductions/discontinuation of therapy for pediatric patients are based on PPK and PBPK modeling analyses.

interruption/reduction guidelines used in clinical studies including the STARTRK-2 study should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

- In the event of adverse reactions, withhold or reduce the dosage of entrectinib, or discontinue entrectinib therapy, as per the criteria below.

[Adult patients] Recommended dosage reductions/discontinuation of therapy

Dosage reduction levels	Dosage
Usual dosage	600 mg/day
First dosage reduction	400 mg/day
Second dosage reduction	200 mg/day
Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 200 mg/day.

[Pediatric patients] Recommended dosage reductions/discontinuation of therapy

Body surface area (m^2)	Dosage reduction levels	Dosage
0.43-0.50	Usual dosage	100 mg/day
	First dosage reduction	100 mg/day 5 times per week
	Second dosage reduction	100 mg/day 3 times per week
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 100 mg/day 3 times per week.
0.51-0.80	Usual dosage	200 mg/day
	First dosage reduction	200 mg/day 5 times per week
	Second dosage reduction	100 mg/day 5 times per week
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 100 mg/day 5 times per week.
0.81-1.10	Usual dosage	300 mg/day
	First dosage reduction	200 mg/day
	Second dosage reduction	100 mg/day
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 100 mg/day.
1.11-1.50	Usual dosage	400 mg/day
	First dosage reduction	300 mg/day
	Second dosage reduction	200 mg/day 5 times per week
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 200 mg/day 5 times per week.
≥1.51	Usual dosage	600 mg/day
	First dosage reduction	400 mg/day
	Second dosage reduction	200 mg/day
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 200 mg/day.

See below for the 5 times and 3 times per week schedules:
The 5 times per week schedule: To be administered on Monday, Wednesday, Friday, Saturday, and Sunday.
The 3 times per week schedule: To be administered on Monday, Thursday, and Saturday.

Recommended dosage modifications for dose interruption, dosage reduction, discontinuation of therapy at the onset of adverse reactions

Adverse reaction	Grade [Note)]	Recommended action	
		Adult patients	Pediatric patients
Cardiac disorders (excluding QT interval prolongation)	All Grades	Withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at one dosage level lower.	
QT interval prolongation	Grade 2	Withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at the same dosage.	
	Grade 3	Withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at one dosage level lower.	Withhold entrectinib until resolution to Grade ≤1 or baseline. • Resume at one dosage level lower if resolution occurs within 7 days. • Permanently discontinue if resolution does not occur within 7 days.
	Grade 4	Permanently discontinue entrectinib.	
Cognitive impairment, Ataxia	Grade 2 or higher	• For 1st occurrence, withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at one dosage level lower. • For recurrence, reduce the dosage to the next lower level or permanently discontinue.	
Syncope	All Grades	• For 1st occurrence, withhold entrectinib until resolution to baseline, then resume at one dosage level lower. • For recurrence, reduce the dosage to the next lower level or permanently discontinue.	
Anaemia or Neutropenia	Grade 3	Withhold entrectinib until resolution to Grade ≤2 or baseline, then resume at one dosage level lower or at the same dosage.	
	Grade 4	Withhold entrectinib until resolution to Grade ≤2 or baseline, then resume at one dosage level lower.	
ILD	Grade 1 or 2	• For 1st occurrence, withhold entrectinib until resolution to baseline, then resume at the same dosage. • For recurrence, permanently discontinue entrectinib.	
	Grade 3 or 4	Permanently discontinue entrectinib.	
Other non-hematologic toxicities	Grade 3 or 4	Withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at one dosage level lower.	

Note) Severity grade based on NCI-CTCAE ver4.03

7.R.6 Post-marketing investigations

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

The applicant is planning to conduct post-marketing surveillance, covering all patients treated with entrectinib, to investigate (1) the nature and time of onset of the initial symptoms of cognitive impairment, (2) compliance with the entrectinib dosage modification guidelines (dose interruption, dosage reduction, discontinuation of therapy) and the outcome in patients with cognitive impairment, and (3) the efficacy of entrectinib, in clinical practice.

The safety specification for the surveillance includes cognitive impairment, taking account of the incidence of adverse events, etc. according to an integrated analysis of the ALKA study, the STARTRK-1 study, the STARTRK-2 study, and the STARTRK-NG study. The efficacy specification includes the response rate as assessed by the primary physician.

Given the incidence of cognitive impairment, etc. according to an integrated analysis of the ALKA study, the STARTRK-1 study, the STARTRK-2 study, and the STARTRK-NG study, a planned sample size of 200 patients has been chosen to collect 50 cases of cognitive impairment needed for the above investigations (1) and (2).

The observation period is 1 year because most cognitive impairment events occurred within 24 weeks after the start of treatment with entrectinib, and most of those events whose final outcome was "resolved" were assessed as "resolved" within 26 weeks of onset in the ALKA study, the STARTRK-1 study, the STARTRK-2 study, and the STARTRK-NG study.

Taking account of the response rate, duration of response, etc. in the ALKA study, the STARTRK-1 study, the STARTRK-2 study, and the STARTRK-NG study, the efficacy of entrectinib can also be investigated with the above planned sample size and observation period.

PMDA's discussion:
Since the safety information from patients treated with entrectinib, including Japanese patients, is limited, and the number of patients with *NTRK* fusion-positive, advanced/recurrent solid tumors (patients eligible for entrectinib therapy) is extremely limited, etc., it is necessary to conduct post-marketing surveillance covering all patients treated with entrectinib over a specified period of time in order to collect information in a prompt and unbiased manner, and provide the obtained efficacy and safety information to healthcare professionals in clinical practice as soon as possible.

For safety evaluation in the surveillance, based on the considerations etc. in Section "7.R.3 Safety," the safety specification should include cardiac disorders (excluding QT interval prolongation), cognitive impairment/ataxia, QT interval prolongation, syncope, ILD, and delayed growth and development, and the safety of entrectinib should be investigated in clinical practice. For efficacy evaluation in the surveillance, given that some tumor types were not enrolled in clinical studies, and that the limited number of patients were studied for the tumor types enrolled in clinical studies, the efficacy specification proposed by the applicant should be included, and efficacy information should be collected in clinical practice.

The planned sample size and observation period need to be reconsidered, taking account of the above efficacy and safety specifications.

In addition, based on the considerations in Sections "5.R.1 Use of entrectinib in pediatric patients" and "7.R.5.2 Dosage and administration for pediatric patients," it is necessary to investigate delayed growth and development following administration of entrectinib in pediatric patients. Thus, a separate use-results survey for this purpose should be conducted.

7.2 Adverse events etc. observed in clinical studies

Among clinical study data submitted for safety evaluation, deaths are described in Section "7.1 Evaluation data." The main adverse events other than deaths are described below.

7.2.1 Global phase II study (STARTRK-2 study)

Adverse events occurred in 205 of 206 subjects (99.5%), and those for which a causal relationship to entrectinib

could not be ruled out occurred in 188 of 206 subjects (91.3%). Adverse events reported by ≥20% of subjects are shown in Table 47.

Table 47. Adverse events reported by ≥20% of subjects

SOC PT (MedDRA/J ver.21.0)	n (%) N = 206 All Grades	 Grade 3 or higher
Any adverse event	205 (99.5)	131 (63.6)
General disorders and administration site conditions		
Fatigue	63 (30.6)	9 (4.4)
Oedema peripheral	67 (32.5)	2 (1.0)
Pyrexia	42 (20.4)	1 (0.5)
Gastrointestinal disorders		
Constipation	110 (53.4)	1 (0.5)
Diarrhoea	80 (38.8)	5 (2.4)
Nausea	55 (26.7)	0
Nervous system disorders		
Dysgeusia	95 (46.1)	1 (0.5)
Dizziness	78 (37.9)	3 (1.5)
Investigations		
Weight increased	63 (30.6)	20 (9.7)
Blood creatinine increased	59 (28.6)	3 (1.5)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	60 (29.1)	12 (5.8)
Cough	46 (22.3)	0
Musculoskeletal and connective tissue disorders		
Arthralgia	47 (22.8)	1 (0.5)
Blood and lymphatic system disorders		
Anaemia	61 (29.6)	22 (10.7)

Serious adverse events occurred in 81 of 206 subjects (39.3%). Those reported by ≥2 subjects were pneumonia (10 subjects [4.9%]); pleural effusion (9 subjects [4.4%]); dyspnoea (6 subjects [2.9%]); pulmonary embolism; hypoxia; and sepsis (5 subjects each [2.4%]); pyrexia; and urinary tract infection (4 subjects each [1.9%]); pericardial effusion; hypotension; cognitive disorder; anaemia; and acute respiratory failure (3 subjects each [1.5%]); and seizure; congestive cardiac failure; orthostatic hypotension; blood creatinine increased; mental status changes; pneumonitis; dizziness; diarrhoea; upper respiratory tract infection; pyelonephritis; dehydration; fall; cardio-respiratory arrest; pneumothorax; femoral neck fracture; acute kidney injury; and acute pyelonephritis (2 subjects each [1.0%]). A causal relationship to entrectinib could not be ruled out for pyrexia; hypotension; blood creatinine increased; and cognitive disorder (2 subjects each); and orthostatic hypotension; mental status changes; diarrhoea; dehydration; dyspnoea; congestive cardiac failure; and dizziness (1 subject each).

Adverse events leading to entrectinib discontinuation occurred in 21 of 206 subjects (10.2%), which were pneumonia (3 subjects [1.5%]); acute respiratory failure; and cardio-respiratory arrest (2 subjects each [1%]); and myoclonus; diarrhoea; dyspnoea; cardiac tamponade; cardiogenic shock; pericardial effusion; pneumonitis; limbic encephalitis; oedema peripheral; vomiting; anorectal disorder; congestive cardiac failure; weight increased; sepsis; fatigue; vertigo; cognitive disorder; and pulmonary oedema (1 subject each [0.5%]). A causal relationship to entrectinib could not be ruled out for myoclonus; pneumonitis; limbic encephalitis; oedema peripheral; anorectal disorder; congestive cardiac failure; weight increased; fatigue; vertigo; cognitive

disorder; and pulmonary oedema (1 subject each).

7.2.2 Foreign phase I study (STARTRK-1 study)

Adverse events occurred in 75 of 76 subjects (98.7%), and those for which a causal relationship to entrectinib could not be ruled out occurred in 70 of 76 subjects (92.1%). Adverse events reported by ≥20% of subjects are shown in Table 48.

Table 48. Adverse events reported by ≥20% of subjects

SOC PT (MedDRA/J ver.21.0)	n (%) N = 76 All Grades	 Grade 3 or higher
Any adverse event	75 (98.7)	51 (67.1)
General disorders and administration site conditions		
Fatigue	47 (61.8)	6 (7.9)
Oedema peripheral	21 (27.6)	0
Gastrointestinal disorders		
Nausea	28 (36.8)	1 (1.3)
Constipation	28 (36.8)	0
Diarrhoea	19 (25.0)	1 (1.3)
Vomiting	18 (23.7)	2 (2.6)
Nervous system disorders		
Dysgeusia	34 (44.7)	0
Dizziness	27 (35.5)	0
Investigations		
Weight increased	18 (23.7)	2 (2.6)
Respiratory, thoracic and mediastinal disorders		
Dyspnoea	19 (25.0)	2 (2.6)
Cough	16 (21.1)	0
Musculoskeletal and connective tissue disorders		
Myalgia	18 (23.7)	0
Blood and lymphatic system disorders		
Anaemia	19 (25.0)	9 (11.8)

Serious adverse events occurred in 30 of 76 subjects (39.5%), which were mental status changes (3 subjects [3.9%]); metastases to meninges; osteonecrosis; hydrocephalus; cognitive disorder; back pain; fatigue; pneumonia; and pleural effusion (2 subjects each [2.6%]); and shunt infection; localised infection; confusional state; myocarditis; mental disorder; wound dehiscence; large intestine perforation; hypotension; cauda equina syndrome; pyrexia; steroid withdrawal syndrome; parasitic gastroenteritis; abdominal abscess; stress fracture; ataxia; dyspnoea; respiratory failure; syncope; tumour lysis syndrome; atrial flutter; hyponatraemia; fall; sepsis; pulmonary embolism; febrile neutropenia; pathological fracture; ascites; abdominal pain; abdominal distension; vision blurred; vomiting; and dysphagia (1 subject each [1.3%]). A causal relationship to entrectinib could not be ruled out for cognitive disorder (2 subjects); and myocarditis; mental status changes; fatigue; ataxia; hyponatraemia; fall; vision blurred; and dysphagia (1 subject each).

Adverse events leading to entrectinib discontinuation occurred in 6 of 76 subjects (7.9%), which were myocarditis; large intestine perforation; extrasystoles; malaise; tumour lysis syndrome; decreased appetite; and fatigue (1 subject each [1.3%]). A causal relationship to entrectinib could not be ruled out for myocarditis; malaise; decreased appetite; and fatigue (1 subject each).

7.2.3 Foreign phase I study (ALKA study)

Adverse events occurred in all subjects, and those for which a causal relationship to entrectinib could not be ruled out occurred in 51 of 57 subjects (89.5%). Adverse events reported by ≥20% of subjects were nausea (31 subjects [54.4%]); paraesthesia (26 subjects [45.6%]); asthenia (24 subjects [42.1%]); vomiting; and dyspnoea (23 subjects each [40.4%]); dysgeusia (21 subjects [36.8%]); myalgia (20 subjects [35.1%]); diarrhoea (19 subjects [33.3%]); constipation (18 subjects [31.6%]); pyrexia (17 subjects [29.8%]); fatigue (16 subjects [28.1%]); cough; abdominal pain; and dizziness (14 subjects each [24.6%]); headache (13 subjects [22.8%]); and arthralgia (12 subjects [21.1%]).

Serious adverse events occurred in 24 of 57 subjects (42.1%), which were dyspnoea (6 subjects [10.5%]); general physical condition decreased (3 subjects [5.3%]); pulmonary embolism; abdominal pain; respiratory failure; confusional state; pneumonia; pyrexia; and vomiting (2 subjects each [3.5%]); and syncope; cardiac tamponade; troponin increased; nausea; gastric obstruction; device related infection; jaundice; pneumothorax; tumour associated fever; mediastinal disorder; myocardial infarction; hydrocephalus; dehydration; ascites; asthenia; and seizure (1 subject each [1.8%]). A causal relationship to entrectinib was denied for all those events.

Adverse events leading to entrectinib discontinuation occurred in 2 of 57 subjects (3.5%), which were pulmonary embolism; and atrial fibrillation (1 subject each [1.8%]). A causal relationship to entrectinib was denied for both events.

7.2.4 Foreign phase I study (Study CA14707)

Adverse events occurred in 7 of 24 subjects (29.2%) in the A group, 13 of 24 subjects (54.2%) in the B group, 7 of 11 subjects (63.6%) in the C group, 6 of 12 subjects (50.0%) in the D group, 15 of 24 subjects (62.5%) in the E group, 16 of 23 subjects (69.6%) in the F group, 5 of 12 subjects (41.7%) in the G group, 5 of 10 subjects (50.0%) in the H group, 18 of 24 subjects (75.0%) in the I group, 17 of 22 subjects (77.3%) in the J group, 8 of 11 subjects (72.7%) in the K group, and 6 of 10 subjects (60.0%) in the L group, and those for which a causal relationship to entrectinib could not be ruled out occurred in 6 of 24 subjects (25.0%) in the A group, 10 of 24 subjects (41.7%) in the B group, 7 of 11 subjects (63.6%) in the C group, 6 of 12 subjects (50.0%) in the D group, 13 of 24 subjects (54.2%) in the E group, 12 of 23 subjects (52.2%) in the F group, 5 of 12 subjects (41.7%) in the G group, 4 of 10 subjects (40.0%) in the H group, 17 of 24 subjects (70.8%) in the I group, 17 of 22 subjects (77.3%) in the J group, 8 of 11 subjects (72.7%) in the K group, and 6 of 10 subjects (60.0%) in the L group. Adverse events reported by ≥20% of subjects in each group were oral paraesthesia (7 subjects [29.2%]) in the B group, oral paraesthesia; and dysgeusia (4 subjects each [36.4%]) in the C group, oral paraesthesia (6 subjects [50.0%]) in the D group, headache (7 subjects [29.2%]) and oral paraesthesia (6 subjects [25.0%]) in the E group, oral paraesthesia (7 subjects [30.4%]) in the F group, oral paraesthesia (3 subjects [30.0%]) in the H group, oral paraesthesia (8 subjects [33.3%]) in the I group, oral paraesthesia; and constipation (10 subjects each [45.5%]) in the J group, oral paraesthesia (4 subjects [36.4%]) and constipation;

and dysgeusia (3 subjects each [27.3%]) in the K group, and oral paraesthesia (4 subjects [40.0%]), constipation (3 subjects [30.0%]), and pain in extremity (2 subjects [20.0%]) in the L group.

No serious adverse events or adverse events leading to entrectinib discontinuation were reported.

7.2.5 Foreign phase I study (Study 101-04)

Adverse events occurred in 14 of 24 subjects (58.3%) in (1) the 400 mg fasted group, 15 of 24 subjects (62.5%) in (2) the 600 mg fasted group, and 15 of 23 subjects (65.2%) in (3) the 600 mg fed group, and those for which a causal relationship to entrectinib could not be ruled out occurred in (1) 14 of 24 subjects (58.3%), (2) 13 of 24 subjects (54.2%), and (3) 13 of 23 subjects (56.5%). Adverse events reported by ≥20% of subjects in each group were (1) dysgeusia (11 subjects [45.8%]), (2) oral hypoaesthesia (7 subjects [29.2%]) and oral paraesthesia (5 subjects [20.8%]), and (3) oral hypoaesthesia (7 subjects [30.4%]).

No serious adverse events or adverse events leading to entrectinib discontinuation were reported.

7.2.6 Foreign phase I study (Study 101-05)

Adverse events occurred in 2 of 7 subjects (28.6%), and those for which a causal relationship to entrectinib could not be ruled out occurred in 2 of 7 subjects (28.6%). No adverse events were reported by ≥2 subjects.

No serious adverse events were reported.

An adverse event leading to entrectinib discontinuation occurred in 1 of 7 subjects (14.3%), which was vomiting (1 subject [14.3%]). Its causal relationship to entrectinib could not be ruled out.

7.2.7 Foreign phase I study (Study 101-06)

Adverse events occurred in 4 of 8 subjects (50.0%) in the A group, 2 of 16 subjects (12.5%) in the B group, 2 of 16 subjects (12.5%) in the C group, 1 of 8 subjects (12.5%) in the D group, and 2 of 8 subjects (25.0%) in the E group, and those for which a causal relationship to entrectinib could not be ruled out occurred in 4 of 8 subjects (50.0%) in the A group, 2 of 16 subjects (12.5%) in the B group, 2 of 16 subjects (12.5%) in the C group, 1 of 8 subjects (12.5%) in the D group, and 2 of 8 subjects (25.0%) in the E group. Adverse events reported by ≥20% of subjects in each group were oral paraesthesia (3 of 8 subjects [37.5%]) and headache (2 of 8 subjects [25.0%]) in the A group and oral paraesthesia (2 of 8 subjects [25.0%]) in the E group.

No serious adverse events or adverse events leading to entrectinib discontinuation were reported.

7.2.8 Foreign phase I study (Study 101-07)

Adverse events occurred in 18 of 48 subjects (37.5%) in the A group, 25 of 48 subjects (52.1%) in the B group, 23 of 48 subjects (47.9%) in the C group, 16 of 48 subjects (33.3%) in the D group, 5 of 12 subjects (41.7%) in the E group, 2 of 12 subjects (16.7%) in the F group, 4 of 12 subjects (33.3%) in the G group, and 3 of 11

subjects (27.3%) in the H group, and those for which a causal relationship to entrectinib could not be ruled out occurred in 18 of 48 subjects (37.5%) in the A group, 25 of 48 subjects (52.1%) in the B group, 21 of 48 subjects (43.8%) in the C group, 16 of 48 subjects (33.3%) in the D group, 5 of 12 subjects (41.7%) in the E group, 2 of 12 subjects (16.7%) in the F group, 4 of 12 subjects (33.3%) in the G group, and 3 of 11 subjects (27.3%) in the H group. Adverse events reported by ≥20% of subjects in each group were oral paraesthesia (12 subjects [25.0%]) in the B group and oral paraesthesia (3 subjects [25.0%]) in the E group.

No serious adverse events or adverse events leading to entrectinib discontinuation were reported.

7.2.9 Foreign phase I study (Study 101-08)

Adverse events occurred in 5 of 24 subjects (20.8%) in the A group and 4 of 24 subjects (16.7%) in the B group, and those for which a causal relationship to entrectinib could not be ruled out occurred in 5 of 24 subjects (20.8%) in the A group and 3 of 24 subjects (12.5%) in the B group. Adverse events reported by ≥2 subjects in each group were oral hypoaesthesia (3 subjects [12.5%]) in the A group and oral hypoaesthesia (2 subjects [8.3%]) in the B group.

No serious adverse events or adverse events leading to entrectinib discontinuation were reported.

7.2.10 Foreign phase I study (Study 101-09)

Adverse events occurred in 10 of 19 subjects (52.6%) in the A group and 7 of 19 subjects (36.8%) in the B group, and those for which a causal relationship to entrectinib could not be ruled out occurred in 9 of 19 subjects (47.4%) in the A group and 7 of 19 subjects (36.8%) in the B group. Adverse events reported by ≥2 subjects in each group were oral paraesthesia (5 subjects [26.3%]), constipation (3 subjects [15.8%]), and oral hypoaesthesia; and dysgeusia (2 subjects each [10.5%]) in the A group and oral paraesthesia (4 subjects [21.1%]), oral hypoaesthesia (3 subjects [15.8%]), and dysgeusia (2 subjects [10.5%]) in the B group.

No serious adverse events or adverse events leading to entrectinib discontinuation were reported.

7.2.11 Foreign phase I study (Study 101-12)

Adverse events occurred in 3 of 10 subjects (30.0%) in the entrectinib + itraconazole group and 10 of 10 subjects (100%) in the entrectinib + rifampicin group, and no adverse events for which a causal relationship to study drug could not be ruled out were reported. Adverse events reported by ≥2 subjects in each group were chromaturia (10 subjects [100%]) in the entrectinib + rifampicin group.

No serious adverse events were reported.

An adverse event leading to study drug discontinuation occurred in 1 of 10 subjects (10.0%) in the entrectinib + itraconazole group, which was ALT increased (1 subject [10.0%]). The event occurred before administration of entrectinib.

7.2.12 Foreign phase I study (Study 101-13)

Adverse events occurred in 4 of 10 subjects (40.0%) in the entrectinib + digoxin group, and those for which a causal relationship to study drug could not be ruled out occurred in 3 of 10 subjects (30.0%) in the entrectinib + digoxin group. Adverse events reported by ≥20% of subjects were oral paraesthesia (2 subjects [20.0%]) in the entrectinib + digoxin group.

No serious adverse events or adverse events leading to study drug discontinuation were reported.

7.2.13 Foreign phase I study (Study 101-14)

Adverse events occurred in 12 of 14 subjects (85.7%), and those for which a causal relationship to entrectinib could not be ruled out occurred in 11 of 14 subjects (78.6%). Adverse events reported by ≥20% of subjects were fatigue; and dysgeusia (7 subjects each [50.0%]), gait disturbance (6 subjects [42.9%]), diarrhoea (5 subjects [35.7%]), peripheral sensory neuropathy; confusional state; and anaemia (4 subjects each [28.6%]), and muscle spasms; and muscular weakness (3 subjects each [21.4%]).

Serious adverse events occurred in 2 of 14 subjects (14.3%), which were orthostatic hypotension; muscular weakness; dehydration; hypoxia; urinary tract infection; and pneumonia (1 subject each [7.1%] [some subjects had more than 1 event]). A causal relationship to entrectinib could not be ruled out for orthostatic hypotension, muscular weakness, and hypoxia.

An adverse event leading to treatment discontinuation occurred in 1 of 14 subjects (7.1%), which was pneumonia (1 subject [7.1%]). Its causal relationship to entrectinib was denied.

7.2.14 Foreign phase I study (Study 101-15)

Adverse events occurred in 28 of 48 subjects (58.3%) in the A group, 28 of 48 subjects (58.3%) in the B group, 22 of 47 subjects (46.8%) in the C group, and 17 of 46 subjects (37.0%) in the D group, and those for which a causal relationship to study drug could not be ruled out occurred in 23 of 48 subjects (47.9%) in the A group, 23 of 48 subjects (47.9%) in the B group, 19 of 47 subjects (40.4%) in the C group, and 13 of 46 subjects (28.3%) in the D group. Adverse events reported by ≥20% of subjects in each group were oral paraesthesia (18 subjects [37.5%]) in the A group, oral paraesthesia (19 subjects [39.6%]) and constipation (10 subjects [20.8%]) in the B group, oral paraesthesia (13 subjects [27.7%]) in the C group, and oral paraesthesia (12 subjects [26.1%]) in the D group.

No serious adverse events were reported.

Adverse events leading to entrectinib discontinuation occurred in 1 of 47 subjects (2.1%) in the C group and 1 of 46 subjects (2.2%) in the D group, which were blood creatine phosphokinase increased; and AST increased (1 subject each [2.1%]) in the C group and blood creatine phosphokinase increased (1 subject [2.2%]) in the

D group. A causal relationship to entrectinib was denied for both events.

7.2.15 Foreign phase I/Ib study (STARTRK-NG study)

Adverse events occurred in all subjects, and those for which a causal relationship to entrectinib could not be ruled out also occurred in all subjects. Adverse events reported by ≥30% of subjects were AST increased; cough; blood creatinine increased; and anaemia (9 subjects each [56.3%]); ALT increased; nausea; and fatigue (8 subjects each [50.0%]); pyrexia; and constipation (7 subjects each [43.8%]); pain in extremity; and decreased appetite (6 subjects each [37.5%]); and vomiting; platelet count decreased; diarrhoea; oropharyngeal pain; hyperglycaemia; neutrophil count decreased; headache; weight increased; dehydration; sinus tachycardia; nasal congestion; and dysgeusia (5 subjects each [31.3%]).

Serious adverse events occurred in 2 of 16 subjects (12.5%), which were device related infection; pleural effusion; femur fracture; thermal burn; lung infection; and pulmonary oedema (1 subject each [6.3%]). A causal relationship to entrectinib could not be ruled out for 1 case of pulmonary oedema.

An adverse event leading to entrectinib discontinuation occurred in 1 of 16 subjects (6.3%), which was dyspnoea (1 subject [6.3%]). Its causal relationship to entrectinib was denied.

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 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.

8.2 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. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that entrectinib has a certain level of efficacy in the treatment of *NTRK* fusion-positive, advanced/recurrent solid tumors, and that entrectinib has acceptable safety in view of its benefits. Entrectinib is a drug with a new active ingredient that is considered to inhibit

tumor growth by blocking the signaling pathways of TRK fusion proteins. Entrectinib is clinically meaningful because it offers a treatment option for patients with *NTRK* fusion-positive, advanced/recurrent solid tumors. PMDA considers that the indication, dosage and administration, post-marketing investigations, etc. need to be further discussed.

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

Review Report (2)

May 21, 2019

Product Submitted for Approval

Brand Name	Rozlytrek Capsules 100 mg, Rozlytrek Capsules 200 mg
Non-proprietary Name	Entrectinib
Applicant	Chugai Pharmaceutical Co., Ltd.
Date of Application	December 19, 2018

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Clinical positioning and efficacy

PMDA's conclusion:

Based on the considerations in Section "7.R.2 Clinical positioning and efficacy" in the Review Report (1), given the response rate [95% CI] of 56.9% [42.3, 70.7] in the *NTRK* fusion-positive solid tumor cohort of a global phase II study in patients with *NTRK, ALK*, or *ROS1* fusion-positive, advanced/recurrent solid tumors (≥18 years of age) (STARTRK-2 study) and the significance of *NTRK* fusions in *NTRK* fusion-positive solid tumors in the context of cancer biology [see Section 7.R.2.1] etc., a certain level of efficacy of entrectinib was demonstrated in patients with *NTRK* fusion-positive, advanced/recurrent solid tumors, and entrectinib is positioned as a treatment option for patients with *NTRK* fusion-positive, advanced/recurrent solid tumors.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.2 Safety

PMDA's conclusion:

Based on the considerations in Section "7.R.3 Safety" in the Review Report (1), adverse events that require particular attention following administration of entrectinib in patients with *NTRK* fusion-positive, advanced/recurrent solid tumors are ataxia, cognitive impairment, syncope, ILD, QT interval prolongation, and cardiac disorders (excluding QT interval prolongation).

Although attention should be paid to the possible occurrence of the above adverse events during treatment with entrectinib, entrectinib is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, e.g. monitoring for and management of adverse events and entrectinib dosage modifications.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.3 Indication

PMDA's conclusion:

Based on the considerations in Sections "7.R.4 Indication" and "7.R.5.2 Dosage and administration for pediatric patients" in the Review Report (1), the types of tumors etc. of patients enrolled in the STARTRK-2 study etc. should be listed in the CLINICAL STUDIES section of the package insert, and the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section. Then, the proposed indication should be modified to "*NTRK* fusion-positive, advanced/recurrent solid tumors." "FoundationOne CDx Cancer Genomic Profile" that is marketed by the applicant should be used to identify patients who may be eligible for treatment with entrectinib.

Precautions Concerning Indication

- The efficacy and safety of entrectinib as adjuvant therapy following surgery have not been established.
- Eligible patients must be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section concerning the types of tumors etc. of patients enrolled in clinical studies, and of the efficacy and safety of entrectinib, after carefully considering the use of other treatments as well.
- Entrectinib should be used in patients with an *NTRK* fusion as detected by testing performed by a pathologist or laboratory with adequate experience. The approved *in vitro* diagnostic etc. should be used for testing.
- The use of entrectinib in pediatric patients should be determined carefully by physicians with a full understanding of the information presented in the "Pediatric Use" and "CLINICAL STUDIES" sections concerning the age of patients enrolled in clinical studies.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

Based on the above, PMDA instructed the applicant to amend the INDICATION and PRECAUTIONS CONCERNING INDICATION sections accordingly. The applicant agreed.

1.4 Dosage and administration

PMDA's conclusion:

Based on the considerations in Section "7.R.5 Dosage and administration" in the Review Report (1), the age etc. of children enrolled in clinical studies should be mentioned in the Pediatric Use and CLINICAL STUDIES sections of the package insert, and the following statements should be included in the PRECAUTIONS

CONCERNING DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING INDICATION sections. Then, the wording for dosage and administration should be modified as shown below.

Dosage and Administration

The usual adult dosage is 600 mg of entrectinib administered orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition.

The usual pediatric dosage is 300 mg/m^2 (body surface area) of entrectinib administered orally once daily. The dose should not exceed 600 mg. The dosage should be reduced, as appropriate, according to the patient's condition.

Dosing in pediatric patients (300 mg/m^2 administered orally once daily)

Body surface area (m^2)	Dosage (once daily)
0.43-0.50	100 mg
0.51-0.80	200 mg
0.81-1.10	300 mg
1.11-1.50	400 mg
≥1.51	600 mg

Precautions Concerning Dosage and Administration

- The efficacy and safety of entrectinib in combination with other anti-neoplastic drugs have not been established.
- In the event of adverse reactions, withhold or reduce the dosage of entrectinib, or discontinue entrectinib therapy, as per the criteria below.

[Adult patients] Recommended dosage reductions/discontinuation of therapy

Dosage reduction levels	Dosage
Usual dosage	600 mg/day
First dosage reduction	400 mg/day
Second dosage reduction	200 mg/day
Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 200 mg/day.

[Pediatric patients] Recommended dosage reductions/discontinuation of therapy

Body surface area (m^2)	Dosage reduction levels	Dosage
0.43-0.50	Usual dosage	100 mg/day
	First dosage reduction	100 mg/day 5 times per week
	Second dosage reduction	100 mg/day 3 times per week
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 100 mg/day 3 times per week.
0.51-0.80	Usual dosage	200 mg/day
	First dosage reduction	200 mg/day 5 times per week
	Second dosage reduction	100 mg/day 5 times per week
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 100 mg/day 5 times per week.
0.81-1.10	Usual dosage	300 mg/day
	First dosage reduction	200 mg/day
	Second dosage reduction	100 mg/day
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 100 mg/day.
1.11-1.50	Usual dosage	400 mg/day
	First dosage reduction	300 mg/day
	Second dosage reduction	200 mg/day 5 times per week
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 200 mg/day 5 times per week.
≥1.51	Usual dosage	600 mg/day
	First dosage reduction	400 mg/day
	Second dosage reduction	200 mg/day
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 200 mg/day.

See below for the 5 times and 3 times per week schedules:
The 5 times per week schedule: To be administered on Monday, Wednesday, Friday, Saturday, and Sunday.
The 3 times per week schedule: To be administered on Monday, Thursday, and Saturday.

Recommended dosage modifications for dose interruption, dosage reduction, discontinuation of therapy at the onset of adverse reactions

Adverse reaction	Grade Note)	Recommended action	
		Adult patients	Pediatric patients
Cardiac disorders (excluding QT interval prolongation)	All Grades	Withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at one dosage level lower.	
QT interval prolongation	Grade 2	Withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at the same dosage.	
	Grade 3	Withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at one dosage level lower.	Withhold entrectinib until resolution to Grade ≤1 or baseline. • Resume at one dosage level lower if resolution occurs within 7 days. • Permanently discontinue if resolution does not occur within 7 days.
	Grade 4	Permanently discontinue entrectinib.	
Cognitive impairment, Ataxia	Grade 2 or higher	• For 1st occurrence, withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at one dosage level lower. • For recurrence, reduce the dosage to the next lower level or permanently discontinue.	
Syncope	All Grades	• For 1st occurrence, withhold entrectinib until resolution to baseline, then resume at one dosage level lower. • For recurrence, reduce the dosage to the next lower level or permanently discontinue.	
Anaemia or Neutropenia	Grade 3	Withhold entrectinib until resolution to Grade ≤2 or baseline, then resume at one dosage level lower or at the same dosage.	
	Grade 4	Withhold entrectinib until resolution to Grade ≤2 or baseline, then resume at one dosage level lower.	
ILD	Grade 1 or 2	• For 1st occurrence, withhold entrectinib until resolution to baseline, then resume at the same dosage. • For recurrence, permanently discontinue entrectinib.	
	Grade 3 or 4	Permanently discontinue entrectinib.	
Other non-hematologic toxicities	Grade 3 or 4	Withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at one dosage level lower.	

Note) Severity grade based on NCI-CTCAE ver4.03

Precautions Concerning Indication

- The use of entrectinib in pediatric patients should be determined carefully by physicians with a full understanding of the information presented in the "Pediatric Use" and "CLINICAL STUDIES" sections concerning the age of patients enrolled in clinical studies.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

Based on the above, PMDA instructed the applicant to amend the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections accordingly. The applicant agreed.

1.5 Risk management plan (draft)

The applicant is planning to conduct post-marketing surveillance with a planned sample size of 200 and an observation period of 1 year, covering all patients treated with entrectinib, to investigate (1) the nature and time of onset of the initial symptoms of cognitive impairment, (2) compliance with the entrectinib dosage modification guidelines (dose interruption, dosage reduction, discontinuation of therapy) and the outcome in patients with cognitive impairment, and (3) the efficacy of entrectinib, in clinical practice. The

applicant is planning to include cognitive impairment in the safety specification for the surveillance and the efficacy of entrectinib in the treatment of *NTRK* fusion-positive, advanced/recurrent solid tumors in clinical practice in the efficacy specification.

PMDA concluded that it is necessary to conduct post-marketing surveillance covering all patients treated with entrectinib over a specified period of time in order to collect information in a prompt and unbiased manner, and provide the obtained efficacy and safety information to healthcare professionals in clinical practice as soon as possible. Then, PMDA made the following conclusions on the surveillance plan.

- The safety specification should include cardiac disorders (excluding QT interval prolongation), cognitive impairment/ataxia, QT interval prolongation, syncope, ILD, and delayed growth and development, and the incidences of these events, etc., should be investigated.
- The efficacy specification planned by the applicant is acceptable.
- The planned sample size and observation period need to be reconsidered, taking account of the above specifications.

Based on the considerations in Sections "5.R.1 Use of entrectinib in pediatric patients" and "7.R.5.2 Dosage and administration for pediatric patients" in the Review Report (1), PMDA concluded that as it is necessary to investigate delayed growth and development following administration of entrectinib in pediatric patients, a separate post-marketing survey for this purpose should be conducted.

At the Expert Discussion, the expert advisors supported the above conclusions by PMDA. The expert advisors made the following comments.

- Since tumor types with a ≤1% prevalence of *NTRK* fusions such as NSCLC and pancreatic cancer are also included in the indication for entrectinib [see Section 7.R.2.1] etc., if entrectinib is indicated for "solid tumors," it is important to use entrectinib appropriately, including *NTRK* fusion diagnosis.
- If "FoundationOne CDx Cancer Genomic Profile" is used as a companion diagnostic for entrectinib, not only *NTRK* fusions, but also entrectinib resistance mutations can be detected. Since detection of entrectinib resistance mutations prior to the use of entrectinib contributes to the proper use of entrectinib, information on the relationship between the types of mutations in *NTRK* fusions and the efficacy of entrectinib should be collected via post-marketing surveillance.

Based on the comments from the Expert Discussion and taking also account of limited clinical experience with entrectinib in Japan, the current limited information on the efficacy and safety of entrectinib in patients with *NTRK* fusion-positive, advanced/recurrent solid tumors, etc., PMDA asked the applicant to explain measures to promote appropriate use of entrectinib.

The applicant's explanation:
The applicant will restrict the use of the medicine (define the qualifications of physicians and medical institutions, prescribing physicians' explanation to the patients or their families, request to the pharmacies for

cooperation, etc.) as an additional risk minimization activity, until sufficient information on the efficacy and safety of entrectinib is accumulated.

PMDA's discussion:
Since it is important to use entrectinib appropriately at medical institutions meeting certain requirements that can take necessary action promptly in the event of adverse reactions, until sufficient information on the efficacy and safety of entrectinib is accumulated, etc., PMDA accepted the above explanation by the applicant concerning the restricted use of the medicine. The safety specification should include cardiac disorders (excluding QT interval prolongation), cognitive impairment/ataxia, QT interval prolongation, syncope, and ILD.

Taking account of the comments from the Expert Discussion, information on the relationship between the types of mutations in *NTRK* fusions and the efficacy of entrectinib should be collected via post-marketing surveillance.

Based on the above, PMDA instructed the applicant to reconsider the post-marketing surveillance plan etc., including the method of information collection.

The applicant's response:
- The all-case surveillance plan will be amended as follows.
  - The safety specification includes cardiac disorders (excluding QT interval prolongation), cognitive impairment/ataxia, QT interval prolongation, syncope, ILD, and delayed growth and development, and the incidences of these events, etc., will be investigated.
  - The efficacy specification includes the efficacy of entrectinib in the treatment of *NTRK* fusion-positive, advanced/recurrent solid tumors in clinical practice.
  - The planned sample size is 200, based on the incidences of specific events included in the safety specification for all-case surveillance, according to an integrated analysis of the STARTRK-1 study, STARTRK-2 study, and ALKA study, the estimated number of patients to be treated with entrectinib during the surveillance period, etc. Given the point estimate of the response rate with entrectinib, etc., from the integrated analysis of the STARTRK-1 study, the STARTRK-2 study, and the ALKA study, 32 patients are required to achieve 90% power at one-sided significance level of 2.5%, assuming a desired response rate of 57.4% and an unacceptable rate of 30%. Thus, the efficacy of entrectinib can also be investigated with a planned sample size of 200.
  - The observation period is 1 year, based on the incidences of specific events included in the safety specification for all-case surveillance, in the STARTRK-1 study, the STARTRK-2 study, and the ALKA study. Given the median time to response from entrectinib initiation of 1 month and the maximum time to response of 6.4 months in the STARTRK-1 study, the STARTRK-2 study, and the ALKA study, and the time required to determine best overall response, the efficacy of entrectinib can also be investigated with an observation period of 1 year.

- A separate specified use-results survey to investigate delayed growth and development (height, body weight, bone age, etc.) in pediatric patients treated with entrectinib will be conducted. The specified use-results survey plan is as follows.
  - The safety specification includes delayed growth and development, and the incidence of this event, etc., will be investigated.
  - Since the estimated number of pediatric patients to be treated with entrectinib is extremely limited, the planned sample size is all pediatric patients treated with entrectinib during the 7-year enrollment period after marketing of entrectinib will be enrolled, wherever possible. Pediatric patients enrolled in all-case surveillance will enter a specified use-results survey after completing the observation period of the surveillance, and the collection of information on delayed growth and development will be continued.
  - The observation period is from the start of treatment with entrectinib until 8 years after marketing of entrectinib.

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for entrectinib should include the safety and efficacy specifications presented in Table 49, and that the applicant should conduct additional pharmacovigilance activities, surveillance/study for efficacy, and additional risk minimization activities presented in Table 50, Table 51, and Table 52. PMDA has also concluded that the applicant should decide whether or not to continue the restricted use of entrectinib, etc., taking also account of the latest information at an appropriate time point, e.g., when the results of the planned post-marketing surveillance become available.

Table 49. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Cardiac disorders (excluding QT interval prolongation) • Cognitive impairment/ataxia	• QT interval prolongation • Syncope • ILD • Delayed growth and development	• Use in patients with hepatic impairment
Efficacy specification		
• Efficacy in the treatment of NTRK fusion-positive, advanced/recurrent solid tumors in clinical practice		

Table 50. Summary of additional pharmacovigilance activities, surveillance/studies for efficacy, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Surveillance/studies for efficacy	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey (all-case surveillance) • Specified use-results survey (investigation of delayed growth and development in pediatric patients)	• General use-results survey (all-case surveillance)	• Disseminate data gathered during early post-marketing phase vigilance. • Restrict the use of the medicine. • Develop information materials to be distributed to healthcare professionals.

Table 51. Outline of post-marketing surveillance (all-case surveillance) (draft)

Objective	To investigate (1) the nature and time of onset of the initial symptoms of cognitive impairment/ataxia, (2) compliance with the entrectinib dosage modification guidelines (dose interruption, dosage reduction, discontinuation of therapy) and the outcome in patients with cognitive impairment/ataxia, (3) the incidences of cardiac disorders (excluding QT interval prolongation), QT interval prolongation, syncope, ILD, and delayed child growth and development, (4) the incidences of serious adverse events other than specific events included in the safety specification, and (5) the efficacy of entrectinib, in clinical practice.
Survey method	All-case surveillance
Population	All patients treated with entrectinib
Observation period	1 year
Planned sample size	200 patients
Main survey items	Safety specification: cardiac disorders (excluding QT interval prolongation), cognitive impairment/ataxia, QT interval prolongation, syncope, ILD, and delayed growth and development Efficacy specification: efficacy in the treatment of *NTRK* fusion-positive, advanced/recurrent solid tumors in clinical practice Other main survey items: patient characteristics (age, sex, disease stage, medical history, complications, types of mutations in *NTRK* fusions, etc.), the use of entrectinib, serious adverse events, etc.

Table 52. Outline of post-marketing surveillance (investigation of delayed growth and development in pediatric patients) (draft)

Objective	To investigate delayed growth and development in pediatric patients in clinical practice.
Survey method	Central registry system
Population	Pediatric patients treated with entrectinib
Observation period	From the start of treatment with entrectinib until 8 years after marketing of entrectinib
Planned sample size	Collect information from all pediatric patients treated with entrectinib during the 7-year enrollment period after marketing of entrectinib, wherever possible (including pediatric patients enrolled in general use-results survey [all-case surveillance]).
Main survey items	Safety specification: delayed growth and development Other main survey items: patient characteristics (age, sex, disease stage, medical history, complications, etc.), the use of entrectinib, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following conditions, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is appropriately disseminated after the market launch, and provided that the proper use of the product is ensured under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. As the product has been designated as an orphan drug, the re-examination period is 10 years. The product is not classified as a biological product or a specified biological product, and the drug product and its drug substance are both classified as powerful drugs.

Indication

NTRK fusion-positive, advanced/recurrent solid tumors

Dosage and Administration

The usual adult dosage is 600 mg of entrectinib administered orally once daily. The dosage should be reduced, as appropriate, according to the patient's condition.

The usual pediatric dosage is 300 mg/m^2 (body surface area) of entrectinib administered orally once daily. The dose should not exceed 600 mg. The dosage should be reduced, as appropriate, according to the patient's condition.

Dosing in pediatric patients (300 mg/m^2 administered orally once daily)

Body surface area (m^2)	Dosage (once daily)
0.43-0.50	100 mg
0.51-0.80	200 mg
0.81-1.10	300 mg
1.11-1.50	400 mg
≥1.51	600 mg

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because the number of patients participating in clinical trials in Japan is very limited, the applicant is required to conduct a post-marketing use-results survey covering all patients treated with the product, until data from a certain number of patients are collected, in order to obtain information on the characteristics of patients treated with the product, to promptly collect data on the safety and efficacy of the product, and to take necessary measures to ensure proper use of the product.

Warnings

Entrectinib should be administered only to patients eligible for entrectinib therapy, under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. Prior to initiation of treatment, patients or their families should be fully informed of its efficacy and risks, and their consent should be obtained.

Contraindication

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

Precautions Concerning Indication

1. The efficacy and safety of entrectinib as adjuvant therapy following surgery have not been established.
2. Eligible patients must be selected by physicians with a full understanding of the information presented in the "17. CLINICAL STUDIES" section concerning the types of tumors etc. of patients enrolled in clinical studies, and of the efficacy and safety of entrectinib, after carefully considering the use of other treatments as well.
3. Entrectinib should be used in patients with an *NTRK* fusion as detected by testing performed by a pathologist or laboratory with adequate experience. The approved *in vitro* diagnostic etc. should be used for testing.
4. The use of entrectinib in pediatric patients should be determined carefully by physicians with a full understanding of the information presented in the "9.7 Pediatric Use" and "17. CLINICAL STUDIES" sections concerning the age of patients enrolled in clinical studies.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of entrectinib in combination with other anti-neoplastic drugs have not been established.
2. In the event of adverse reactions, withhold or reduce the dosage of entrectinib, or discontinue entrectinib therapy, as per the criteria below.

[Adult patients] Recommended dosage reductions/discontinuation of therapy

Dosage reduction levels	Dosage
Usual dosage	600 mg/day
First dosage reduction	400 mg/day
Second dosage reduction	200 mg/day
Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 200 mg/day.

[Pediatric patients] Recommended dosage reductions/discontinuation of therapy

Body surface area (m^2)	Dosage reduction levels	Dosage
0.43-0.50	Usual dosage	100 mg/day
	First dosage reduction	100 mg/day 5 times per week
	Second dosage reduction	100 mg/day 3 times per week
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 100 mg/day 3 times per week.
0.51-0.80	Usual dosage	200 mg/day
	First dosage reduction	200 mg/day 5 times per week
	Second dosage reduction	100 mg/day 5 times per week
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 100 mg/day 5 times per week.
0.81-1.10	Usual dosage	300 mg/day
	First dosage reduction	200 mg/day
	Second dosage reduction	100 mg/day
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 100 mg/day.
1.11-1.50	Usual dosage	400 mg/day
	First dosage reduction	300 mg/day
	Second dosage reduction	200 mg/day 5 times per week
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 200 mg/day 5 times per week.
≥1.51	Usual dosage	600 mg/day
	First dosage reduction	400 mg/day
	Second dosage reduction	200 mg/day
	Discontinuation	Permanently discontinue entrectinib in patients who are unable to tolerate 200 mg/day.

See below for the 5 times and 3 times per week schedules:
The 5 times per week schedule: To be administered on Monday, Wednesday, Friday, Saturday, and Sunday.
The 3 times per week schedule: To be administered on Monday, Thursday, and Saturday.

Recommended dosage modifications for dose interruption, dosage reduction, discontinuation of therapy at the onset of adverse reactions

Adverse reaction	Grade [Note)]	Recommended action	
		Adult patients	Pediatric patients
Cardiac disorders (excluding QT interval prolongation)	All Grades	Withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at one dosage level lower.	
QT interval prolongation	Grade 2	Withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at the same dosage.	
	Grade 3	Withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at one dosage level lower.	Withhold entrectinib until resolution to Grade ≤1 or baseline. • Resume at one dosage level lower if resolution occurs within 7 days. • Permanently discontinue if resolution does not occur within 7 days.
	Grade 4	Permanently discontinue entrectinib.	
Cognitive impairment, Ataxia	Grade 2 or higher	• For 1st occurrence, withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at one dosage level lower. • For recurrence, reduce the dosage to the next lower level or permanently discontinue.	
Syncope	All Grades	• For 1st occurrence, withhold entrectinib until resolution to baseline, then resume at one dosage level lower. • For recurrence, reduce the dosage to the next lower level or permanently discontinue.	
Anaemia or Neutropenia	Grade 3	Withhold entrectinib until resolution to Grade ≤2 or baseline, then resume at one dosage level lower or at the same dosage.	
	Grade 4	Withhold entrectinib until resolution to Grade ≤2 or baseline, then resume at one dosage level lower.	
Interstitial lung disease	Grade 1 or 2	• For 1st occurrence, withhold entrectinib until resolution to baseline, then resume at the same dosage. • For recurrence, permanently discontinue entrectinib.	
	Grade 3 or 4	Permanently discontinue entrectinib.	
Other non-hematologic toxicities	Grade 3 or 4	Withhold entrectinib until resolution to Grade ≤1 or baseline, then resume at one dosage level lower.	

Note) Severity grade based on NCI-CTCAE ver4.03

Appendix

List of Abbreviations

ACK1	activated CDC42 kinase 1
Active substance	entrectinib
AFAP1	actin filament associated protein 1
A/G	albumin-globulin ratio
AKT	protein kinase B
ALB	albumin
ALCL	anaplastic large cell lymphoma
Alectinib	alectinib hydrochloride
ALK	anaplastic lymphoma kinase
ALKA study	Study ALKA-372-001
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
Application	marketing application
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC_{ss}	area under the plasma concentration-time curve at steady state
BA	bioavailability
BCAN	brevican
BCRP	breast cancer resistance protein
BICR	blinded independent central review
BID	bis in die
BSEP	bile salt export pump
$C_{max,ss}$	maximum plasma concentration at steady state
CI	confidence interval
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CRC	colorectal cancer
CYP	cytochrome P450
^{14}C-entrectinib	^{14}C-labeled entrectinib
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
ECG	electrocardiography
ECOG	Eastern Cooperative Oncology Group
efflux ratio	the ratio of apparent permeability coefficient in the secretory direction to the absorptive direction
EML4	echinoderm microtubule-associated protein-like 4
ERK1/2	extracellular signal-regulated kinase 1/2
ETV6	E26 transformation-specific sequence (ETS) variant 6
FISH	fluorescence *in situ* hybridization
F_{rel}	relative bioavailability
GC	gas chromatography
GGT	gamma-glutamyltransferase
hERG	human *ether-a-go-go*-related gene
HLT	high level term
HPLC	high performance liquid chromatography
HDPE	high-density polyethylene
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use

ICH Q1A guideline	"Revision of the Guideline on Stability Testing of New Drug Substances and Products" (PMSB/ELD Notification No. 0603001 dated June 3, 2003)
ICH Q1E guideline	"Guideline on Evaluation of Stability Data" (PMSB/ELD Notification No. 0603004 dated June 3, 2003)
ICH Q3A guideline	"Revision of the Guideline on Impurities in New Drug Substances" (PMSB/ELD Notification No.1216001 dated December 16, 2002)
ICH Q3B guideline	"Revision of the Guideline on Impurities in New Drug Products" (PMSB/ELD Notification No. 0624001 dated June 24, 2003)
ILD	interstitial lung disease
IR	infrared absorption spectrum
JAK2	Janus kinase 2
k_a	absorption rate constant
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LDPE	low-density polyethylene
LMNA	lamin A/C
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MPRIP	myosin phosphatase Rho interacting protein
mRNA	messenger ribonucleic acid
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NGS	next-generation sequencing
NMR	nuclear magnetic resonance spectrum
NPM1	nucleophosmin 1
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
NZW	New Zealand White
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
PBPK	physiologically based pharmacokinetics
PD	progressive disease
P-gp	P-glycoprotein
PI3K	phosphatidylinositol 3-kinase
PK	pharmacokinetics
PLC-γ	phospholipase C-γ
PLEKHA6	pleckstrin homology domain containing A6
PMDA	Pharmaceuticals and medical devices agency
PPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term
QbD	quality by design
QD	quaque die
QT	QT interval
QTc	QT interval corrected
ΔQTcF	Change from baseline in QT interval corrected using the Fridericia formula
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors

ROS1	c-ros oncogene 1
RP2D	recommended Phase II dose
SD	stable disease
SDC4	syndecan 4
SCYL3	SCY1 like pseudokinase 3
SMQ	standardised MedDRA queries
SOC	system organ class
SQSTM1	sequestosome 1
STARTRK-1 study	Study RXDX-101-01
STARTRK-2 study	Study RXDX-101-02
STARTRK-NG study	Study RXDX-101-03
STAT3	signal transducer and activator of transcription 3
Study 101-04	Study RXDX-101-04
Study 101-05	Study RXDX-101-05
Study 101-06	Study RXDX-101-06
Study 101-07	Study RXDX-101-07
Study 101-08	Study RXDX-101-08
Study 101-09	Study RXDX-101-09
Study 101-12	Study RXDX-101-12
Study 101-13	Study RXDX-101-13
Study 101-14	Study RXDX-101-14
Study 101-15	Study RXDX-101-15
TK	toxicokinetics
TPM3	tropomyosin 3
TRIP13	thyroid hormone receptor interactor 13
TRK	tropomyosin receptor kinase
UDPGA	uridine diphosphate glucuronic acid
UGT	uridine diphosphate glucuronosyl transferase
ULN	upper limit of normal
UV	ultraviolet spectrum
UVR	ultraviolet radiation
UV/VIS	ultraviolet/visible spectrum
VCL	vinculin
V_{ss}	volume of distribution at steady state