

Report on the Deliberation Results

September 5, 2024

Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau

Ministry of Health, Labour and Welfare

Brand Name	Augtyro Capsules 40 mg
Non-proprietary Name	Repotrectinib (JAN*)
Applicant	Bristol-Myers Squibb K.K.
Date of Application	October 25, 2023

Results of Deliberation

In its meeting held on August 30, 2024, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

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

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

This English translation of this Japanese review report is intended to serve as reference material made available for the convenience of users. In the event of any inconsistency between the Japanese original and this English translation, the Japanese original shall take precedence. PMDA will not be responsible for any consequence resulting from the use of this reference English translation.

Review Report

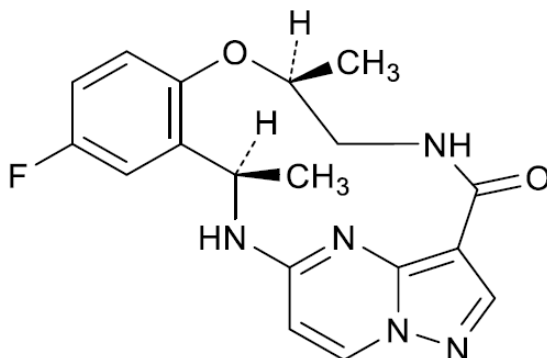
August 15, 2024

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	Augtyro Capsules 40 mg
Non-proprietary Name	Repotrectinib
Applicant	Bristol-Myers Squibb K.K.
Date of Application	October 25, 2023
Dosage Form/Strength	Capsules: Each capsule contains 40 mg of repotrectinib.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{18}H_{18}FN_5O_2$

Molecular weight: 355.37

Chemical name: (3R,6S)-4⁵-Fluoro-3,6-dimethyl-5-oxa-2,8-diaza-1(5,3)-pyrazolo[1,5-a]
pyrimidin-4(1,2)-benzenacyclononaphan-9-one

Items Warranting Special Mention

None

Reviewing Office Office of New Drug V

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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 *ROS1* fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indication

ROS1 fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer

Dosage and Administration

The usual adult dosage is 160 mg of repotrectinib orally administered once daily for 14 days, followed by 160 mg of repotrectinib orally administered twice daily. The dose may be reduced according to the patient's condition.

Approval Condition

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

Review Report (1)

June 27, 2024

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	Augtyro Capsules 40 mg
Non-proprietary Name	Repotrectinib
Applicant	Bristol-Myers Squibb K.K.
Date of Application	October 25, 2023
Dosage Form/Strength	Capsules: Each capsule contains 40 mg of repotrectinib.
Proposed Indication	<i>ROS1</i> fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer

Proposed Dosage and Administration

The usual adult dosage is 160 mg of repotrectinib orally administered once daily for 14 days, followed by 160 mg of repotrectinib orally administered twice daily. The dose may be reduced according to the patient's condition.

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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

C-ros oncogene 1 (ROS1) gene rearrangement has occurred in a subset of non-small cell lung cancers (NSCLCs), resulting in production of fusion proteins with the other proteins such as CD74 (CD74-ROS1 and others), which mediate ligand-independent activation of signaling pathways, including mitogen-activated protein kinase (MAPK) and janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways, and thereby contribute to growth and survival of cancer cells and neoplastic transformation of normal cells (*Nat Rev Clin Oncol.* 2021;18:35-55, etc.).

Repotrectinib is a low molecular weight compound that inhibits multiple tyrosine kinases such as ROS1 and tropomyosin receptor kinase (TRK), which was discovered by Turning Point Therapeutics in the US. Repotrectinib is considered to inhibit tumor growth by suppressing phosphorylation of the kinases such as ROS1 and TRK and consequently phosphorylation of their downstream signaling molecules.

1.2 Development history, etc.

To proceed with clinical development of repotrectinib for treatment of *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC, Turning Point Therapeutics in the US and the applicant initiated a global phase I/II study in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC (Study TPX-0005-01 [TRIDENT-1 study]) in February 2017.

In the US and EU, an application for marketing approval (application) of repotrectinib was submitted in March 2023 and ■ 20■, respectively, using results of the TRIDENT-1 study as the pivotal study data. In the US, the application was approved in November 2023 for the following indication: “AUGTYRO is indicated for the treatment of adult patients with locally advanced or metastatic *ROS1*-positive non-small cell lung cancer (NSCLC).” In the EU, it is currently under review. As of June 2024, repotrectinib is approved for the indication of *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC in 3 countries or regions.

In Japan, the enrollment of patients in the TRIDENT-1 study was started in ■ 20■.

An application of repotrectinib for the treatment of *ROS1* fusion gene-positive advanced or recurrent NSCLC has been submitted, using results of the TRIDENT-1 study as the pivotal study data.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance occurs as a white to off-white powder. The general properties of the drug substance, including description, thermal analysis, hygroscopicity, X-ray powder diffraction, optical rotation, solubility, pH in its aqueous solution, acid dissociation constant, and partition coefficient, have been determined. The drug substance has been found in 2 crystal forms (Crystal Forms A and B), but only Crystal Form A is produced in the commercial manufacturing process, which is stable at room temperature.

Its chemical structure of the drug substance has been elucidated by ultraviolet-visible spectroscopy (UV-VIS), infrared absorption spectroscopy (IR), nuclear magnetic resonance spectroscopy (^1H -NMR, ^{13}C -NMR, and ^{19}F -NMR), mass spectrometry (MS), elemental analysis, and single crystal X-ray diffractometry.

2.1.2 Manufacturing process

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

Based on the following investigations, the quality control strategy has been constructed (Table 1):

- Identification of critical quality attributes (CQAs)
- Investigation of process parameters based on quality risk assessment

Table 1. Outline of control strategy of drug substance

CQA	Control method
Content	Specifications
Identification	Specifications
Related substances	[REDACTED], specifications
[REDACTED]	[REDACTED], specifications
Residual solvents	[REDACTED], specifications
Elemental impurities	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Processes for [REDACTED] and [REDACTED], as well as [REDACTED] have been defined as critical steps, and in each of these processes, the process control items and process control values are specified. [REDACTED]³⁾ and [REDACTED]⁴⁾ have been controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR, high-performance liquid chromatography [HPLC]), purity (related substances [HPLC]), [REDACTED], residual solvents (gas chromatography [GC]), [REDACTED], and assay (HPLC).

2.1.4 Stability of drug substance

Table 2 shows the main stability studies conducted with the drug substance. The results indicate the stability of the drug substance. The photostability testing demonstrated that the drug substance is stable to light.

1) [REDACTED]
2) [REDACTED]
3) [REDACTED]
4) [REDACTED]

Table 2. Stability studies of drug substance

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 pilot scale batches	25°C	60%RH	Polyethylene bag (double layered) + high-density polyethylene bottle (tightly closed)	■ months
Accelerated	3 pilot scale batches	40°C	75%RH		6 months

Based on the above, a retest period of ■ months was proposed for the drug substance when stored at room temperature in double-layered polyethylene bags, which are then placed in a high-density polyethylene drum.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is immediate-release hard capsules, each containing 40 mg of the drug substance. The drug product contains microcrystalline cellulose, sodium laurylsulfate (SLS), croscarmellose sodium, and light anhydrous silicic acid as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of ■■■■■, ■■■■■, ■■■■■, capsule filling, packaging/labeling/testing, and storage. ■■■■■ is defined as a critical step, and the process control items and process control values are specified.

Based on the following investigations, the quality control strategy has been constructed (Table 3):

- Identification of CQAs
- Investigation of critical process parameters (CPPs) based on quality risk assessment

Table 3. Outline of control strategy of drug product

CQA	Control method
Content	Manufacturing process, specifications
Identification	Specifications
Uniformity of dosage units	Manufacturing process, specifications
Degradation products	Specifications
Dissolution	Manufacturing process, specifications
Microbial limit	Manufacturing process, specifications

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (UV-VIS, HPLC), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), microbial limit, dissolution, and assay (HPLC).

2.2.4 Stability of drug product

Table 4 shows the main stability studies conducted with the drug product. The results indicate the stability of the drug product. The photostability testing demonstrated that the drug product is stable to light.

Table 4. Stability studies of drug product

Study	Primary batches	Temperature	Humidity	Storage form	Storage period
Long-term	3 small-scale batches	25°C	60%RH	Blister pack	24 months
Accelerated	3 small-scale batches	40°C	75%RH		6 months

Based on the above, a shelf life of 36 months was proposed for the drug product when stored at room temperature in a blister pack (2-layer film comprised of polyvinyl chloride and polychlorotrifluoroethylene/aluminum foil), according to the ICH Q1E guideline. Long-term testing will be continued up to ■■ months.

2.R Outline of the review conducted by PMDA

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

2.R.1 Primary batches used in stability studies of drug product

Although the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Q1A (R2) guideline states that of 3 primary batches subjected to stability studies of drug product at least 2 should be batches manufactured at a pilot scale or larger scale,⁵⁾ the primary batches used in the present application were all smaller than the pilot scale.⁶⁾

The applicant's explanation:

In view of the points shown below, the primary batches subjected to the stability studies of the drug product for the present application were considered to have been manufactured by a process that reflected the commercial manufacturing process, justifying the stability evaluation of the drug product based on the stability study data using the concerned batches as the primary ones.

- ■■■■■, ■■■■■, ■■■■■, and ■■■■■ used in manufacture of the primary batches are identical to those to be used in the commercial manufacture.
- Although ■■■■■ may affect ■■■■■, no clear differences were observed in ■■■■■ between commercial-scale batches and the primary batches of the drug product.

PMDA accepted the applicant's explanation.

2.R.2 Novel excipients

The drug product contains SLS, a novel excipient, in an amount exceeding that of the previous uses for oral formulations.

2.R.2.1 Specifications and stability

SLS used in the drug product conforms to the specifications of the Japanese Pharmacopeia, and PMDA found no problem in the specifications or stability.

⁵⁾ For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a commercial scale or 100,000 tablets (capsules), whichever is the larger.

⁶⁾ While the commercial scale was ■■■■■ capsules, the manufacturing scale of the primary batches was ■■■■■ capsules.

2.R.2.2 Safety

For the proposed dosage and administration, the maximum daily intake of SLS, an excipient of the drug product, is ■■■ mg, which exceeds the amounts present in existing oral formulations, and SLS is thus classified as a novel excipient. For the following reasons, the applicant explains that SLS in the proposed dosage and administration is unlikely to raise safety concerns.

- The no-observed-adverse-effect level (NOAEL) in the drinking water study of SLS in rats was reported to be equivalent to 630 mg/60 kg/day in humans,⁷⁾ which exceeds the maximum daily intake of SLS in the proposed dosage and administration of repotrectinib.
- Neither genotoxicity nor reproductive and developmental toxicity was observed with SLS.⁷⁾
- In the EU, the daily oral intake of 600 mg is allowed for SLS (Alecensa: EPAR-Public assessment report [EMA/197343/2017]).
- In the US, the maximum daily intake of 600 mg is specified for SLS in capsules (Inactive Ingredient Search for Approved Drug Products).

PMDA's view:

Use of the concerned excipient in the proposed drug product is acceptable because (1) the maximum daily intake of SLS is below the NOAEL in the non-clinical study; and (2) no adverse effects attributable to SLS exposure have been observed in results of clinical studies such as the TRIDENT-1 study and foreign post-marketing use results with the formulation in the same composition as that of the proposed drug product as well as foreign clinical use results of SLS at the maximum daily intake of 600 mg through the other products. However, the maximum daily intake of ■■■ mg for SLS in the proposed dosage and administration does not have adequate safety margin to the amount in humans equivalent to the NOAEL in rats and dogs; and use of repotrectinib in clinical studies and foreign clinical settings has been limited to a specific patient population and condition. Therefore, the maximum daily intake of ■■■ mg for SLS in the proposed drug product, even if approved, should not be handled as a precedent for other products to be developed in the future.

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

3.1 Primary pharmacodynamics

3.1.1 Inhibitory effect against kinases such as ROS1 (CTD 4.2.1.1-1 and 4.2.1.1-21)

The inhibitory effect of repotrectinib against the following kinases was investigated using ³³P-labeled adenosine triphosphate (ATP) incorporation into the substrate as an indicator: Human ROS1, anaplastic lymphoma kinase (ALK), TRKA, TRKB, and TRKC; human ROS1 and ALK with resistance mutations; and ROS1 and ALK fusion proteins (recombinant proteins). Table 5 shows concentration that results in 50% inhibition (IC₅₀) values of repotrectinib.

⁷⁾ Report published in support of the 'Questions and answers on sodium laurilsulfate used as an excipient in medicinal products for human use' (EMA/CHMP/606830/2017). Available from: https://www.ema.europa.eu/en/documents/report/sodium-laurilsulfate-used-excipient-report-published-support-questions-answers-sodium-laurilsulfate_en.pdf (last accessed on June 27, 2024)

Table 5. Inhibitory effect of repotrectinib against kinases such as ROS1, ALK, and TRK

Kinase	IC ₅₀ (nmol/L)	Kinase	IC ₅₀ (nmol/L)	Kinase	IC ₅₀ (nmol/L)
ROS1	0.0706	ALK ^{F1174S}	1.02	ALK ^{G1269A}	5.50
ROS1 ^{G2032R}	0.456	ALK ^{C1156Y}	0.932	ALK ^{G1269S}	14.1
TPM3-ROS1*1	0.113	ALK ^{S1206R}	0.525	ALK-NPM1*2	1.23
ALK	1.04	ALK ^{L1152R}	1.23	TRKA	0.826
ALK ^{L1196M}	1.08	ALK ^{R1275Q}	2.79	TRKB	0.0517
ALK ^{G1202R}	1.21	ALK ^{I151Tins}	2.16	TRKC	0.0956
ALK ^{F1174L}	1.46	ALK ^{T1151M}	0.491		

n = 1

*1 Protein produced from the fusion gene with *TPM3* exon 8 joined to *ROS1* exon 35*2 Protein produced from the fusion gene with *ALK* exon 20 joined to *NPM1* exon 4

The inhibitory effect of repotrectinib against various kinases (recombinant proteins) other than the above was investigated using ³³P-ATP incorporation into the substrate as an indicator. Table 6 shows IC₅₀ values of repotrectinib against the various kinases.

Table 6. Inhibitory effect of repotrectinib against various kinases

Kinase	IC ₅₀ (nmol/L)	Kinase	IC ₅₀ (nmol/L)	Kinase	IC ₅₀ (nmol/L)
JAK2	1.04	HCK	16.4	GRK7	35.2
FYN	1.05	IRR	18.1	PYK2	39.9
LYN	1.66	LCK	18.6	RET	47.1
YES	2.15	JAK1	18.8	JAK3	49.9
FGR	3.05	TYK2	21.6	EPHA8	50.2
TXK	3.17	TYK1	21.8	IGF1R	111
ARK5	4.46	DDR2	23.0	PLK4	126
SRC	5.29	BTk	23.5	AXL	149
DDR1	5.73	ACK1	24.1	MARK3	512
FAK	6.96	EPHA1	25.0		
SNARK	13.0	BLK	32.3		

n = 1

3.1.2 Inhibitory effect against phosphorylation of ROS1

3.1.2.1 *In vitro* (CTD 4.2.1.1-3)

The inhibitory effect of repotrectinib and crizotinib against phosphorylation of ROS1 in mouse fibroblast NIH3T3 cell line transfected with various forms of *CD74-ROS1*⁸⁾ fusion gene was investigated by Western blotting. Table 7 shows IC₅₀ values of repotrectinib and crizotinib.

Table 7. Inhibitory effect against phosphorylation of ROS1 in NIH3T3 cell line expressing ROS1 fusion protein

	IC ₅₀ (nmol/L)			
	Without resistance mutations	With resistance mutations		
		G2032R	L2026M	D2033N
Repotrectinib	<1	3	10	1
Crizotinib	10	>1,000	>1,000	100

n = 1

3.1.2.2 *In vivo* (CTD 4.2.1.1-12)

Severe combined immunodeficiency-beige mice (SCID-beige mice) subcutaneously transplanted with mouse pro-B Ba/F3 cell line transfected with *CD74-ROS1* fusion gene harboring a resistance mutation (G2032R [glycine at position 2,032 substituted by arginine]) were used in an investigation. The following results were obtained:

⁸⁾ *CD74* exon 6 fused to *ROS1* exon 34

- A single dose of repotrectinib at 15 mg/kg was orally administered to the mice after the mean tumor volume reached approximately 230 mm³. At 3 hours, the inhibitory effect of repotrectinib against phosphorylation of ROS1 in the tumor tissue was investigated by Western blotting. Percentage of phosphorylated ROS1 in the repotrectinib group⁹⁾ (mean $\pm$ standard error [SE], n = 4) was 0.47% $\pm$ 0.19%.
- A total of 3 doses of repotrectinib at 15 or 75 mg/kg were orally administered to the mice at intervals of 12 hours after the mean tumor volume reached approximately 510 mm³. At 12 hours after the final dose, the inhibitory effect of repotrectinib against phosphorylation of ROS1 in the tumor tissue was investigated by Western blotting. Percentage of phosphorylated ROS1 in the repotrectinib 15 mg/kg group⁹⁾ (mean $\pm$ SE, n = 3) was 2.97% $\pm$ 1.00%. Repotrectinib 75 mg/kg remarkably reduced the tumor volume, and thus tumor tissue sampling was not possible.

3.1.3 Inhibitory effect against phosphorylation of TRKs and their downstream signaling molecules

3.1.3.1 *In vitro* (CTD 4.2.1.1-4 and 4.2.1.1-5)

The inhibitory effect of repotrectinib against phosphorylation of TRKA and its downstream signaling molecules (protein kinase B [AKT] and extracellular signal-regulated kinase [ERK]) in human colorectal cancer KM12 cell line with *TPM3-neurotrophic receptor tyrosine kinase (NTRK)1*¹⁰⁾ fusion gene was investigated by Western blotting. Repotrectinib was shown to inhibit phosphorylation of TRKA, AKT, and ERK.

The inhibitory effect of repotrectinib, entrectinib, and larotrectinib against phosphorylation of TRKA and TRKB in NIH3T3 cell line transfected with *LMNA-NTRK1*¹¹⁾ or *TEL-NTRK2*¹²⁾ fusion gene or *LMNA-NTRK1* or *TEL-NTRK2* fusion gene harboring resistance mutations was investigated by Western blotting. Table 8 shows IC₅₀ values of each drug.

Table 8. Inhibitory effect against phosphorylation of TRKA and TRKB in NIH3T3 cell line expressing TRK fusion protein

	IC ₅₀ (nmol/L)			
	LMNA-TRKA		TEL-TRKB	
	Without resistance mutations	G595R*	Without resistance mutations	G639R*
Repotrectinib	<0.01	0.1	0.1	3
Entrectinib	0.3	1,000	3	1,000
Larotrectinib	3	1,000	10	1,000

* Resistance mutation

3.1.3.2 *In vivo* (CTD 4.2.1.1-16)

The inhibitory effect of repotrectinib against phosphorylation of TRKA in tumor tissue in nude mice subcutaneously transplanted with NIH3T3 cell line transfected with *LMNA-NTRK1* fusion gene harboring the resistance mutation (G595R [glycine at position 595 substituted by arginine]) was investigated by Western blotting. A total of 3 doses of repotrectinib at 3 or 15 mg/kg were orally

⁹⁾ A ratio of the amount of phosphorylated ROS1 in the repotrectinib group relative to that in the control group. In the control group, a solution containing 1% polysorbate 80 and 0.5% carboxymethylcellulose in water was administered.

¹⁰⁾ *TPM3* exon 7 fused to *NTRK1* exon 10

¹¹⁾ *LMNA* exon 2 fused to *NTRK1* exon 11

¹²⁾ *TEL* exon 5 fused to *NTRK2* exon 14

administered to the mice at intervals of 12 hours after the mean tumor volume reached approximately 580 mm³. At 3 or 12 hours after the final dose, tumor tissues were collected. Table 9 shows percentages of phosphorylated TRKA in the repotrectinib group.¹³⁾

Table 9. Inhibitory effect against phosphorylation of TRKA in tumor tissue in mice subcutaneously transplanted with NIH3T3 cell line expressing TRK fusion protein

Dose	Time to tumor tissue collection	Percentage of phosphorylated protein (%)
3 mg/kg	3	15.1 ± 4.1
	12	44.5 ± 7.7
15 mg/kg	3	3.7 ± 2.6
	12	25.7 ± 3.8

Mean ± SE, n = 4

3.1.4 Inhibitory effect against phosphorylation of ALK and its downstream signaling molecules

3.1.4.1 *In vitro* (CTD 4.2.1.1-6 and 4.2.1.1-7)

The inhibitory effect of repotrectinib against phosphorylation of ALK and its downstream signaling molecules (STAT3, AKT, and ERK) in human T-cell lymphoma Karpas299 cell line with *NPM-ALK*¹⁴⁾ fusion gene was investigated by Western blotting. Repotrectinib was shown to inhibit phosphorylation of ALK and its downstream signaling molecules.

The inhibitory effect of repotrectinib and ceritinib against phosphorylation of ALK in Ba/F3 cell line transfected with various forms of *EML4-ALKv1*¹⁵⁾ fusion gene was investigated by Western blotting. IC₅₀ (n = 1) of repotrectinib was 30 nmol/L irrespective of the resistance mutation (G1202R [glycine at position 1,202 substituted by arginine]), while IC₅₀ (n = 1) of ceritinib was 30 nmol/L for the fusion gene without resistance mutations and 300 nmol/L for that with the resistance mutation (G1202R).

3.1.4.2 *In vivo* (CTD 4.2.1.1-17)

The inhibitory effect of repotrectinib against phosphorylation of ALK and its downstream signaling molecules in tumor tissue in SCID-beige mice subcutaneously transplanted with Karpas299 cell line with *NPM-ALK* fusion gene was investigated by Western blotting. Repotrectinib at 15 or 50 mg/kg was orally administered twice daily (BID) to the mice for 7 days after the mean tumor volume reached approximately 190 mm³. At 3 or 12 hours after the final dose, tumor tissues were collected. Table 10 shows percentages of phosphorylated ALK and its downstream signaling molecules in the repotrectinib group.¹⁶⁾

¹³⁾ A ratio of the amount of phosphorylated TRKA in the repotrectinib group relative to that in the control group. In the control group, a solution containing 1% polysorbate 80 and 0.5% carboxymethylcellulose in water was administered.

¹⁴⁾ *NPM* exon 4 fused to *ALK* exon 20

¹⁵⁾ *EML4* exon 13 fused to *ALK* exon 20

¹⁶⁾ A ratio of the amount of phosphorylated ALK or its downstream signaling molecule in the repotrectinib group relative to that in the control group. In the control group, a solution containing 1% polysorbate 80 and 0.5% carboxymethylcellulose in water was administered.

Table 10. Inhibitory effect against phosphorylation of ALK and its downstream signaling molecules in tumor tissue in mice subcutaneously transplanted with Karpas299 cell line

Dose	n	Time to tumor tissue collection	Percentage of phosphorylated protein (%)			
			ALK	STAT3	AKT	ERK1/2
15 mg/kg	4	3	9.5 ± 1.6	7.6 ± 1.0	13.3 ± 1.5	10.7 ± 1.1
	4	12	21.0 ± 5.9	33.5 ± 6.6	14.2 ± 3.3	22.1 ± 6.6
50 mg/kg	3	3	3.7 ± 1.0	3.2 ± 0.4	12.5 ± 2.1	18.5 ± 2.6
	4	12	10.5 ± 0.7	22.8 ± 3.9	13.4 ± 2.2	27.5 ± 1.2

Mean ± SE

3.1.5 Growth inhibitory effect against malignant tumor cell lines

3.1.5.1 *In vitro*

3.1.5.1.1 Cell line with ROS1 fusion protein (CTD 4.2.1.1-2)

The inhibitory effect of repotrectinib, crizotinib, alectinib, lorlatinib, cabozantinib, and entrectinib against growth of Ba/F3 cell line transfected with various forms of *SDC4-ROS1*¹⁷⁾ or *CD74-ROS1* fusion gene was investigated by an ATP-based cell viability assay. Table 11 shows IC₅₀ values of each drug.

Table 11. Inhibitory effect against growth of Ba/F3 cell line expressing ROS1 fusion protein

	IC ₅₀ (nmol/L)					
	SDC4-ROS1		CD74-ROS1			
	Without resistance mutations	With resistance mutations	Without resistance mutations	With resistance mutations		
		G2032R		G2032R	D2033N	L2026M
Repotrectinib	<0.2	3	<0.2	8.4	0.15	10
Crizotinib	20	4,661	9.7	1,402	139	606.4
Alectinib	2,181	>10,000	1,786	>5,000	-	-
Lorlatinib	<0.2	352.9	0.5	262.4	2.4	930.6
Cabozantinib	8.3	30.3	1.0	60.7	<0.1	29.1
Entrectinib	-	-	23.5	2,549	137.4	2,056

n = 1; -, Not investigated

3.1.5.1.2 Cell line with TRK fusion protein (CTD 4.2.1.1-4 and 4.2.1.1-5)

The inhibitory effect of repotrectinib, crizotinib, entrectinib, and larotrectinib against growth of KM12 cell line with *TPM3-NTRK1* fusion gene was investigated by an ATP-based cell viability assay. IC₅₀ values (n = 1) of repotrectinib, crizotinib, entrectinib, and larotrectinib were 0.2, 70, 9.2, and 12.3 nmol/L, respectively.

The inhibitory effect of repotrectinib, entrectinib, and larotrectinib against growth of Ba/F3 cell line expressing various forms of LMNA-TRKA, TEL-TRKB, or TEL-TRKC¹⁸⁾ protein was investigated by an ATP-based cell viability assay. Table 12 shows IC₅₀ values of each drug.

¹⁷⁾ *SDC4* exon 2 fused to *ROS1* exon 32

¹⁸⁾ *TEL* exon 5 fused to *NTRK3* exon 13

Table 12. Inhibitory effect against growth of Ba/F3 cell line expressing TRK fusion protein

	IC ₅₀ (nmol/L)					
	LMNA-TRKA		TEL-TRKB		TEL-TRKC	
	Without resistance mutations	G595R*	Without resistance mutations	G639R*	Without resistance mutations	G623R*
Repotrectinib	<0.2	0.4	<0.2	0.6	<0.2	0.39
Entrectinib	0.5	705	<0.5	1,834	0.6	1,623
Larotrectinib	4	1,024	10.9	3,000	10.2	3,239

n = 1; * Resistance mutation

3.1.5.1.3 Cell line expressing ALK fusion protein (CTD 4.2.1.1-6 and 4.2.1.1-7)

The inhibitory effect of repotrectinib, crizotinib, ceritinib, alectinib, and lorlatinib against growth of Karpas299 cell line with *NPM-ALK* fusion gene was investigated by an ATP-based cell viability assay. IC₅₀ values (n = 1) of repotrectinib, crizotinib, ceritinib, alectinib, and lorlatinib were 23.7, 40, 7.3, 25.6, and 1.6 nmol/L, respectively.

The inhibitory effect of repotrectinib, crizotinib, ceritinib, alectinib, and lorlatinib against growth of Ba/F3 cell line transfected with various forms of *EML4-ALKv1* fusion gene was investigated by an ATP-based cell viability assay. Table 13 shows IC₅₀ values of each drug.

Table 13. Inhibitory effect against growth of Ba/F3 cell line expressing EML4-ALKv1 fusion protein

	IC ₅₀ (nmol/L)						
	Without resistance mutations	With resistance mutations					
		G1202R	L1196M	F1174C	C1156Y	L1152P	G1269S
Repotrectinib	21.1	20.5	74	54.2	24	60.1	430.4
Crizotinib	69.8	359.4	918.1	114.4	475	343.1	1,415
Ceritinib	8.7	388	52.2	210.4	414	630.6	51.6
Alectinib	13.7	606.9	120.8	58.1	108	>5,000	161.7
Lorlatinib	0.9	1,000	11.3	2	30	1,500	85.1

n = 1

3.1.5.2 In vivo

3.1.5.2.1 Cell line with ROS1 fusion protein (CTD 4.2.1.1-9, 4.2.1.1-10, and 4.2.1.1-11)

The inhibitory effect of repotrectinib against tumor growth was investigated in nude mice (n = 8/group) subcutaneously transplanted with NIH3T3 cell line transfected with *SDC4-ROS1* fusion gene. Repotrectinib at 15 or 50 mg/kg was orally administered to the mice BID for 26 days after the mean tumor volume reached approximately 100 mm³. Days were counted from the day of transplantation (Day 0), and the tumor volume was calculated. On Day 31, repotrectinib at both doses achieved statistically significant inhibitory effect against tumor growth compared with the control¹⁹⁾ (*P* < 0.001 for both doses, two-way repeated measures analysis of variance [ANOVA]).

The inhibitory effect of repotrectinib against tumor growth was investigated in nude mice (n = 6/group) subcutaneously transplanted with NIH3T3 cell line transfected with *CD74-ROS1* fusion gene harboring the resistance mutation (G2032R). Repotrectinib at 3, 15, or 75 mg/kg was orally administered to the mice BID for 7 days after the mean tumor volume reached approximately 200 mm³. Days were counted from the day of transplantation (Day 0), and the tumor volume was calculated. On Day 14, repotrectinib

¹⁹⁾ A solution containing 1% polysorbate 80 and 0.5% carboxymethylcellulose in water was administered.

at 15 and 75 mg/kg achieved statistically significant inhibitory effect against tumor growth compared with the control¹⁹⁾ ($P < 0.001$ and $P < 0.0001$, respectively, two-way repeated measures ANOVA).

The inhibitory effect of repotrectinib against tumor growth was investigated in SCID-beige mice ($n = 8/\text{group}$) subcutaneously transplanted with Ba/F3 cell line transfected with *CD74-ROS1* fusion gene. Repotrectinib at 15 or 75 mg/kg was orally administered to the mice BID for 12 days after the mean tumor volume reached approximately 200 mm³. Days were counted from the day of transplantation (Day 0), and the tumor volume was calculated. On Day 19, repotrectinib at both doses achieved statistically significant inhibitory effect against tumor growth compared with the control¹⁹⁾ ($P < 0.0001$ for both doses, two-way repeated measures ANOVA).

The inhibitory effect of repotrectinib against tumor growth was investigated in SCID-beige mice ($n = 8/\text{group}$) subcutaneously transplanted with Ba/F3 cell line transfected with *CD74-ROS1* fusion gene harboring the resistance mutation (G2032R). Repotrectinib at 15 or 75 mg/kg was orally administered to the mice BID for 11 days immediately after the mean tumor volume reached approximately 200 mm³. Days were counted from the day of transplantation (Day 0), and the tumor volume was calculated. On Day 21, repotrectinib at both doses achieved statistically significant inhibitory effect against tumor growth compared with the control¹⁹⁾ ($P < 0.0001$ for both doses, two-way repeated measures ANOVA).

3.1.5.2.2 Cell line with TRK fusion protein (CTD 4.2.1.1-13 and 4.2.1.1-15)

The inhibitory effect of repotrectinib against tumor growth was investigated in nude mice ($n = 8/\text{group}$) subcutaneously transplanted with KM12 cell line with *TPM3-NTRK1* fusion gene. Repotrectinib at 15 or 75 mg/kg was orally administered to the mice BID for 7 days after the mean tumor volume reached approximately 100 mm³. Days were counted from the day of transplantation (Day 0), and the tumor volume was calculated. On Day 14, repotrectinib at both doses achieved statistically significant inhibitory effect against tumor growth compared with the control¹⁹⁾ ($P < 0.05$ for both doses, two-way repeated measures ANOVA).

The inhibitory effect of repotrectinib and entrectinib against tumor growth was investigated in nude mice ($n = 8$ or $10/\text{group}$) subcutaneously transplanted with NIH3T3 cell line transfected with *LMNA-NTRK1* fusion gene harboring the resistance mutation (G595R). Repotrectinib at 3, 15, or 60 mg/kg or entrectinib at 60 mg/kg was orally administered to the mice BID for 8 days after the mean tumor volume reached approximately 240 mm³. Days were counted from the day of transplantation (Day 0), and the tumor volume was calculated. On Day 9 when either drug had been orally administered for 5 days,²⁰⁾ repotrectinib at all the doses and entrectinib achieved statistically significant inhibitory effect against tumor growth compared with the control¹⁹⁾ ($P < 0.001$ for repotrectinib 3 mg/kg, $P < 0.0001$ for repotrectinib 15 and 60 mg/kg, and entrectinib, two-way repeated measures ANOVA). On Day 12, repotrectinib at 15 and 60 mg/kg achieved remarkable inhibitory effect against tumor growth compared with entrectinib ($P < 0.05$ and $P < 0.01$, respectively, two-way repeated measures ANOVA).

²⁰⁾ Because mice in the control group were euthanized after 5-day treatment (Day 9), the tumor volume on Day 9 was used in the statistical test.

3.1.5.2.3 Cell line expressing ALK fusion protein (CTD 4.2.1.1-18 and 4.2.1.1-19)

The inhibitory effect of repotrectinib against tumor growth was investigated in nude mice (n = 8 per group) subcutaneously transplanted with NIH3T3 cell line transfected with *EML4-ALKv1* fusion gene. Repotrectinib at 15 or 50 mg/kg was orally administered to the mice BID for 12 days after the mean tumor volume reached approximately 100 mm³. Days were counted from the day of transplantation (Day 0), and the tumor volume was calculated. On Day 17, repotrectinib at both doses achieved statistically significant inhibitory effect against tumor growth compared with the control¹⁹⁾ ($P < 0.0001$ for both doses, two-way repeated measures ANOVA).

The inhibitory effect of repotrectinib against tumor growth was investigated in SCID-beige mice (n = 8/group) subcutaneously transplanted with Ba/F3 cell line transfected with *EML4-ALKv1* fusion gene harboring the resistance mutation (G1202R). Repotrectinib at 15 or 75 mg/kg was orally administered to the mice BID for 17 days after the mean tumor volume reached approximately 200 mm³. Days were counted from the day of transplantation (Day 0), and the tumor volume was calculated. On Day 31, repotrectinib at both doses achieved statistically significant inhibitory effect against tumor growth compared with the control¹⁹⁾ ($P < 0.001$ and $P < 0.0001$, two-way repeated measures ANOVA).

3.2 Secondary pharmacodynamics

3.2.1 Effects on receptors, enzymes, ion channels, and transporters (CTD 4.2.1.2-1)

The inhibitory effect of repotrectinib against 44 types of receptors, enzymes, ion channels, and transporters was investigated using radiolabeled ligands. Receptors or the other molecules inhibited by $\geq 50\%$ at the repotrectinib concentration of 10 $\mu\text{mol/L}$ were the human adenosine A_{2A} receptor, rat L-form Ca ion channel, and human lymphocyte-specific protein tyrosine kinase (LCK), against which IC₅₀ values (n = 1) were 6.3, 3.5, and 0.11 $\mu\text{mol/L}$, respectively.

The applicant's explanation about a possibility of safety issues caused by the inhibitory effect of repotrectinib against the above receptors and other molecules as well as the kinases other than ROS1, TRK, and ALK (Table 6) in clinical use of repotrectinib:

- The IC₅₀ values against the human adenosine A_{2A} receptor and rat L-form Ca ion channel were 95 and 53 fold the plasma unbound repotrectinib concentration (0.066 $\mu\text{mol/L}$)²¹⁾ at the mean C_{max} reached with the clinical dose of repotrectinib. In view of these manyfold figures, the inhibitory effect of repotrectinib against the human adenosine A_{2A} receptor and rat L-form Ca ion channel are unlikely to raise safety issues.
- A possibility of clinical issues caused by the inhibitory effect of repotrectinib against kinases (Table 6) other than ROS1, TRK, and ALK, including LCK, which was inhibited by $\geq 50\%$ at the repotrectinib concentration of 10 $\mu\text{mol/L}$, should be discussed in view of clinical study results because discussion about the possibility based on non-clinical pharmacology study results has limitations [see Section 7.R.3].

²¹⁾ Calculated from C_{max} of repotrectinib (514 ng/mL) in patients with ROS1 fusion gene-positive unresectable advanced or recurrent NSCLC who received repotrectinib 160 mg BID in the phase Ia part of a global phase I/II study (TRIDENT-1 study) and the plasma protein unbound fraction (4.6%) [see Section 4.2.2]

3.3 Safety pharmacology

3.3.1 Effects on central nervous system

In a 91-day repeated-dose toxicity study in rats [see Section 5.2], repotrectinib at 5, 15, 40, or 50 mg/kg²²⁾ was administered once daily (QD), and effects of repotrectinib on clinical sign were investigated. Ataxia and tremor were observed in the repotrectinib 40 and 50 mg/kg groups.

Adverse events related to central nervous system disorders occurred in clinical studies as well [see Section 7.R.3.4], and the applicant explained that they planned to raise caution about potential central nervous system disorders using the package insert and other materials.

3.3.2 Effects on cardiovascular system

3.3.2.1 Effects on hERG potassium (CTD 4.2.1.3-1)

The effect of repotrectinib at 1, 3, 10 and 30 µmol/L on human *ether-a-go-go*-related gene (hERG) potassium current was investigated using Chinese hamster ovary cell line (CHO cell line) transfected with *hERG*. Inhibition rates against hERG potassium current (mean ± standard deviation [SD], n = 3) were 3% ± 2.4%, 13% ± 1.2%, 27% ± 1.7%, and 70% ± 0.5%, respectively, and the IC₅₀ value was 18 µmol/L.

3.3.2.2 Effects on myocardial ion channel (CTD 4.2.1.3-1)

The effect of repotrectinib at 10 and 30 µmol/L on various myocardial ion channels was investigated using human embryonic kidney (HEK)293 cell line expressing human Nav1.5 or Cav1.2. Repotrectinib 10 µmol/L did not inhibit Nav1.5 or Cav1.2. Inhibition rates of repotrectinib 30 µmol/L against Nav1.5 and Cav1.2 (n = 2, individual values) were 15% and <10% as well as 33% and 37%, respectively.

3.3.2.3 Effects on heart rate and electrocardiogram

In a 91-day repeated-dose toxicity study in cynomolgus monkeys [see Section 5.2], effects of repotrectinib on the heart rate and electrocardiogram (RR interval, PR interval, QRS interval, and QT interval [QT]) were investigated. No effects of repotrectinib were observed.

3.3.3 Effects on respiratory system

In a 91-day repeated-dose toxicity study in rats [see Section 5.2], repotrectinib at 5, 15, 40, or 50 mg/kg²²⁾ was administered QD, and effects of repotrectinib on the respiratory system were investigated. An increased respiratory rate was observed in the repotrectinib ≥40 mg/kg groups, and labored breathing was observed in the 40 mg/kg group.

3.R Outline of the review conducted by PMDA

Based on the submitted data and the review in the following section, PMDA concluded that the applicant's explanation about non-clinical pharmacology of repotrectinib is acceptable.

²²⁾ In female rats, treatment with repotrectinib 40 mg/kg was suspended on Day 18, and the treatment at the decreased dose of 30 mg/kg was resumed on Day 25. In male rats, treatment with repotrectinib 50 mg/kg was suspended on Day 21, and the treatment at the decreased dose of 40 mg/kg was resumed on Day 25.

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

The applicant's explanation about the mechanism of action of repotrectinib, efficacy in patients with *ROS1* fusion gene-positive NSCLC, and different pharmacological properties from those of approved *ROS1*-tyrosine kinase inhibitors (*ROS1*-TKIs):

ROS1 fusion gene is an oncogenic driver vital in the malignant transformation of *ROS1* fusion gene-positive NSCLC. The *ROS1* fusion protein is deemed to activate signaling pathways such as MAPK pathway in a ligand-independent manner, consequently enhancing cell growth (*Nat Rev Clin Oncol.* 2021;18:35-55, *Biochim Biophys Acta.* 2009;1795:37-52, etc.). In addition, CD74-*ROS1* is frequently observed in *ROS1* fusion gene-positive NSCLC, and expression of *ROS1* fusion proteins such as EZR-*ROS1* and SDC4-*ROS1* are also noted (*Nat Rev Clin Oncol.* 2021;18:35-55).

Repotrectinib is deemed to bind to the ATP-binding site in the *ROS1* kinase domain (*Cancer Discov.* 2018;8:1227-36), thereby suppress phosphorylation of *ROS1*, and consequently inhibit tumor growth of *ROS1* fusion gene-positive NSCLC [see Sections 3.1.1 and 3.1.2]. Although no non-clinical study results on the inhibitory effect of repotrectinib against growth of *ROS1* fusion gene-positive NSCLC cell lines are available, the efficacy of repotrectinib in *ROS1* fusion gene-positive NSCLC can be expected in view of the oncogenic mechanism of the *ROS1* fusion gene and mechanism of action of repotrectinib as well as documented inhibitory effect of repotrectinib against growth of cell lines expressing various forms of *ROS1* fusion protein including CD74-*ROS1* [see Sections 3.1.5.1.1 and 3.1.5.2.1].

Pharmacological properties of repotrectinib in comparison with those of crizotinib and entrectinib, which have been approved for the indication of *ROS1* fusion gene-positive NSCLC, are as follows:

- All of repotrectinib, crizotinib, and entrectinib inhibit not only *ROS1* but also ALK, sharing the same action.
- The inhibitory effect against TRKA and TRKB differs in strength between repotrectinib, crizotinib, and entrectinib; the inhibitory effect of crizotinib against TRKA and TRKB is weaker than that against *ROS1* and ALK (attached document for the initial approval of “Xalkori Capsules 200 mg, Xalkori Capsules 250 mg”), while the inhibitory effect of repotrectinib and entrectinib against TRKA and TRKB is similar to that against *ROS1* and ALK (see “Review Report on Vitrakvi Capsules 25 mg, Vitrakvi Capsules 100 mg, Vitrakvi Oral Solution 20 mg/mL, dated January 19, 2021”).
- Repotrectinib inhibited growth of cell lines expressing mutant *ROS1* fusion proteins with G2032R and D2033N (aspartate at position 2,033 substituted by asparagine) mutations (*N Engl J Med.* 2013;368:2395-401, *Clin Cancer Res.* 2016;22:2351-8, etc.) and L2026M (leucine at position 2,026 substituted by methionine) mutation (*Nat Rev Clin Oncol.* 2021;18:35-55, etc.), which are reported to cause resistance to crizotinib and entrectinib [see Sections 3.1.2, 3.1.5.1.1, and 3.1.5.2.1].

For resistance mutation of repotrectinib, 6 patients with *ROS1* fusion gene-positive NSCLC who had received prior *ROS1*-TKI therapy and then experienced disease progression while receiving were found to have G2032R or L2086F (leucine at position 2,086 substituted by phenylalanine) mutation (in 5 patients or 1 patient, respectively), and 2 patients with the G2032R mutation were also found to have F2004I (phenylalanine at position 2,004 substituted by isoleucine) or L2026M mutation (*N Engl J Med.* 2024;390:118-31). However, the sample size in the analysis for resistance mutation is limited, and

mechanism of acquiring resistance to repotrectinib remains to be elucidated, further investigation is warranted.

PMDA's view:

PMDA accepted the applicant's explanation. The detailed mechanism of acquiring resistance to repotrectinib has not been elucidated so far but is potentially important for clinical use of repotrectinib from viewpoints of predicting the efficacy and selecting eligible patients. The applicant should continue the investigation and appropriately provide healthcare professionals with new findings when available.

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

The pharmacokinetics (PK) of repotrectinib in animals was investigated in rats, monkeys, etc. Plasma protein binding, drug-metabolizing enzymes, and transporters of repotrectinib were investigated using human or animal biological specimens.

An assay of repotrectinib in monkey plasma was performed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (lower limit of quantification, 2.00 ng/mL). A radioactivity assay in rat tissues was performed by quantitative whole-body autoradiography (lower limit of quantification, 331 ng Eq./g).

4.1 Absorption

4.1.1 Single-dose study

After female monkeys received a single dose of repotrectinib at 2 mg/kg intravenously or at 20 mg/kg orally, plasma repotrectinib concentrations were determined (Table 14). The bioavailability (BA) of orally administered repotrectinib was 14%.

Table 14. PK parameters of repotrectinib (female monkeys, single intravenous or oral dose)

Dose (route of administration)	n	C _{max} (ng/mL)	t _{max} * (h)	AUC _{inf} (ng•h/mL)	t _{1/2} (h)	CL (mL/h/kg)	Vd (L/kg)
2 mg/kg (intravenous)	3	-	-	2,764 ± 233.1	10.7 ± 2.1	252 ± 28.2	11.4 ± 1.7
20 mg/kg (oral)	3	722.7 ± 42.1	2.0 (2.0, 2.0)	3,743 ± 284.1	29.4 ± 9.6	-	-

Mean ± SD; * Median (minimum, maximum); -, Not calculated

4.1.2 Repeated-dose study

Repotrectinib at 5, 15, or 50 mg/kg was orally administered to male and female monkeys QD for 91 days, and plasma repotrectinib concentrations were determined (Table 15). No definite differences were observed in exposure to repotrectinib between males and females. C_{max} and AUC₀₋₂₄ of repotrectinib increased in a less than dose-proportional manner over the dose range investigated. The applicant explained that the less than dose-proportional increase in exposure to repotrectinib might be attributable to saturation of soluble repotrectinib in the gastrointestinal lumen owing to the increased dose.

**Table 15. PK parameters of repotrectinib
(male and female monkeys, repeated oral administration for 91 days)**

Day of measurement (Day)	Dose (mg/kg)	n	C _{max} (ng/mL)		t _{max} * ¹ (h)		AUC ₀₋₂₄ (ng•h/mL)	
			Male	Female	Male	Female	Male	Female
1	5	4	46.7 ± 22.3	54.6 ± 18.3	2.0 (1, 4)	4.0 (2, 8)	548 ± 233	706 ± 166
	15	4	110 ± 85.5	121 ± 40.9	-	4.0 (4, 4)	1,110 ± 411	1,490 ± 422
	50	6	300 ± 175	166 ± 51.5	4.0 (4, 12)	4.0 (2, 4)	3,000 ± 1,470	1,650 ± 366
91	5	4	94.4 ± 34.8	100 ± 49.2	2.0 (1, 2)	2.0 (1, 4)	855 ± 105	1,040 ± 371
	15	4	189 ± 74.1	173 ± 38.4* ²	1.0 (1, 4)	2.0 (2, 12)* ²	1,630 ± 625	2,020 ± 206* ²
	50	6	294 ± 115	267 ± 54.4	4.0 (2, 8)	2.0 (2, 8)	3,910 ± 1,220	2,390 ± 673

Mean ± SD; *1 Median (minimum, maximum); *2 n = 3; -, Not calculated

4.1.3 *In vitro* membrane permeability

Membrane permeability of repotrectinib was investigated using human colon cancer-derived Caco-2 cell line. The apparent permeability in apical to basal direction (P_{app A→B}) and apparent permeability in basolateral to apical direction (P_{app B→A}) of repotrectinib at 10 µmol/L in the presence of a P-glycoprotein (P-gp) inhibitor (verapamil, 100 µmol/L) were 15.3 × 10⁻⁶ and 16.3 × 10⁻⁶ cm/sec, respectively. The applicant explained that the membrane permeability of repotrectinib is considered to be high in view of the P_{app A→B} and P_{app B→A} of warfarin known for high membrane permeability, which are 25.0 × 10⁻⁶ and 17.7 × 10⁻⁶ cm/sec, respectively.

4.2 Distribution

4.2.1 Tissue distribution

A single dose of ¹⁴C-labeled repotrectinib (¹⁴C-repotrectinib) at 30 mg/kg was orally administered to male and female pigmented rats, and the tissue distribution of the radioactivity was investigated. The radioactivity was shown to be extensively distributed in male and female pigmented rats. In most of the tissues, the radioactivity concentration peaked by 8 hours post-dose. The tissue/blood ratio of radioactivity concentration was particularly high in the liver, pigmented skin, renal cortex, kidney, and uvea (the maximum ratio was 21.5, 13.8, 12.5, 10.4, and 5.7 in male rats, respectively, and 25.4, 69.2, 5.51, 5.42, and 8.59 in female rats, respectively). In all the tissues, except the liver in male rats and the preputial gland in female rats, the radioactivity concentrations were decreased to below the lower limit of quantification by 168 hours post-dose. The radioactivity concentrations in uvea and pigmented skin, melanin-containing tissues, were decreased to below the lower limit of quantification by 168 and 72 hours post-dose in male rats, respectively, and 72 and 168 hours post-dose in female rats, respectively. Based on the above results, the applicant explained that repotrectinib or its metabolites were not suggested to bind to melanin selectively.

4.2.2 Plasma protein binding

Repotrectinib (2 µmol/L) was incubated with mouse, rat, dog, monkey, and human plasma specimens at 37°C for 6 hours, and plasma protein binding of repotrectinib was investigated by the equilibrium dialysis method. The plasma protein unbound fractions of repotrectinib in mouse, rat, dog, monkey, and human specimens were 4.2%, 5.1%, 7.9%, 7.4%, and 4.6%, respectively.

Repotrectinib (0.3-2 µmol/L) was incubated with human serum albumin (40 mg/mL) or human α1-acid glycoprotein (0.5 mg/mL) at 37°C for 4 hours, and binding of repotrectinib to human serum albumin

and human α 1-acid glycoprotein was investigated by the equilibrium dialysis method. The bound fractions of repotrectinib to human serum albumin and human α 1-acid glycoprotein were 95.2% to 96.0% and 7.6% to 10.5%, respectively. Based on the above results, the applicant explained that repotrectinib mainly binds to human serum albumin in human plasma.

4.2.3 Distribution in blood cells

Repotrectinib (0.1-10 μ mol/L) was incubated with human blood specimens at 37°C for 15 minutes, and the distribution of repotrectinib in blood cells was investigated. The blood/plasma ratios of repotrectinib concentration were 0.50 to 0.60. Based on the above results, the applicant explained that the distribution of repotrectinib in blood cells is considered to be limited in humans.

4.2.4 Placental and fetal transfer

Placental and fetal transfer of repotrectinib was not investigated. The applicant, however, explained that repotrectinib may possibly cross the placenta and be distributed in fetuses in view of the teratogenicity found in an embryo-fetal development study in rats [see Section 5.5].

4.3 Metabolism

4.3.1 *In vitro*

Mouse, rat, dog, monkey, and human hepatocytes were incubated with repotrectinib (5 μ mol/L) at 37°C for 4 hours, and metabolites of repotrectinib were investigated. In all the animal and human hepatocyte cultures, unchanged repotrectinib was mainly detected, and no human-specific metabolites were detected. The metabolites detected in human hepatocyte culture were M1 (glucuronate conjugate of hydroxyl form), M2 (glucuronate conjugate of dihydroxyl form), and M3 (hydroxyl form).

Recombinant human cytochrome P450 (CYP) isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) were incubated with repotrectinib (1 μ mol/L) in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) at 37°C for 1 hour to identify CYP isoforms involved in the metabolism of repotrectinib. In the presence of CYP3A4, $t_{1/2}$ of repotrectinib was 3.9 minutes, while in the presence of any of the other CYP isoforms tested, $t_{1/2}$ of repotrectinib was $\geq$ 180 minutes. Based on the above results, the applicant explained that CYP3A4 is suggested to have a major role in the metabolism of repotrectinib in humans.

4.3.2 *In vivo*

A single dose of 14 C-repotrectinib 50 mg/kg was orally administered to non-bile duct-cannulated or bile-duct cannulated male rats, and its metabolites in plasma, urine, feces, and bile were investigated. The following results were obtained:

- In plasma collected from the non-bile duct-cannulated male rats until 24 hours post-dose, unchanged repotrectinib and M5 (hydroxyl form) were mainly detected (accounting for 75.1% and 17.6%, respectively, of the total radioactivity in plasma).
- In urine collected from the non-bile duct-cannulated male rats until 48 hours post-dose, M5 was mainly detected (accounting for 1.13% of the radioactivity administered).
- In feces collected from the non-bile duct cannulated male rats until 48 hours post-dose, unchanged repotrectinib was mainly detected (accounting for 78.4% of the radioactivity administered).

- In bile collected from the bile-duct cannulated male rats until 48 hours post-dose, M2, M15 (glucuronate conjugate of the hydroxyl form), and M16 (glucuronate conjugate of the dihydroxy form) were mainly detected (accounting for 2.15% of the radioactivity administered²³).

4.4 Excretion

4.4.1 Excretion in urine, feces, and bile

The applicant explanation:

Based on the following investigation results, repotrectinib is considered to be mainly excreted through feces.

- A single dose of ¹⁴C-repotrectinib 50 mg/kg was orally administered to non-bile duct-cannulated male rats, and urinary and fecal excretion rates of the radioactivity (percentages of the radioactivity administered) until 168 hours post-dose were 2.00% and 94.00%, respectively.
- A single dose of ¹⁴C-repotrectinib 50 mg/kg was orally administered to bile-duct cannulated male rats, urinary, fecal, and biliary excretion rates (percentages to the radioactivity administered) until 72 hours post-dose were 3.61%, 81.31%, and 10.27%, respectively.

4.4.2 Excretion in milk

Excretion of repotrectinib in milk was not investigated. The applicant explained that repotrectinib may possibly be excreted in milk in view of factors including its physicochemical properties (molecular weight, 355; logP, 3.49) and its acting as a substrate of breast cancer resistance protein (BCRP) [see Section 4.5.3].

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation about pharmacokinetic interactions mediated by inhibition of repotrectinib against metabolic enzymes:

In view of the following investigation results, clinical use of repotrectinib may cause pharmacokinetic interactions mediated by its inhibition against CYP2C8, CYP2C9, CYP3A, and uridine 5'-diphosphoglucuronosyltransferase (UGT)1A1. Pharmacokinetic interactions between repotrectinib and a substrate of CYP3A are discussed in Section "6.2.3 Drug-drug interaction studies."

- Repotrectinib (0.068-50 µmol/L) was incubated with human liver microsomes in the presence of each substrate²⁴ of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A) and NADPH, and the inhibitory effect of repotrectinib against each of the CYP isoforms was investigated. Repotrectinib inhibited the metabolism of substrates of CYP2C8, CYP2C9, CYP2C19, and CYP3A with IC₅₀ values of 9.36, 5.72, 12.6, and 12.3 µmol/L,²⁵ respectively. On the other hand, repotrectinib did not clearly inhibit the metabolism of any substrate of the other CYP isoforms investigated.

²³) Because M2, M15, and M16 were coeluted, the percentage of the total radioactivity of these metabolites to the radioactivity administered is presented.

²⁴) Substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 used were phenacetin, bupropion, paclitaxel, tolbutamide, S-mephenytoin, and bufuralol, respectively, and substrates of CYP3A used were midazolam and testosterone.

²⁵) IC₅₀ value against CYP3A was determined using testosterone as its substrate. IC₅₀ value determined using midazolam exceeded 50 µmol/L.

- Repotrectinib (0.068-50 $\mu\text{mol/L}$) was pre-incubated with human liver microsomes in the absence or presence of NADPH followed by incubation with each substrate²⁶⁾ of CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A), and time-dependent inhibitory effect of repotrectinib against each of the CYP isoforms was investigated. Repotrectinib did not show clear time-dependent inhibitory effect against the metabolism of any substrate of the CYP isoforms investigated.
- Repotrectinib (0.1-100 $\mu\text{mol/L}$) was incubated with liver microsomes in the presence of each substrate²⁷⁾ of UGT isoforms (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7) and uridine diphosphate glucuronic acid (UDPGA), and the inhibitory effect of repotrectinib against each of the UGT isoforms was investigated. Repotrectinib inhibited the metabolism of substrates of UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 with IC_{50} values of 1.60, 29.0, 46.4, 35.7, and 48.7 $\mu\text{mol/L}$, respectively. On the other hand, repotrectinib did not clearly inhibit the metabolism of the substrate of UGT1A3.

4.5.2 Enzyme induction

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

In view of the following investigation results, clinical use of repotrectinib may cause pharmacokinetic interactions mediated by its induction of CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A. Pharmacokinetic interactions between repotrectinib and a substrate of CYP3A are discussed in Section "6.2.3 Drug-drug interaction studies."

- Human cryopreserved primary hepatocytes were incubated in the presence of repotrectinib (0.3-75 $\mu\text{mol/L}$) for 3 days, and messenger ribonucleic acid (mRNA) expression levels of CYP isoforms (CYP1A2, CYP2B6, and CYP3A4) were investigated. Repotrectinib increased mRNA expression levels of CYP2B6 and CYP3A4 by 76.0% to 462% and 24.8% to 54.1%, respectively, compared with the positive control.²⁸⁾ On the other hand, repotrectinib did not clearly increase the mRNA level of CYP1A2.
- Human cryopreserved primary hepatocytes were incubated in the presence of repotrectinib (0.025-30 $\mu\text{mol/L}$) for 3 days, and mRNA expression levels of CYP isoforms (CYP2C8, CYP2C9, and CYP2C19) were investigated. Repotrectinib increased mRNA expression levels of CYP2C8, CYP2C9, and CYP2C19 by 27.8% to 88.4%, 211% to 326%,²⁹⁾ and 24.4% to 96.5%, respectively, compared with the positive control.³⁰⁾

4.5.3 Transporters

The applicant's explanation about pharmacokinetic interactions mediated by transporters of repotrectinib:

The following investigation results indicated that repotrectinib is a substrate of P-gp, BCRP, and multidrug and toxin extrusion (MATE)2-K.

²⁶⁾ Substrates of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A used were phenacetin, bupropion, paclitaxel, tolbutamide, S-mephenytoin, bufuralol, and midazolam, respectively.

²⁷⁾ Substrates of UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, and UGT2B7 used were estradiol, sulindac sulfone, trifluoperazine, naphthol, propofol, and naloxone, respectively.

²⁸⁾ Positive controls for CYP1A2, CYP2B6, and CYP3A4 used were omeprazole (50 $\mu\text{mol/L}$), phenobarbital (750 $\mu\text{mol/L}$), and rifampicin (20 $\mu\text{mol/L}$), respectively.

²⁹⁾ Hepatocytes from 3 donors were used in the investigation, and the result in hepatocytes from 2 donors is presented.

³⁰⁾ Positive control for CYP2C8, CYP2C9, and CYP2C19 used was rifampicin (20 $\mu\text{mol/L}$).

- Transport of repotrectinib (10 $\mu\text{mol/L}$) mediated by P-gp and BCRP was investigated using Caco-2 cell line. The efflux ratios (ratios of secretion permeability coefficient in the secretive direction to that in the absorptive direction) of repotrectinib in the absence of a P-gp inhibitor and a BCRP inhibitor, in the presence of a P-gp inhibitor (verapamil 100 $\mu\text{mol/L}$), and in the presence of a BCRP inhibitor (novobiocin 50 $\mu\text{mol/L}$) were 7.3, 1.1, and 3.3, respectively.
- Using HEK293 cell line expressing human organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)1, OCT2, organic anion transporting polypeptide (OATP)1B1, OATP1B3, MATE1, or MATE2-K, transport of repotrectinib (1-10 $\mu\text{mol/L}$) mediated by each of these transporters was investigated. Maximum ratios of repotrectinib uptake in the cell lines expressing each of OAT1, OAT3, OCT1, OATP1B3, MATE1, and MATE2-K to that in the cell line not expressing these transporters were 2.91, 7.18, 3.16, 3.59, 4.30, and 4.96, respectively. On the other hand, ratios of repotrectinib uptake in the cell lines expressing each of OCT2 and OATP1B1 to that in the cell line not expressing OCT2 or OATP1B1 were both <2.
- Using HEK293 cell line expressing human OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1 or MATE2-K and vesicles expressing human bile salt export pump (BSEP), transport of repotrectinib (1 $\mu\text{mol/L}$) was investigated in the presence and absence of the inhibitor of each transporter. The ratio of repotrectinib uptake in the cell line expressing MATE2-K to that in the cell line not expressing MATE2-K was decreased by $\geq 50\%$ in the presence of the MATE2-K inhibitor compared with the ratio in the absence of the MATE2-K inhibitor. On the other hand, the ratio of repotrectinib uptake in the cell line expressing any of the other transporters to that in the cell line not expressing was not decreased by $\geq 50\%$ in the presence of an inhibitor of the corresponding transporter compared with the ratio in the absence of the inhibitor.

In addition, clinical use of repotrectinib may cause pharmacokinetic interactions mediated by its inhibitory effect against P-gp, BCRP, OATP1B1, MATE1, and MATE2-K, in view of the following investigation results and the C_{max} of repotrectinib (2.1 $\mu\text{mol/L}$ ³¹⁾) and estimated repotrectinib concentration (1,801 $\mu\text{mol/L}$) in the gastrointestinal lumen after administration of repotrectinib 160 mg.

- Using Caco-2 cell line and canine kidney MDCK cell line expressing human P-gp, the inhibitory effect of repotrectinib (0.25-60 $\mu\text{mol/L}$) against transport of a substrate³²⁾ of each transporter was investigated. Repotrectinib inhibited transport of substrates of P-gp and BCRP with IC_{50} values of 16.7 and 6.90 $\mu\text{mol/L}$, respectively.
- Using HEK293 cell line expressing human OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, or MATE2-K, the inhibitory effect of repotrectinib (0.3-100 $\mu\text{mol/L}$) against transport of a substrate³³⁾ of each transporter was investigated. Repotrectinib inhibited transport of substrates of OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K with IC_{50} values of 42.7, 15.2, 50.7, 2.35, 25.3, 4.13, and 0.726 $\mu\text{mol/L}$, respectively.

³¹⁾ C_{max} of repotrectinib (747 ng/mL) at steady state in patients receiving repotrectinib 160 mg QD after a meal in the phase Ic part of the global phase I/II study (TRIDENT-1 study).

³²⁾ Substrates of P-gp and BCRP used were loperamide (10 $\mu\text{mol/L}$) and estrone-3-sulfate (10 $\mu\text{mol/L}$).

³³⁾ Substrates used were ^3H -*p*-aminohippuric acid (20 $\mu\text{mol/L}$) for OAT1, ^3H -estrone-3-sulfate (14.5 $\mu\text{mol/L}$) for OAT3, ^{14}C -metformin (100 $\mu\text{mol/L}$) for OCT2, MATE1, and MATE2-K, and ^3H -estradiol-17 β -glucuronide (0.02 $\mu\text{mol/L}$) for OATP1B1 and OATP1B3.

4.R Outline of the review conducted by PMDA

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

4.R.1 Pharmacokinetic interactions

The applicant's explanation about pharmacokinetic interactions mediated by inhibition of repotrectinib against CYP2C8, CYP2C9, UGT1A1, P-gp, BCRP, OATP1B1, MATE1, and MATE2-K, its induction of CYP2B6, CYP2C8, CYP2C9, and CYP2C19 as well as BCRP and MATE2-K:

Results from *in vitro* studies suggested that clinical use of repotrectinib might cause pharmacokinetic interactions mediated by its inhibition against CYP2C8, CYP2C9, UGT1A1, P-gp, BCRP, OATP1B1, MATE1, and MATE2-K as well as its induction of CYP2B6, CYP2C8, CYP2C9, and CYP2C19 [see Sections 4.5.1, 4.5.2, and 4.5.3].

In addition, results from *in vitro* studies showed that repotrectinib is a substrate of P-gp, BCRP, and MATE2-K [see Section 4.5.3].

However, in the global phase I/II study (TRIDENT-1 study), concomitant use with substrates of CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A1, P-gp, BCRP, OATP1B1, MATE1, and MATE2-K as well as inhibitors of BCRP and MATE2-K were found to have no particular effects on adverse events. The concomitant use with these substrates and inhibitors is deemed unlikely to cause problems in clinical use of repotrectinib. The applicant therefore considers it unnecessary to raise caution about the concerned concomitant use.

The applicant plans to conduct a clinical study for pharmacokinetic interactions of repotrectinib with substrates of CYP2B6, CYP2C9, CYP2C19, P-gp, BCRP, OATP1B1, MATE1, and MATE2-K.

PMDA's view:

PMDA largely accepted the applicant's explanation. However, information about pharmacokinetic interactions of repotrectinib mediated by CYP2B6, CYP2C8, CYP2C9, CYP2C19, UGT1A1, P-gp, BCRP, OATP1B1, MATE1, and MATE2-K, including results from the planned clinical study, is critical for proper use of repotrectinib. The applicant is required to appropriately provide the information available at the present time to healthcare professionals using the package insert, continue collecting the concerned information, and appropriately inform healthcare professionals of useful information when it becomes available.

Pharmacokinetic interactions of repotrectinib with CYP3A inhibitors and inducers as well as P-gp inhibitors are discussed in Sections "6.2.3 Drug-drug interaction studies" and "6.R.2 Pharmacokinetic interactions with CYP3A inhibitors and P-gp inhibitors."

5. Toxicology and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

Acute toxicity of repotrectinib was evaluated in rats (CTD 4.2.3.1-1) and monkeys (CTD 4.2.3.1-2) (Table 16). In rats and monkeys, no deaths related to repotrectinib occurred at up to the maximum dose

evaluated. The approximate lethal dose of oral repotrectinib was determined to be >1000 mg/kg in rats and monkeys. No acute symptoms after a single-dose administration were observed in rats or monkeys.

Table 16. Single-dose toxicity

Test system	Route of administration	Dose (mg/kg)	Main findings related to acute toxicity	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	0,* ¹ 400, 600, 800, 1000	None	>1000	4.2.3.1-1
Male and female cynomolgus monkeys	Oral	0,* ¹ 30, 100, 300, 1000	None	>1000	4.2.3.1-2

*1 A solution containing 0.5% carboxymethylcellulose and 1% polysorbate 80 in water

5.2 Repeated-dose toxicity

In rats, 28- and 91-day repeated-dose toxicity studies were conducted (Table 17). During the 91-day repeated oral administration, NOAEL was determined to be 15 mg/kg/day. The plasma exposure (AUC_{0-24h}) to repotrectinib after repeated administration at the concerned dose was 7,190 ng•h/mL in males and 20,500 ng•h/mL in females, which were approximately 1.1- and 3.2-fold, respectively, higher than the clinical exposure (6,320 ng•h/mL).³⁴⁾ The main systemic toxicity or abnormal findings are as shown below.

- Death owing to poor clinical sign
- Ataxia and tremor
- Skin findings (abrasion, crust formation, erosion, ulcer, inflammatory change) as well as their associated changes of hematology and blood chemistry parameters and granulocytic hyperplasia in the bone marrow
- Hypocellular marrow and associated findings listed below
 - Low erythroid parameters
 - Megakaryocytic hyperplasia in the bone marrow and high platelet count
 - Low lymphocyte count in blood and lymphocytopenia in the lymphoid tissue

³⁴⁾ AUC_{0-24h} of repotrectinib at steady state in humans receiving repotrectinib 160 mg BID [see Section 6.2.1.1].

Table 17. Repeat-dose toxicity studies in rats

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	28 days + 28-day recovery	Males: 0,*¹ 30, 100/50,*² 300 Females: 0,*¹ 6, 20, 60	[Male] <u>Dead animals</u> 300: 10 of 16 animals 100: 2 of 16 animals Skin abrasion and scab,*⁵ low body weight and food consumption, prone position, perirhinal smudge, thin appearance, tremor, piloerection, tachypnea, splayed stance, prolapse of penis, hunchback position, decreased activity, ataxia, leaning, loss of skin resilience, unstable posture, cool to touch, coarse fur <u>Survived animals</u> ≥30: Perirhinal red smudge*⁶; skin abrasion and scab*⁵; skin erosion, ulcer, bulbil, epidermal hyperplasia, and hyperkeratosis; low white blood cell count*⁷; low red blood cell count, hemoglobin, hematocrit, lymphocyte count, eosinophil count,*⁷ and basophil count*⁷; high platelet count; high neutrophil count and monocyte count*⁸; high RDW; short APTT*⁸; high blood total protein and globulin*^{8,9}; low A/G ratio*⁸ ≥100/50: Thin appearance, piloerection, leaning, tremor, prone position, high reticulocyte count, hypocellular marrow 300: Decreased activity, splayed stance, prolapse of penis, hunchback position, decreased skin resilience, cool to touch, unstable posture, tachypnea, low food consumption and body weight, granulocytic hyperplasia in the bone marrow 100/50: Salivation, periorbital smudge, ataxia 30: Short prothrombin time*⁸ [Female] <u>Dead animals</u> 60: 10 of 16 animals Skin abrasion and scab,*⁵ low food consumption and body weight, prone position, perirhinal smudge, thin appearance, tremor, piloerection, hyperventilation, dyspnea <u>Survived animals</u> ≥6: Thin appearance*⁹; skin abrasion and scab*⁵; skin erosion, ulcer, and bulbil; epidermal hyperplasia and hyperkeratosis; low white blood cell count and red blood cell count; low hemoglobin, hematocrit, lymphocyte count, eosinophil count, and basophil count; high platelet count and monocyte count*⁸ ≥20: Low reticulocyte count, short APTT,*⁸ low blood albumin and A/G ratio*⁸ 60: Prone position, piloerection, tachypnea, low food consumption, hypocellular marrow and granulocytic hyperplasia 20: High neutrophil count*⁸ and RDW, Reversible	Males: 30 Females: 20	4.2.3.2-2

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female rats (Sprague Dawley)	Oral	91 days + 28-day recovery	0,* ¹ 5, 15, 50/40* ³ (males), 40/30* ⁴ (females)	<u>Dead animals</u> 50/40: 2 of 20 males 40/30: 8 of 20 females Low food consumption and body weight, ataxia, thin appearance, tremor, irritability, muscle weakness, skin abrasion and scab,*⁵ pale skin, increased respiratory rate and labored breathing <u>Survived animals</u> ≥5: Skin abrasion and scab*⁵; skin erosion and ulcer; low hemoglobin; high monocyte count*⁸; lymphocytic hypocellularity in the spleen; high platelet count*⁸; megakaryocytic hyperplasia in the bone marrow (male and female); short APTT*⁸ (male); low red blood cell count, hematocrit, lymphocyte count, and eosinophil count (female) ≥15: Low basophil count (male and female); low red blood cell count, hematocrit, and lymphocyte count; lymphocytic hypocellularity in the thymus (male); high fibrinogen*⁸; low albumin*⁸ (female) 50/40 (male): Low food consumption and body weight, low neutrophil count and eosinophil count, high blood globulin,*⁸ lymphocytic hypocellularity in the mandibular and mesenteric lymph nodes 40/30 (female): Low food consumption, lymphocytic hypocellularity in the mandibular and mesenteric lymph nodes and thymus <u>Reversible</u>	15	4.2.3.2-3

*1 A solution containing 1% polysorbate 80 and 0.5% carboxymethylcellulose in water

*2 Treatment suspended on Day 20 and resumed at a decreased dose of 50 mg/kg on Day 22

*3 Treatment suspended on Day 21 and resumed at a decreased dose of 40 mg/kg on Day 25

*4 Treatment suspended on Day 18 and resumed at a decreased dose of 30 mg/kg on Day 25

*5 Finding attributable to excessive play behavior according to the applicant's view

*6 Except the 100/50 mg/kg group

*7 Except males in the 300 mg/kg group or females in the 60 mg/kg group

*8 Finding related to inflammation associated with skin abrasion according to the applicant's view

*9 Except the 20 mg/kg group

In cynomolgus monkeys, 28- and 91-day repeated-dose toxicity studies were conducted (Table 18). During the 91-day repeated oral administration, NOAEL was determined to be 5 mg/kg/day. The plasma exposure (AUC_{0-24h}) to repotrectinib after repeated administration at the concerned dose was 946 ng•h/mL (combined mean in males and females), which was less than the clinical exposure. The main systemic toxicity or abnormal findings were deaths associated with poor clinical sign, mucous gland hyperplasia in the small intestine and large intestine, watery stool and inflammatory changes related to subacute and chronic inflammation, low erythroid parameters, small thymus, and lymphocytic hypocellularity in blood and the lymphoid tissue.

Table 18. Repeat-dose toxicity studies in cynomolgus monkeys

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female cynomolgus monkeys	Oral	28 days + 28-day recovery	0,* ¹ 10, 30, 100	<u>Dead animals</u> 100: 1 of 6 males Supine position; decreased activity; cool to touch; watery stool; low body weight; dehydration; high total protein, albumin, and globulin*²; small thymus; lymphocytic hypocellularity in the lymphoid tissue; hepatocyte glycogen depletion; pancreatic acinar cell atrophy; increased thyroidal colloid; granulocytic hyperplasia in the bone marrow <u>Survived animals</u> ≥30: Low hematocrit (male and female), watery stool, low hemoglobin (male), low red blood cell count, lymphocytic hypocellularity in the thymus (female) 100: Small and low weight thymus (male and female), low red blood cell count, low reticulocyte count, lymphocytic hypocellularity in the thymus (male), low hemoglobin (female) <u>Reversible</u>	30	4.2.3.2-5
Male and female cynomolgus monkeys	Oral	91 days + 28-day recovery	0,* ¹ 5, 15, 50	<u>Dead animals</u> 15: 1 of 4 females Dehydration; soft and watery stool; lateral position; mucosal membrane hyperplasia and villous atrophy in the jejunum and ileum; subacute/chronic inflammation in the jejunum and ileum; jejunal bacterial focus; lymphocytic hypocellularity in the lymphoid tissue; lymphocyte depletion in the splenic follicle and cortical thymus <u>Survived animals</u> ≥5: Mononuclear cell infiltration and subacute/chronic inflammation in the cecum*³; mononuclear cell infiltration in the colon and rectum (male and female); mucosal membrane hyperplasia in the cecum, colon, and rectum; subacute/chronic inflammation in the colon*⁴ (male); low hemoglobin and reticulocyte count; subacute/chronic inflammation in the rectum*⁴ (female) ≥15: Low red blood cell count and hematocrit; lymphocyte depletion in the thymus (male and female); low hemoglobin, reticulocyte count, and monocyte count (male); watery stool; high blood globulin*²; mucosal membrane hyperplasia in the rectum (female) 50: Watery stool, high white blood cell count and neutrophil count,*² high blood globulin*² (male) 15: Subacute/chronic inflammation in the rectum (male), mucosal membrane hyperplasia and subacute/chronic inflammation in the colon (female) <u>Reversible</u>	5	4.2.3.2-6

*1 A solution containing 1% polysorbate 80 and 0.5% carboxymethylcellulose in water

*2 Finding related to gastrointestinal inflammation according to the applicant's view

*3 Except females in the 50 mg/kg group

*4 Except the 15 mg/kg group

5.3 Genotoxicity

A bacterial reverse mutation assay (Ames test) and micronucleus assays in human lymphoblast cell line (*in vitro*) and rats (*in vivo*) were conducted (Table 19). Because aneuploidy and induction of

micronucleus formation were observed *in vitro* and *in vivo* micronucleus assays, respectively, the applicant explained that repotrectinib might induce micronucleus formation.

Table 19. Genotoxicity

Type of test		Test system	Metabolic activation (treatment)	Concentrations or dose	Test result	Attached document CTD
<i>In vitro</i>	Ames test	<i>Salmonella typhimurium</i> : TA98, TA100, TA1535, TA1537 <i>Escherichia coli</i> : WP2uvrA	S9-/+	0,* ¹ 15, 50, 150, 500, 1,500, 5,000 µg/plate	Negative	4.2.3.3.1-1
	Micronucleus assay	Human lymphoblast cell line (TK6 cells)	S9 - (27 hours) S9 + (4 hours)	0,* ¹ 0.3, 0.4 µg/mL 0,* ¹ 12, 14 µg/mL	Positive Aneugenic	4.2.3.3.1-2
<i>In vivo</i>	Micronucleus assay	Male rat (Sprague Dawley), Bone marrow, single dose, oral		0,* ² 500, 1,000, 2,000 mg/kg (24 hours later)	Positive	4.2.3.3.2-1
				0,* ² 2,000 mg/kg (48 hours later)		
		Male rat (Sprague Dawley), Bone marrow, single dose, oral		0,* ² 20, 50, 100 mg/kg (24 hours later)	Negative	4.2.3.3.2-2
				0,* ² 20, 50, 100 mg/kg (48 hours later)		

*¹ Dimethylsulfoxide (DMSO)

*² A solution containing 1% polysorbate 80 and 0.5% carboxymethylcellulose in water

5.4 Carcinogenicity

Repotrectinib is an antineoplastic agent intended to treat patients with advanced cancer, and no carcinogenicity studies were conducted.

5.5 Reproductive and developmental toxicity

In the repeated-dose toxicity studies in rats and monkeys (Tables 17 and 18), the effects on male and female reproductive organs were evaluated, and no abnormal findings were noted. An embryo-fetal development study in pregnant rats was conducted (Table 20). Major adverse embryonic/fetal findings were low fetal body weight and external malformations.

Table 20. Reproductive and developmental toxicity

Type of test	Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg)	Attached document CTD
Preliminary embryo-fetal development study	Female rat (Sprague Dawley)	Oral	Gestation Days 6-17 Caesarean section: Gestation Day 21	0,* ¹ 2, 6, 12, 20	<u>Maternal animals</u> ≥6: High food consumption ≥12: Skin abrasion and scab on the neck and chest <u>Embryo-fetal development</u> ≥12: Hindlimb abduction* ² 20: Low body weight	_* ³	4.2.3.5.2-1

*¹ A solution containing 1% polysorbate 80 and 0.5% carboxymethylcellulose in water

*² Finding of malformation

*³ No NOAEL evaluated

The applicant explanation:

The above study results and the induction of micronucleus formation observed in the genotoxicity studies [see Section 5.3] indicate that repotrectinib may adversely affect embryo-fetal development. Therefore, the applicant will take the following actions.

- Results from the embryo-fetal development toxicity study will be included in package insert, etc. to provide the information to healthcare professionals.
- The following cautionary statements will be included in package insert:
 - Repotrectinib should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.
 - Physicians should advise women of childbearing potential to use appropriate contraception during treatment with repotrectinib and for 2 months after the end of the treatment.³⁵⁾

5.6 Toxicity in juvenile animals

In juvenile rats, repeated-dose toxicity studies were conducted (Table 21). During the 59-day repeated oral administration from Postnatal Days 12 to 70, the NOAEL was determined to be 1 mg/kg. The main systemic toxicity findings were deaths associated with poor clinical sign, ataxia/decreased activity and body weight, and short femoral length.

Table 21. Toxicity studies in juvenile animals

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female juvenile rats (Sprague Dawley)	Oral	Postnatal Days 12-40	0,* ¹ 0.1, 0.3, 1, 3, 10, 30	<u>Dead and euthanized animals</u> 10: 10 of 10 males and females 30: 10 of 10 males and females Ataxia, decreased activity, labored breathing, low respiratory rate, hypothermia, hindlimb splayed stance <u>Survived animals</u> ≥3: Low food consumption, body weight, and body weight gain (male and female)* ²	—* ⁴	4.2.3.5.4-1
Male and female juvenile rats (Sprague Dawley)	Oral	Postnatal Days 12-70 + 28-day recovery	0,* ¹ 0.3, 1, 3	3: Low food consumption, body weight, and body weight gain, high platelet count, short femoral length (male and female), delayed vaginal opening* ³ (female) Recovery period 3: Short femoral length (male and female) The other findings were found reversible.	1	4.2.3.5.4-2

*1 A solution containing 1% polysorbate 80 and 0.5% carboxymethylcellulose in water

*2 Baseline body weight in the 0.1 and 0.3 mg/kg groups were outside of the normal range, and body weight, food consumption, and organ weight were excluded from the evaluation.

*3 Considered as a change secondary to the low body weight

*4 NOAEL not evaluated

5.7 Other toxicity study

5.7.1 Photosafety

A photosafety testing was conducted in pigmented rats (Table 22). Because no findings suggestive of phototoxicity were observed, the applicant explained that repotrectinib is unlikely to raise concerns about phototoxicity.

³⁵⁾ It was specified based on $t_{1/2}$ of repotrectinib in humans (40.3 hours) (CTD 5.3.3.5-2) in view of the “Guidance for the need for contraception related to use of pharmaceuticals (in Japanese)” (PSEHB/PED Notification No. 0216-1 and PSEHB/PSD Notification No. 0216-1 dated February 16, 2023) and the reproductive and developmental toxicity of repotrectinib.

Table 22. Photosafety

Test system	Test method	Main findings	Attached document CTD
Female rat (Long Evans)	UVA (10.29-10.54 J/cm ²) and UVB (145-148 mJ/cm ²) irradiation after 3-day oral administration at 0,* ¹ 100, 300, 1,000 mg/kg/day	No abnormal findings	4.2.3.7.7-1

*1 A solution containing 1% polysorbate 80 and 0.5% carboxymethylcellulose in water

5.R Outline of the review conducted by PMDA

Based on the submitted data and the review in the following section, PMDA concluded that the applicant's explanation about toxicity of repotrectinib is acceptable.

5.R.1 Effect on central nervous system

The applicant's explanation about the findings suggestive of effects on the central nervous system such as tremor and ataxia, which were observed in the repeated-dose toxicity studies in mature and juvenile rats [see Sections 5.2 and 5.6]:

- Kinases belonging to the TRK family are highly expressed in the central and peripheral nervous systems and involved in development and differentiation of neurons (*J Neurobiol.* 1994;25:1386-403, *Philos Trans R Soc Lond B Biol Sci.* 1996;351:365-73). The concerned findings are thus considered attributable to TRK inhibition by repotrectinib.
- The effects on the central nervous system in clinical studies were mild [see Section 7.R.3.4] and manageable with dose adjustment and conventional treatment. In view of these points and the severity of the disease to be treated with repotrectinib, the therapeutic benefits are considered to outweigh the possible risks.

PMDA's view:

PMDA accepted the applicant's explanation. In view of the occurrence of the findings suggestive of effects on the central nervous system in the repeated-dose toxicity studies in mature and juvenile rats as well as repotrectinib's nature of inhibiting TRKs, the findings suggestive of effects on the central nervous system such as skin abrasion, also observed at NOAEL or lower doses [see Section 5.2], are also attributable to repotrectinib. The safety in humans related to the concerned adverse findings is discussed in Section "7.R.3.4 Central nervous system disorders" in view of the incidence of central nervous system disorders in clinical studies.

5.R.2 Effects on bone marrow and immune system

The applicant's explanation:

Hypocellular marrow, decreased erythroid parameters, and lymphocytic hypocellularity in blood and the lymphoid tissue were observed in the repeated-dose studies in rats and cynomolgus monkeys [see Section 5.2], and anaemia and decreased neutrophil count occurred in clinical studies of repotrectinib [see Section 7.R.3.5]. However, because of the limited number of Grade ≥ 3 events and other reasons, the applicant considers it unnecessary to raise special cautions.

PMDA's view:

PMDA accepted the applicant's explanation. In view of the occurrence of the findings suggestive of effects on the bone marrow and immune system in the repeated-dose toxicity studies, such findings

observed at NOAEL or lower doses [see Section 5.2] are also attributable to repotrectinib. The safety in humans related to the concerned adverse findings is also discussed in Section “7.R.3.5(c) Blood disorders” in view of the incidence of blood disorders in clinical studies.

5.R.3 Effects on gastrointestinal tract

The applicant’s explanation:

The repeated-dose studies in cynomolgus monkeys showed findings suggestive of effects on the gastrointestinal tract such as mucosal membrane hyperplasia, villous atrophy, and subacute and chronic inflammation in the small and large intestines, and fecal abnormality [see Section 5.2]. In the phase II part of the TRIDENT-1 study, adverse events such as constipation and nausea occurred in patients with *ROS1* fusion gene-positive NSCLC in the safety analysis population (Table 23). However, since Grade ≥ 3 events were limited, the applicant considers it unnecessary to raise special cautions.

Table 23. Incidences of gastrointestinal disorders reported by $\geq 10\%$ of subjects in either population (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

PT (MedDRA ver.25.0)	n (%)			
	ROS1-TKI- naïve EXP-1 N = 107		ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Gastrointestinal disorders*	78 (72.9)	4 (3.7)	130 (63.4)	5 (2.4)
Constipation	49 (45.8)	0	66 (32.2)	0
Nausea	17 (15.9)	0	39 (19.0)	2 (1.0)
Diarrhoea	11 (10.3)	1 (0.9)	28 (13.7)	0

* Total number of events to be tabulated

PMDA accepted the applicant’s explanation. In view of the occurrence of the findings suggestive of effects on the gastrointestinal tract in the repeated-dose toxicity studies, such findings also observed at NOAEL or lower doses [see Section 5.2] are also considered attributable to repotrectinib.

5.R.4 Contraception in male patients

The applicant’s explanation about contraception in male patients:

In a female partner exposed to repotrectinib through the semen of a male patient orally taking repotrectinib, the blood exposure is estimated to be 10,290-fold and 1,790-fold, respectively, lower than the exposure (AUC_{0-24h}) in rats at the NOAEL (100 mg/kg/day) in the micronucleus assay [see Section 5.3] and the estimated exposure (AUC_{0-24h}) in pregnant rats at the no-effect level (6 mg/kg/day) in the embryo-fetal development toxicity study [see Section 5.5]. A risk of development toxicity through the semen of male patients orally taking repotrectinib is thus considered low. However, in view of the literature on humans with congenital mutations altering TRK signaling (*Hum Mutat.* 2001;18:462-71, *J Biol Chem.* 2016;291:21363-74) as well as the aneugenic potential and embryo-fetal development toxicity of repotrectinib, a potential development toxicity of repotrectinib cannot be ruled out. Physicians will be requested to advise male patients with a female partner of childbearing potential to use appropriate contraception for a certain period.

PMDA's view:

The package insert should include information about the aneugenic potential and embryo-fetal development toxicity of repotrectinib observed in toxicity studies. However, since a certain level of safety margin is ensured in the development toxicity of repotrectinib through semen, advising male patients with a female partner of childbearing potential to use contraception is not meaningful.

5.R.5 Effects on central nervous system and bone in juvenile animals

The applicant's explanation about (a) effects on the central nervous system such as tremor and ataxia observed in juvenile animals and (b) short femoral length observed even after the recovery period:

- (a) The effects of repotrectinib on the central nervous system were observed at lower doses in juvenile animals than in mature animals in the repeated-dose toxicity studies, suggesting that juvenile animals are more susceptible to the concerned effects.
- (b) Although no histopathological changes related to the above finding were observed, a potential direct effect of repotrectinib on bones in juvenile animals cannot be ruled out.

PMDA's view:

PMDA accepted the applicant's explanation. Healthcare professionals should be informed that the effects on the central nervous system were observed at lower doses in juvenile animals than in mature animals and that the effect on bones was observed. To expand the target population of repotrectinib by additionally including pediatric patients, careful measures such as monitoring the effects on the central nervous system and bones in clinical studies should be taken.

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

PK of repotrectinib was investigated using capsules, oral liquid, and injections of repotrectinib (Table 24). The proposed commercial formulation is 40 mg capsules.

Amounts of repotrectinib in human plasma and urine were determined by LC-MS/MS (lower limit of quantification, 1.0 and 0.5 ng/mL).

Table 24. Formulations used in clinical studies

Formulation	Study
Injection containing ¹⁴ C-repotrectinib	Foreign phase I study (Study 09)
Oral liquid containing ¹⁴ C-repotrectinib	Foreign phase I study (Study 09)
Capsule (160 mg)	Foreign phase I study (Study 14)
Proposed commercial capsule (40 mg)	Foreign phase I studies (Studies 09, 10, 11, and 14), global phase I/II study (TRIDENT-1 study)

6.1.1 Foreign studies

6.1.1.1 Foreign phase I study (CTD 5.3.3.4-2, Study TPX-0005-11 [Study 11], December 2020 to March 2021)

A 2-treatment, 2-period crossover study was conducted in 14 healthy adults (14 subjects included in the PK analysis) to investigate the effect of food on the PK of repotrectinib. A single dose of repotrectinib

160 mg was orally administered to subjects in the fasted state³⁶⁾ or 30 minutes after the start of eating a high-fat meal³⁷⁾ with a 14-day washout period between the doses.

The geometric mean ratios [90% confidence interval (CI)] of C_{max} and AUC_{inf} of repotrectinib after administration in the high-fat meal-fed state relative to those after administration in the fasted state were 2.489 [2.098, 2.953] and 1.562 [1.368, 1.783], respectively.

6.1.2 Effects of gastric pH on PK of repotrectinib

No clinical studies to investigate effects of gastric pH on the PK of repotrectinib were conducted. Solubility of repotrectinib was not clearly impacted by pH (0.006-0.008 mg/mL in a range from pH 1.2 to 7.4). In view of this finding, the applicant explained that gastric pH increased by proton pump inhibitors would be unlikely to have an effect on the PK of repotrectinib.

6.2 Clinical pharmacology

6.2.1 Global study

6.2.1.1 Global phase I/II study (CTD 5.3.5.2-1, phase Ia dose escalation part of the TRIDENT-1 study, February 2017 to December 2022)

An open-label, uncontrolled study was conducted in 44 patients with advanced solid tumor (42 subjects included in the PK analysis) to investigate the PK of repotrectinib. Repotrectinib was orally administered in the modified fasted state³⁸⁾ as shown below, and plasma repotrectinib concentrations were determined.

- A single dose of repotrectinib 40, 80, 160, or 240 mg was administered on Day 1, and then repotrectinib 40, 80, 160, or 240 mg was administered QD from Day 4.
- A single dose of repotrectinib 160 or 200 mg was administered on Day 1, and then repotrectinib 160 or 200 mg was administered BID from Day 4.

Table 25 shows PK parameters of repotrectinib. The accumulation rate³⁹⁾ of repotrectinib after oral administration of repotrectinib 160 mg QD was 0.672. The applicant explained that the decreased accumulation rate of repotrectinib by multiple doses might be attributable to repotrectinib's induction of CYP3A4, which could have an effect on the PK of repotrectinib.

³⁶⁾ Fasted for at least 10 hours before administration and for 4 hours after that

³⁷⁾ Of a total of 916 kcal, 56% is from fat.

³⁸⁾ Drinking and eating except water was prohibited for at least 1 hour before administration and for 2 hours after that.

³⁹⁾ Ratio of AUC_{0-24} on Day 18 to that on Day 1

Table 25. PK parameters of repotrectinib

Regimen	Dose (mg)	Day of measurement* ¹ (Day)	n	C _{max} (ng/mL)	t _{max} * ² (h)	AUC ₀₋₂₄ (ng•h/mL)	t _{1/2} (h)
QD	40	1	6	312 (44.6)	2.04 (1.97, 4.00)	2,760 (67.0)	28.4 (40.9)
		18	5	370 (42.3)	1.08 (1.00, 2.20)	2,720 (27.0)	-
	80	1	6	333 (43.3)	2.04 (1.07, 5.95)	3,160 (76.7)	21.7 (15.1)
		18	6	515 (51.7)	2.00 (1.00, 2.13)	3,550 (56.0)	-
	160	1* ³	18	714 (46.7)	3.01 (1.00, 7.83)	6,870 (59.0)	20.1 (33.6)* ⁴
		18	7	433 (51.1)	2.00 (1.17, 4.17)	4,500 (72.7)	-
	240	1	10	1,190 (74.6)	2.05 (0.97, 5.88)	13,200 (90.3)	20.5 (31.7)* ⁵
		18	6	720 (29.1)	2.10 (2.00, 6.00)	6,250 (20.5)	-
BID	160	1* ³	18	714 (46.7)	3.01 (1.00, 7.83)	6,870 (59.0)	20.1 (33.6)* ⁴
		18	8	514 (37.3)	2.04 (1.42, 4.05)	6,320 (39.4)	-
	200	1	2	271, 373	2.03, 2.07	2,610, 2,700	15.4, 31.6
		18	2	328, 408	1.00, 2.00	3,180, 5,740	-

Geometric mean (geometric coefficient of variation, %) (individual values for n = 2); -, Not calculated

*1 Number of days after the start of the single dose

*2 Median (minimum, maximum)

*3 Pool of the 160 mg QD group and the 160 mg BID group

*4 n = 17

*5 n = 7

6.2.2 Foreign studies

6.2.2.1 Foreign phase I study (CTD 5.3.3.1-1, Study TPX-0005-09 [Study 09], July to August 2020)

An open-label, uncontrolled study was conducted in 7 healthy adults (7 subjects included in the PK analysis) to investigate absolute BA and mass balance of repotrectinib.

A single dose of repotrectinib 160 mg was orally administered on Day 1, and at 1.75 hours post-dose, a single dose of ¹⁴C-repotrectinib 100 µg was intravenously administered. On Day 16, a single dose of ¹⁴C-repotrectinib 160 mg was orally administered. Radioactivity concentrations in plasma, urine, and feces were determined.

The absolute BA calculated from AUC_{inf} of repotrectinib was 45.7%.

In plasma until 168 hours after administration of ¹⁴C-repotrectinib 160 mg on Day 16, unchanged repotrectinib was mainly detected (84.3% of the total radioactivity in plasma).

The urinary and fecal excretion rates of the radioactivity (percentages of the radioactivity administered) until 672 hours after administration of ¹⁴C-repotrectinib 160 mg on Day 16 were 4.84% and 88.8%, respectively. In feces until 240 hours after administration of ¹⁴C-repotrectinib 160 mg on Day 16, unchanged repotrectinib, M4 (hydrate form), and M5 (hydroxy form) were mainly detected (accounting for 50.6%, 13.0%, and 7.11%, respectively, of the radioactivity administered).

6.2.3 Drug-drug interaction studies (CTD 5.3.3.4-1, Study TPX-0005-10 [Study 10], October 2020 to February 2021; CTD 5.3.5.2-2, sub-study of the TRIDENT-1 study, February 2017 to December 2022)

Clinical studies were conducted in healthy adults to investigate pharmacokinetic interactions of repotrectinib with the other drugs (Tables 26 and 27).

**Table 26. Effects of concomitant drugs on PK of repotrectinib
(investigated as objects of repotrectinib)**

Study	Dosage regimen of repotrectinib (oral for all doses)	Concomitant drug	Dosage regimen of concomitant drug (oral for all doses)	n* ¹	Geometric mean ratio* ² [90% CI]	
					C _{max}	AUC _{inf}
10	Single dose 80 mg on Days 1 and 15	Itraconazole (potent CYP3A and P-gp inhibitor)	200 mg QD from Days 11 to 21	16/16	2.67 [2.32, 3.09]	6.89 [6.26, 7.59]
	Single dose 160 mg on Days 1 and 18	Rifampicin (potent CYP3A inducer)	600 mg QD from Days 11 to 24	14/14	0.209 [0.180, 0.244]	0.084 [0.073, 0.097]

*¹ With/Without concomitant drug

*² Ratio of exposure with/without concomitant drug

**Table 27. Effects of repotrectinib on PK of concomitant drugs
(investigated as precipitants of repotrectinib)**

Study	Dosage regimen of repotrectinib (oral for all doses)	Concomitant drug	Dosage regimen of concomitant drug (oral for all doses)	n* ¹	Geometric mean ratio* ² [90% CI]	
					C _{max}	AUC _{inf}
TRIDENT-1	160 mg QD from Days 3 to 16, and then 160 mg BID from Day 17	Midazolam (CYP3A substrate)	A single dose of 5 mg on Days 1 and 24	6/10	0.521 [0.383, 0.711]	0.310 [0.205, 0.467]

*¹ With/Without concomitant drug

*² Ratio of exposure with/without concomitant drug

The applicant's explanation based on the above results:

- Concomitant use of the potent CYP3A inducer decreased exposure to repotrectinib. Concomitant use of potent or moderate CYP3A inducers with repotrectinib thus warrants attention, and cautions about the concerned use will be raised.
- Concomitant use of weak CYP3A inducers is unlikely to have a clinically meaningful effect on the exposure to repotrectinib, and cautions about such concomitant use are not necessary.
- Concomitant use of repotrectinib decreased exposure to midazolam. Concomitant use of CYP3A substrates is thus considered to warrant attention, and cautions about the concerned use will be raised.

Concomitant use of repotrectinib with P-gp inhibitors and CYP3A inhibitors is discussed in Section "6.R.2 Pharmacokinetic interactions with CYP3A inhibitors and P-gp inhibitors."

6.2.4 Use of repotrectinib in patients with renal impairment

No clinical studies were conducted in patients with renal impairment to investigate the effect of renal impairment on the PK of repotrectinib.

The applicant's explanation:

Dose adjustment of repotrectinib is not necessary in patients with renal impairment, in view of the following points:

- Results of the foreign phase I study (Study 09) suggested that renal excretion contributes only minimally to the elimination of repotrectinib [see Section 6.2.2.1].
- In a population pharmacokinetic (PPK) analysis [see Section 6.2.7], exposure to repotrectinib was estimated by renal function level.⁴⁰⁾ The geometric mean of C_{max,ss} and C_{ave,ss} of repotrectinib in

⁴⁰⁾ Renal function was classified according to the following criteria: Normal, eGFR (mL/min/1.73 m²) ≥90; mild impairment, eGFR (mL/min/1.73 m²) ≥60 and <90; and moderate impairment, eGFR (mL/min/1.73 m²) ≥30 and <60.

patients with normal renal function (n = 332), patients with mild renal impairment (n = 139), and patients with moderate renal impairment (n = 27) were 544, 665, and 615 ng/mL as well as 330, 385, and 354 ng/mL, respectively. The exposure to repotrectinib did not clearly differ depending on the renal function level.

- In the global phase I/II study (TRIDENT-1 study), incidences of adverse events by renal function level⁴⁰⁾ are as shown below, and the incidences did not show any clear relationship with renal function level.
 - Incidences of (a) adverse events leading to death, (b) serious adverse events, (c) Grade ≥ 3 adverse events, (d) adverse events leading to treatment discontinuation of repotrectinib, (e) adverse events leading to interruption of repotrectinib, and (f) adverse events leading to dose reduction of repotrectinib in patients with normal renal function (n = 346), patients with mild renal impairment (n = 145), and patients with moderate renal impairment (n = 28) were (a) 4.0%, 6.9%, and 7.1%, (b) 35.8%, 36.6%, and 46.4%, (c) 51.7%, 51.0%, and 57.1%, (d) 7.2%, 10.3%, and 17.9%, (e) 45.4%, 51.0%, and 42.9% as well as (f) 29.5%, 45.5%, and 42.9%, respectively.

6.2.5 Use of repotrectinib in patients with hepatic impairment

No clinical studies were conducted in patients with hepatic impairment to investigate the effect of hepatic impairment on the PK of repotrectinib.

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

- Dose adjustment of repotrectinib is not necessary in patients with mild hepatic impairment, in view of the following points:
 - In the PPK analysis [see Section 6.2.7], exposure to repotrectinib was estimated by hepatic function level.⁴¹⁾ The geometric mean of $C_{\max,ss}$ and $C_{\text{ave},ss}$ of repotrectinib in patients with normal hepatic function (n = 442), patients with mild hepatic impairment (n = 57), and patients with moderate hepatic impairment (n = 1) were 576, 620, and 398 ng/mL as well as 343, 373, and 190 ng/mL, respectively. The exposure to repotrectinib did not clearly differ depending on the hepatic function level.
 - In the global phase I/II study (TRIDENT-1 study), incidences of adverse events by hepatic function level⁴¹⁾ are as shown below, and the incidences did not clearly differ between patients with normal hepatic function and patients with mild hepatic impairment.
 - ✧ Incidences of (a) adverse events leading to death, (b) serious adverse events, (c) Grade ≥ 3 adverse events, (d) adverse events leading to treatment discontinuation of repotrectinib, (e) adverse events leading to interruption of repotrectinib, and (f) adverse events leading to dose reduction of repotrectinib in patients with normal hepatic function (n = 456) and patients with mild hepatic impairment (n = 59) were (a) 5.3% and 1.7%, (b) 36.6% and 32.2%, (c) 51.8% and 49.2%, (d) 9.0% and 6.8%, (e) 46.5% and 50.8% as well as (f) 34.6% and 35.6%, respectively.
- Repotrectinib is mainly metabolized and eliminated through the liver [see Section 6.2.2.1], and no clinical studies in patients with moderate or severe hepatic impairment were conducted. Therefore,

⁴¹⁾ Hepatic function was classified according to the following criteria: Normal, total bilirubin and aspartate aminotransferase (AST) below the upper limit of the normal (ULN); mild impairment, total bilirubin below ULN and AST above ULN or total bilirubin exceed ULN and $\leq 1.5 \times \text{ULN}$; moderate impairment, total bilirubin >1.5 and $\leq 3 \times \text{ULN}$; and severe impairment, total bilirubin $>3 \times \text{ULN}$.

use of repotrectinib in patients with moderate or severe hepatic impairment is considered to warrant attention. The concerned information will be included in the package insert to raise cautions. A clinical study is planned to investigate PK of repotrectinib in patients with moderate or severe hepatic impairment.

6.2.6 Relationship of exposure with changes of QT/QTc interval

Data from the phase Ia, Ic,⁴²⁾ and II parts of the global phase I/II study (TRIDENT-1 study) were analyzed for a relationship of plasma repotrectinib concentrations with changes in QT interval corrected by Fridericia method (QTcF) from baseline (Δ QTcF) using a linear mixed-effects model. The analysis indicated that Δ QTcF tended to shorten with increasing plasma repotrectinib concentrations, but the upper limit of 90% CI of Δ QTcF within a range of the plasma repotrectinib concentrations reached on the dosage regimens investigated was estimated to be below 10 ms.

Based on the above result, the applicant explained that repotrectinib is considered unlikely to prolong QT/QTc interval when used according to the proposed dosage and administration.

6.2.7 PPK analysis

The PPK model was initially constructed based on PK data of repotrectinib (8,167 measuring time points in 525 patients) obtained from the global phase I/II study (TRIDENT-1 study) (data cut off on June 20, 2022) and foreign phase I studies (Study TPX-0005-08,⁴³⁾ Studies 09, 10, 11, 12,⁴⁴⁾ and Study TPX-0005-14 [Study 14]) and then updated with additionally pooled data from the global phase I/II study (TRIDENT-1 study) (data cut off on December 19, 2022) and a foreign phase I/II study (CARE study⁴⁵⁾). A summary of the updated PPK analysis is provided below.

The PPK analysis was performed using a non-linear mixed-effects model (software, NONMEM Version 7.4.3) based on the PK data of repotrectinib (9,220 measuring time points in 644 subjects).⁴⁶⁾ The PK of repotrectinib was described by a 2-compartment model with the lag time and first-order absorption process and the non-linear elimination process.

In this analysis, the model established by modifying the initial model (with the disease status [healthy adults or patients with cancer] taken into account as a covariate for CL) was used, and possible covariates of repotrectinib for (a) CL, Q, and CLMAX, (b) KA and F1 were (a) age and (b) dosage form (capsule or suspension). The initial model was established by integrating (a) body weight and dose, (b) body weight, (c) body weight and disease status (healthy adults or patients with cancer), and (d) meal as

⁴²⁾ Dose escalation part to investigate the PK of repotrectinib in patients with advanced solid tumor in the fed state

⁴³⁾ A foreign phase I study to compare an oral suspension of repotrectinib with the capsule in healthy adults and investigate the BA

⁴⁴⁾ A foreign phase I study to investigate relative BA of the capsule of repotrectinib in healthy adults

⁴⁵⁾ A foreign phase I/II study to investigate the efficacy, safety, and PK of repotrectinib in pediatric or adult patients with malignant tumor harboring *ALK*, *ROS1*, or *NTRK* gene abnormalities

⁴⁶⁾ Characteristics of subjects included in the analysis (the median [minimum, maximum]) or the number of subjects in each category as follows: Body weight, 70.6 (5.90, 169) kg; sex, 344 males and 300 females; age, 51.5 (0.8, 93) years; race, 319 whites, 43 blacks, 245 Asians (including 15 Japanese), 37 subjects of the other races; hepatic function, 582 subjects with normal function, 59 subjects with mild impairment, 1 subject with moderate impairment, 2 subjects with unknown hepatic condition; renal function, 448 with normal function, 157 subjects with mild impairment, 33 subjects with moderate impairment, 6 subjects with unknown renal condition; disease status, 118 healthy adults, 526 patients with cancer; dosage form, 624 subjects receiving capsules, 20 subjects receiving suspension, 7 subjects receiving injection

covariates for (a) CL, (b) Q and V_p, (c) V_c, and (d) KA and F₁. Age (<18 years only) was selected as a covariate for CLMAX.

6.2.8 Relationships between exposure and efficacy or safety

6.2.8.1 Relationship between exposure and efficacy

Based on results in patients with *ROS1* fusion gene-positive NSCLC who were ROS1-TKI-treatment naïve and those who had received 1 prior line of ROS1-TKI treatment in the global phase I/II study (TRIDENT-1 study), relationships between the exposure to repotrectinib⁴⁷⁾ (C_{avg}) and the response rate or progression free survival (PFS) were investigated. The response rate and PFS tended to increase with increasing exposure to repotrectinib.

6.2.8.2 Relationship between exposure and safety

Based on results in the global phase I/II study (TRIDENT-1 study), a relationship between exposure to repotrectinib⁴⁷⁾ (C_{avg}) and cumulative incidence of adverse events (Grade ≥2 dizziness, Grade ≥2 anaemia, Grade ≥3 adverse events, Grade ≥2 neurological adverse events,⁴⁸⁾ and Grade ≥2 adverse events leading to dose reduction or interruption) was investigated. The cumulative incidences of Grade ≥2 dizziness and adverse events leading to dose reduction or interruption tended to increase with increasing exposure to repotrectinib.

6.2.9 Difference in PK between Japanese and non-Japanese patients

The applicant explanation:

Based on the following investigation, no clear differences are observed in PK of repotrectinib between Japanese and non-Japanese patients.

- Table 28 shows PK parameters of repotrectinib in non-Japanese patients in the phase Ia part and Japanese patients in the Japanese lead-in cohort of the phase II part in the global phase I/II study (TRIDENT-1 study). To these patients in the modified fasted state,³⁸⁾ a single dose of repotrectinib 160 mg was administered on Day 1, and then repotrectinib 160 mg was administered QD from Day 4. Although the exposure differed owing to the lower body weight in the Japanese patients than in non-Japanese patients (tended to be higher in the Japanese patients than in non-Japanese patients),⁴⁹⁾ distributions of exposure to repotrectinib in the Japanese and non-Japanese patients overlapped.
- The PPK analysis did not select the race as a significant covariate that could affect the PK of repotrectinib [see Section 6.2.7].

⁴⁷⁾ Estimated by the PPK analysis [see Section 6.2.7].

⁴⁸⁾ Dyspnoea, dysgeusia, paraesthesia, and ataxia

⁴⁹⁾ In the PPK analysis [see Section 6.2.7], body weight was selected as a significant covariate. By the concerned PPK analysis, the C_{max} and C_{ave} at steady state in adult patients with solid tumor to whom repotrectinib 160 mg was administered QD for 14 days and then BID were estimated for patients weighing 47.8 kg, 70 kg, and 104.9 kg. The estimated C_{max} and C_{ave} were 693 and 399 ng/mL, 576 and 344 ng/mL, as well as 473 and 295 ng/mL, respectively.

Table 28. PK parameters of repotrectinib

Day of measurement (Day)	Population	n	C _{max} (ng/mL)	AUC _{0-last} (ng•h/mL)
1	Japanese	6	1,350 (46.4)	11,800 (44.4)
	Non-Japanese	18	714 (46.7)	9,030 (53.0)
17	Japanese	6	816 (40.3)	5,810 (27.1)
18	Non-Japanese	7	433 (51.1)	4,340 (66.0)

Geometric mean (Geometric coefficient of variation, %)

6.R Outline of the review conducted by PMDA

Based on the submitted data and the review in the following section, PMDA concluded that the applicant's explanation about clinical pharmacology of repotrectinib, except the pharmacokinetic interactions with CYP3A inhibitors and P-gp inhibitors, is acceptable. However, in the clinical study below, when results become available, healthcare professionals should be appropriately informed.

- A study to investigate PK of repotrectinib in patients with moderate or severe hepatic impairment [see Section 6.2.5]

6.R.1 Food effect

The applicant's explanation about the food effect on PK of repotrectinib:

The administration after a high-fat meal increased exposure to repotrectinib in the foreign phase I study (Study 11) [see Section 6.1.2.1], but repotrectinib may be administered irrespective of the fed or fasted state, in view of the following points:

- In the phase II part in the global phase I/II study (TRIDENT-1 study) in which repotrectinib was administered without regard to meals, clinical usefulness of repotrectinib was demonstrated [see Sections 7.R.2 and 7.R.3].
- Using the investigation results on a relationship between the exposure and the efficacy or safety [see Sections 6.2.8.1 and 6.2.8.2], the response rate and incidence of Grade ≥ 2 dizziness in patients receiving repotrectinib in the fasted state and in the fed state were predicted. No clear differences were observed in the predicted results (Tables 29 and 30).
- Although the investigation has limitations because of the limited sample size, incidences of adverse events in 8 patients who received repotrectinib 160 mg QD in the modified fasted state in the phase Ia part and in 6 patients who received repotrectinib 160 mg QD in the fed state in the phase Ic part in the global phase I/II study (TRIDENT-1 study) are compared below. The safety profile of repotrectinib does not clearly differ depending on the timing of dosing relative to meals.
 - Incidences of (a) adverse events leading to death, (b) serious adverse events, (c) Grade ≥ 3 adverse events, (d) adverse events leading to treatment discontinuation of repotrectinib, (e) adverse events leading to interruption of repotrectinib, and (f) adverse events leading to dose reduction of repotrectinib were (a) 0% and 16.7%, (b) 12.5% and 83.3%, (c) 25.0% and 83.3%, (d) 25.0% and 16.7%, (e) 12.5% and 33.3% as well as (f) 0% and 16.7%. The incidences of serious events and Grade ≥ 3 events tended to be higher in patients receiving repotrectinib in the fed state, but incidences of adverse events for which a causal relationship to repotrectinib could not be ruled out did not show any clear difference ([a] 0% and 0%, [b] 0% and 16.7%, [c] 0% and 16.7%, [d] 0% and 16.7%, [e] 0% and 16.7% as well as [f] 0% and 16.7%).

Table 29. Model-predicted response rate during the repotrectinib 160 mg QD/BID regimen

Stomach condition	ROS1-TKI-naïve (n = 71)	ROS1-TKI-prior-treated (n = 56)
Fasted state	81.8 [74.3, 87.8]	40.4 [32.4, 52.5]
Modified fasted state	86.8 [81.1, 91.5]	50.4 [41.4, 61.8]
Fed state	88.9 [84.1, 93.1]	55.5 [46.4, 66.2]
Unknown	85.0 [78.7, 90.1]	47.7 [37.8, 58.3]

Median [90% CI] (%)

Table 30. Model-predicted cumulative incidence of Grade ≥ 2 dizziness during the repotrectinib 160 mg QD/BID regimen

Stomach condition	15 days	6 months	12 months
Fasted state	4.5 [1.2, 16]	12 [3.3, 40]	13 [3.5, 42]
Modified fasted state	6.1 [1.6, 24]	15 [4.1, 50]	16 [4.2, 51]
Fed state	6.8 [1.8, 28]	17 [4.6, 54]	18 [4.7, 55]
Unknown	5.6 [1.5, 22]	14 [3.8, 48]	15 [4.0, 49]

Median [90% CI] (%)

PMDA accepted the applicant's explanation.

6.R.2 Pharmacokinetic interactions with CYP3A inhibitors and P-gp inhibitors

The applicant's explanation about concomitant use of repotrectinib with CYP3A inhibitors or P-gp inhibitors:

In the foreign phase I study (Study 10), concomitant use of itraconazole (potent CYP3A and P-gp inhibitor) increased the exposure to repotrectinib [see Section 6.2.3]. Contribution of CYP3A or P-gp inhibition to the increased exposure is unknown. Cautions about concomitant use of repotrectinib with drugs that strongly or moderately inhibit CYP3A and also inhibit P-gp will be raised, instead of cautions about concomitant use of repotrectinib with each class of CYP3A inhibitors and P-gp inhibitors. Concomitant use of repotrectinib with drugs that weakly inhibit CYP3A and also inhibit P-gp is unlikely to have a clinically meaningful effect on the exposure to repotrectinib. Cautions about the concerned concomitant use are considered unnecessary. The applicant plans to conduct a clinical study to investigate pharmacokinetic interactions of repotrectinib with each class of CYP3A inhibitors and P-gp inhibitors.

PMDA's view:

PMDA accepted the applicant's explanation about concomitant use of repotrectinib with drugs that weakly inhibit CYP3A and also inhibit P-gp.

Although the applicant explained that cautions about the concomitant use only with drugs that inhibit both CYP3A and P-gp would be raised, appropriateness of such action is not clear at the present time in view of the following points: (a) Concomitant itraconazole, which strongly inhibits CYP3A and also inhibits P-gp, increased the exposure (AUC) to repotrectinib approximately 6.89 fold; (b) repotrectinib is considered to be a substrate of both CYP3A and P-gp [see Sections 4.3.1 and 4.5.3]; and (c) there are no results from clinical studies to investigate changes in exposure to repotrectinib during concomitant use of repotrectinib with each class of CYP3A inhibitors and P-gp inhibitors. Thus, cautions about concomitant use with each class of P-gp inhibitors and moderate or potent CYP3A inhibitors should be raised in the package insert.

When results from the clinical study to investigate pharmacokinetic interactions of repotrectinib with each class of CYP3A inhibitors and P-gp inhibitors become available, information should be provided appropriately to healthcare professionals.

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

The applicant submitted efficacy and safety evaluation data in the form of results from the studies presented in Table 31.

Table 31. List of clinical studies for efficacy and safety

Data category	Region	Study ID	Phase	Population	No. of subjects enrolled	Dosage regimen	Major endpoints
Evaluation	Global	TRIDENT-1	I/II	Phase I Patients with <i>ROS1</i>, <i>NTRK</i> or <i>ALK</i> fusion gene-positive advanced solid tumor Phase II EXP-1: Patients with <i>ROS1</i>-TKI-naïve <i>ROS1</i> fusion gene-positive NSCLC EXP-2: Patients with <i>ROS1</i> fusion gene-positive NSCLC who received 1 prior line of <i>ROS1</i>-TKI therapy and 1 prior line of platinum-based antineoplastic therapy EXP-3: Patients with <i>ROS1</i> fusion gene-positive NSCLC who received 2 prior lines of <i>ROS1</i>-TKI therapy EXP-4: Patients with <i>ROS1</i> fusion gene-positive NSCLC who received 1 prior line of <i>ROS1</i>-TKI therapy EXP-5: Patients with <i>TRK</i>-TKI-naïve <i>NTRK</i> fusion gene-positive solid tumor EXP-6: Patients with <i>NTRK</i> fusion gene-positive solid tumor who received prior <i>TRK</i>-TKI therapy	Phase I Ia: 44 Ib: 28 Ic: 21 Sub-study: 10 Phase II EXP-1: 107 EXP-2: 46 EXP-3: 58 EXP-4: 102 EXP-5: 43 EXP-6: 61	Phase I Ia: (administered in the modified fasted state) Oral administration of repotrectinib 40 to 240 mg QD or 160 to 200 mg BID Ib: A single oral administration of repotrectinib 40 to 160 mg in the modified fasted state or in the fed state, and then oral administration of repotrectinib 40 to 160 mg QD in the modified fasted state Ic: (administered in the fed state) Oral administration of repotrectinib 120 or 160 mg QD, or 160 mg QD for 7 days, and then oral administration of 160 mg BID Sub-study: Oral administration of repotrectinib 160 mg QD for 14 days in combination with midazolam, and then oral administration of 160 mg BID Phase II Oral administration of repotrectinib 160 mg QD for 14 days, and then 160 mg BID	Phase I: Tolerability Safety PK Phase II: Efficacy Safety
Reference	Foreign	09	I	Healthy adults	7	A single oral administration of repotrectinib 160 mg, followed by a single intravenous administration of ¹⁴ C-repotrectinib 100 µg on Day 1, and then a single oral administration of ¹⁴ C-repotrectinib 160 mg on Day 16	PK
	Foreign	10	I	Healthy adults	Part 1: 16 Part 2: 14	Part 1: A single oral administration of repotrectinib 80 mg itraconazole Part 2: A single oral administration of repotrectinib 160 mg in combination with rifampicin	PK
	Foreign	11	I	Healthy adults	14	A single oral administration of repotrectinib 160 mg in the fasted state or in the fed state	PK
	Foreign	14	I	Healthy adults	36	A single oral administration of repotrectinib (40 mg capsules or 160 mg capsule) 160 mg in the fasted state or in the fed state	PK

Clinical studies are summarized below. The main adverse events other than death reported in clinical studies are described in Section “7.3 Adverse events, etc. observed in clinical studies.”

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase I/II study (CTD 5.3.5.2-1, 5.3.5.2-2, 5.3.5.2-3, and 5.3.5.2-4; TRIDENT-1 study, ongoing since February 2017 [data cut off on June 20, 2022, December 19, 2022])

An open-label, uncontrolled study was conducted in patients with *ROS1* fusion gene-positive⁵⁰⁾ unresectable advanced or recurrent NSCLC to investigate the efficacy, safety, PK, etc. of repotrectinib at 152 study sites in 19 countries and regions including Japan.

In the phase I part, patients with *ROS1*, *NTRK*, or *ALK* fusion gene-positive advanced solid tumor were included, and for the phase II part, the target patients and target sample size were specified as presented in Table 32.

Table 32. Target patients and target sample size for the phase II part

Cohort	Target patients	Target sample size
EXP-1	Patients with <i>ROS1</i> -TKI-naïve <i>ROS1</i> fusion gene-positive unresectable advanced or recurrent NSCLC (irrespective of prior cytotoxic antineoplastic therapy or immune checkpoint inhibitor therapy)	55* ¹
EXP-2	Patients with <i>ROS1</i> fusion gene-positive unresectable advanced or recurrent NSCLC who received 1 prior line of <i>ROS1</i> -TKI therapy and 1 prior line of platinum-based antineoplastic therapy	60* ²
EXP-3	Patients with <i>ROS1</i> fusion gene-positive unresectable advanced or recurrent NSCLC who received 2 prior lines of <i>ROS1</i> -TKI therapy but did not receive prior cytotoxic antineoplastic therapy or immune checkpoint inhibitor therapy* ³	40* ⁴
EXP-4	Patients with <i>ROS1</i> fusion gene-positive unresectable advanced or recurrent NSCLC who received 1 prior line of <i>ROS1</i> -TKI therapy but did not receive prior cytotoxic antineoplastic therapy or immune checkpoint inhibitor therapy	60* ⁵
EXP-5	Patients with TRK-TKI-naïve <i>NTRK</i> fusion gene-positive advanced solid tumor	55
EXP-6	Patients with <i>NTRK</i> fusion gene-positive advanced solid tumor who received prior TRK-TKI therapy	40

*1 Sample size ensuring that the lower limit of 95% CI of the response rate to repotrectinib, which is assumed to be 80%, exceeds 66% (the response rate to crizotinib in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC [United States Prescribing Information (USPI) of crizotinib])

*2 Sample size ensuring that the lower limit of 95% CI of the response rate to repotrectinib, which is assumed to be 35%, exceeds 23% (response rate to concomitant use of docetaxel and ramucirumab in patients with unresectable advanced or recurrent NSCLC who had received prior chemotherapy [USPI of ramucirumab])

*3 The protocol version 7 dated November 13, 2019 specified that patients who had received 2 prior lines of *ROS1*-TKI therapy and 1 prior line of platinum-based antineoplastic therapy should be included, but the efficacy of repotrectinib in the concerned patient population was limited. The protocol was amended to include patients who had not received prior cytotoxic antineoplastic therapy (protocol version 10 dated October 20, 2020).

*4 Sample size ensuring that the lower limit of 95% CI of the response rate to repotrectinib, which is assumed to be 25%, exceeds 10% (response rate to docetaxel or pemetrexed in patients with unresectable advanced or recurrent NSCLC who had received prior chemotherapy [USPI of docetaxel and pemetrexed])

*5 Sample size ensuring that the lower limit of 95% CI of the response rate to repotrectinib, which is assumed to be 50%, exceeds 35% (response rate to platinum-based chemotherapy in chemotherapy-naïve patients with unresectable advanced or recurrent NSCLC [USPI of albumin-bound paclitaxel suspension, pemetrexed, gemcitabine, docetaxel, and bevacizumab])

The dosage regimens are as shown below, and the treatment was continued until disease progression or the criteria for treatment discontinuation were met.

Ia part: Oral administration of repotrectinib 40, 80, 160, or 240 mg QD or 160 or 200 mg in the modified fasted state³⁸⁾ BID

Ib part: A single oral administration of repotrectinib 40, 80, or 160 mg in the modified fasted state or in the fed state, and then 40, 80, or 160 mg QD in the modified fasted state

⁵⁰⁾ In the phase II part, the genotyping was performed with tumor tissue specimens by next generation sequencing (NGS) or polymerase chain reaction (PCR).

- Ic part: (Administered in the fed state) Oral administration of repotrectinib 120 or 160 mg QD or oral administration of 160 mg QD, and if tolerability has no problem on Day 7, then oral administration of 160 mg BID.
- Sub-study: Oral administration of repotrectinib 160 mg QD in combination with midazolam, and if tolerability has no problem on Day 14, then oral administration of 160 mg BID.
- Phase II part: Oral administration of repotrectinib 160 mg QD, and if tolerability has no problem on Day 14, the dose may be increased to 160 mg BID orally (160 mg QD/BID regimen).

Although the patient enrollment in expansion cohort (EXP)-1 was likely to reach the target sample size of 55 patients, that in the other cohorts did not reach the target sample size. To continue the patient enrolment, the enrollment of up to 110 patients was allowed with the condition that the primary efficacy analysis in EXP-1 should be performed in the first enrolled 55 patients (protocol version █ dated █, 20██). The primary analysis in the phase II part in this study was not clearly specified at the start of this part, and the first version of the statistical analysis plan dated █, 20██ specified that the primary analysis should be performed in the first enrolled 55 patients in EXP-1 who completed ≥ 6 months of follow-up after the first post-baseline scan. Study results at the concerned time point or as of the data cut-off date of █, 20██ were discussed with a foreign regulatory authority. As a result of the discussion, the efficacy analysis was planned when the first enrolled 55 patients in EXP-1 and later enrolled 8 patients in EXP-1 who had undergone 2 post-baseline scans as of █, 20██ completed at least 6 and 12 months of follow-up after the first post-baseline scan. Data cut-off was made on June 20, 2022 and December 19, 2022.

For the present application, the applicant submitted study results as of the above data cut-off dates of June 20, 2022 and December 19, 2022. Although results as of both data cut-off dates do not allow statistical interpretation in consideration of the setting of the target sample size and the background leading to the analysis, the response rates at both data cut-off points did not clearly differ [see Section 7.R.2.1]. In this report, results as of the data cut-off date of December 19, 2022 are mainly discussed.

Of 520 patients enrolled in this study (44 in the phase Ia part, 28 in the phase Ib part, 21 in the phase Ic part, 10 in the sub-study, 417 in the phase II part [107 in EXP-1, 46 in EXP-2, 58 in EXP-3, 102 in EXP-4, 43 in EXP-5, 61 in EXP-6]), 519 patients (including 15 Japanese patients) were included in the safety analysis, and the remaining 1 patient in EXP-3 of the phase II part who did not receive repotrectinib was excluded. The efficacy analysis included █ patients who were included in the safety analysis in the phase II part and allowed at least 12 months (EXP-1 to EXP-4) or █ months (EXP-5 and EXP-6) of follow-up after the first post-baseline scan (63 in EXP-1, 23 in EXP-2, 17 in EXP-3,⁵¹⁾ 53 in EXP-4, █ in EXP-5, █ in EXP-6). In this report, of results in the phase II part, those in EXP-1 to 4 are mainly discussed in view of the proposed indication.

In the phase Ia and Ic parts, dose limited toxicity (DLT) was evaluated until Day 21 or 28 after the first dose of repotrectinib. DLT was observed in 2 of 11 patients in the 160 mg BID group (Grade 3 dyspnoea/Grade 3 hypoxia, and Grade 3 dizziness) and in 1 of 8 patients in the 240 mg QD group (Grade

⁵¹⁾ The patients who had received 2 prior lines of ROS1-TKI therapy and 1 prior line of platinum-based antineoplastic therapy and were enrolled before issuance of the protocol version 9 dated March 23, 2020 [see *3 in Table 32] were excluded.

3 dizziness) (both groups in the phase Ia part). In consideration of the incidence of DLT and time to onset of dizziness, the recommended phase 2 dose (RP2D) of 160 mg QD/BID was decided [see Section 7.R.5.1]. Of Japanese patients enrolled in the phase II part of this study, the first 6 (Japanese lead-in cohort) were evaluated for tolerability of repotrectinib. In the concerned 6 patients, no DLT was observed until the end of the DLT evaluation period or Day 28. Tolerability of repotrectinib 160 mg QD/BID was confirmed in the Japanese patients.

The primary endpoint in the phase II part of this study was the response rate according to Response Evaluation Criteria in Solid Tumors (RECIST) ver.1.1 as assessed by independent central review. Table 33 shows results in EXP-1 to EXP-4.

**Table 33. Best overall response and response rate
(RECIST ver.1.1, efficacy analysis population, independent and central assessment, data cut-off on
December 19, 2022)**

Best overall response	n (%)			
	EXP-1 N = 63	EXP-2 N = 23	EXP-3 N = 17	EXP-4 N = 53
CR	7 (11.1)	1 (4.3)	1 (5.9)	3 (5.7)
PR	42 (66.7)	9 (39.1)	4 (23.5)	17 (32.1)
SD	11 (17.5)	6 (26.1)	3 (17.6)	22 (41.5)
PD	2 (3.2)	5 (21.7)	6 (35.3)	8 (15.1)
NE	1 (1.6)	2 (8.7)	3 (17.6)	3 (5.7)
Response (CR + PR) (response rate [95% CI*] [%])	49 (77.8 [65.5, 87.3])	10 (43.5 [23.2, 65.5])	5 (29.4 [10.3, 56.0])	20 (37.7 [24.8, 52.1])

* Clopper-Pearson method

For the safety, deaths during the repotrectinib treatment or within 28 days after the end of the treatment occurred in 20 of 103 patients (19.4%) in the phase I part and 48 of 416 patients (11.5%) in the phase II part (no deaths occurred in the Japanese patients). Other than disease progression (12 patients in the phase I part, 31 patients in the phase II part), causes of the deaths were cardiac arrest in 2 patients, cardio-respiratory arrest, pneumonia, sepsis, sudden death, respiratory failure, and hypoxia in 1 patient each in the phase I part; and death in 3 patients, pneumonia, dyspnoea, and cardiac arrest in 2 patients each, sudden cardiac death, sudden death, hypoxia, respiratory failure, cardiac failure, disseminated intravascular coagulation, tremor, and unknown cause in 1 patient each in the phase II part. A causal relationship to the study drug was ruled out for all of them.

7.2 Reference data

7.2.1 Clinical pharmacology

The applicant submitted results from 4 clinical pharmacology studies (Studies 09, 10, 11, and 14) [see Table 31]. No deaths during the study treatment or within a certain period⁵²⁾ after the end of the treatment occurred.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA determined that, among the evaluation data submitted, the pivotal clinical study for evaluation of the efficacy and safety of repotrectinib in patients with *ROS1* fusion gene-positive unresectable

⁵²⁾ 28 days for Studies 09 and 14, 14 days for Studies 10 and 11

advanced or recurrent NSCLC was the study in EXP-1 to EXP-4 in the phase II part of the global phase I/II study (TRIDENT-1 study), which was intended to investigate the efficacy and safety of repotrectinib in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC, and decided to evaluate the submitted data focusing these cohorts. PMDA decided to evaluate the efficacy in Japanese patients systematically based on data in EXP-1 to EXP-4 in the phase II part of TRIDENT-1 study in accordance with the “Basic Principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, dated September 28, 2007), “Amendment to ‘Basic Principles on Global Clinical Trials (Reference Cases)’” (PSEHB/PED Administrative Notice of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare, dated December 10, 2021), and “Guidelines on General Principles for Planning and Design of Multi-Regional Clinical Trials” (PSEHB/PED Notification No. 0612-1, dated June 12, 2018).

7.R.2 Efficacy

Based on the following review, PMDA has concluded that repotrectinib is demonstrated to have a certain level of efficacy in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC.

7.R.2.1 Timing and population of the efficacy analysis

The applicant’s explanation about timing of the efficacy analysis in the TRIDENT-1 study and the analysis population in EXP-1:

According to the first version of the statistical analysis plan (dated ■■■, 20■■), the efficacy analysis time point specified for the phase II part of the TRIDENT-1 study corresponded to ■■■, 20■■, and the protocol version ■■ (dated ■■■, 20■■) specified that the efficacy analysis in EXP-1 should include the first enrolled 55 patients. In view of the following points, the efficacy evaluation of repotrectinib based on results as of the data cut-off date of December 19, 2022 is considered appropriate:

- The response rate in each cohort did not clearly differ among data cut-off dates on and after ■■■, 20■■ (Table 34).
- The longer follow-up period is considered to ensure more appropriate evaluation for response continuation.
- Results as of data cut-off date of December 19, 2022 can include data in more patients who completed ≥12 months of follow-up than those as of the other data cut-off dates.

Table 34. Response rate as of each data cut-off date

Data cut-off	Response rate (% [n/N])			
	EXP-1	EXP-2	EXP-3	EXP-4
■■■, 20■■*1	79.0 (49/62)*2	43.5 (10/23)	35.7 (5/14)	37.3 (19/51)
June 20, 2022	77.8 (49/63)	43.5 (10/23)	29.4 (5/17)	37.7 (20/53)
December 19, 2022	77.8 (49/63)*3	43.5 (10/23)	29.4 (5/17)	37.7 (20/53)

*1 Patients who had the results assessed by independent central review as of ■■■, 20■■

*2 77.8% (42 of 54) of patients who were a part of the first enrolled 55 patients in EXP-1 and had the results assessed by independent central review

*3 76.4% (42 of 55) of the first enrolled 55 patients in EXP-1

PMDA’s view:

The analysis results in the phase II part of the TRIDENT-1 study are difficult to interpret statistically because (1) the target sample size was not determined based on the hypothesis testing principle; and (2) the efficacy analysis time point was specified after the start of the phase II part. In addition, in

consideration that the pre-determined sample sizes for EXP-2 to EXP-4 were not reached as of any data-cut-off date, possible overestimation cannot be ruled out for results in the concerned cohorts.

However, PMDA decided to investigate clinical meaning of the results in the phase II part of the TRIDENT-1 study presented as of data cut-off date of December 19, 2022, taking account of the followings, and then evaluate the efficacy of repotrectinib.

- The response rate did not considerably change among the above data cut-off dates.
- In EXP-1, the response rate in the first enrolled 55 patients was not clearly different from that in 63 patients included in the efficacy analysis in the evaluation as of the data cut-off date of December 19, 2022 (Table 34).

7.R.2.2 Efficacy endpoints and evaluation results

The applicant's explanation about the primary endpoint and the efficacy of repotrectinib in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC in the phase II part of the TRIDENT-1 study:

In patients in the phase II part of the TRIDENT-1 study, tumor regression is expected to improve tumor-related symptoms (*J Clin Oncol.* 2006;24:3831-7, *JAMA.* 2003;290:2149-58) and thereby maintain the quality of life, and the response is considered to be clinically meaningful. Thus, the primary endpoint in the phase II part of the TRIDENT-1 study was specified as the response rate.

Table 33 shows results on the response rate in the phase II part of the TRIDENT-1 study are. In the efficacy analysis population of EXP-1, the response rates in patients without prior cytotoxic antineoplastic therapy and those with such prior therapy were 82.4% (42 of 51 patients) and 58.3% (7 of 12 patients).

The response rate [95% CI] to repotrectinib in EXP-1 of the TRIDENT-1 study (77.8% [65.5%, 87.3%]) tended to exceed the results of conventional therapies below, and use of repotrectinib in patients with *ROS1*-TKI-naïve *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC is considered clinically meaningful.

- The response rate [95% CI] to crizotinib in a foreign phase I study was 66% [51%, 79%] (United States Prescribing Information [USPI] of crizotinib).
- In the pooled analysis of 2 foreign phase I studies and 1 global phase II study, the response rate [95% CI] to entrectinib in patients with *ROS1*-TKI-naïve *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC was 67.1% [59.3%, 74.3%] (*J Clin Oncol.* 2021;39:1253-63).

In view of the following points, use of repotrectinib in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC who received prior *ROS1*-TKI therapy is considered clinically meaningful:

- In EXP-2 and 4 of the TRIDENT-1 study, the response rates [95% CI] to repotrectinib (EXP-2, 43.5% [23.2%, 65.5%]; EXP-4, 37.7% [24.8%, 52.1%]) tended to exceed the results of conventional therapies below.

- The response rate to concomitant use of ramucirumab and docetaxel in patients with unresectable advanced or recurrent NSCLC who had received prior chemotherapy was 22.9% (USPI of ramucirumab).
- The response rate to chemotherapy including platinum-based antineoplastic therapy (except PD-1/PD-L1 inhibitors) in patients with unresectable advanced or recurrent NSCLC was 30.1% to 35% (*Ann Oncol.* 2007;18:317-23, *N Engl J Med.* 2006;355:2542-50, etc.).
- In the efficacy analysis population of EXP-2 to EXP-4, some of the patients harboring resistance mutations to ROS1-TKIs responded to repotrectinib (8 of 15 subjects harboring G2032R, 1 of 1 subject harboring L2026M, 0 of 1 subject harboring F2004I, 0 of 2 subjects harboring L2086F, 1 of 1 subject harboring S1986F (serine at position 1,986 substituted by phenylalanine)/S1986Y (serine at position 1,986 substituted by tyrosine)⁵³).
- In the efficacy analysis population of EXP-2 to EXP-4, the response rate by prior ROS1-TKI was 38.9% (7 of 18 subjects) in EXP-2, 29.4% (5 of 17 subjects) in EXP-3, and 37.8% (17 of 45 subjects) in EXP-4 in patients pretreated with crizotinib and 50.0% (2 of 4 subjects) in EXP-2, 66.7% (2 of 3 subjects) in EXP-3, and 28.6% (2 of 7 subjects) in EXP-4 in patients pretreated with entrectinib, demonstrating that the response to repotrectinib was observed even in patients pretreated with either drug to a certain extent.

Figures 1 to 4 show the maximum percent changes in total tumor size of the target lesion in EXP-1 to EXP-4 of the TRIDENT-1 study based on the assessment by independent central review. The median duration of response⁵⁴ [95% CI] (months) based on the assessment by independent central review was not estimative [25.6, not estimative] in EXP-1, 8.03 [4.5, not estimative] in EXP-2, 7.36 [3.5, not estimative] in EXP-3, and 14.75 [7.5, not estimative] in EXP-4.

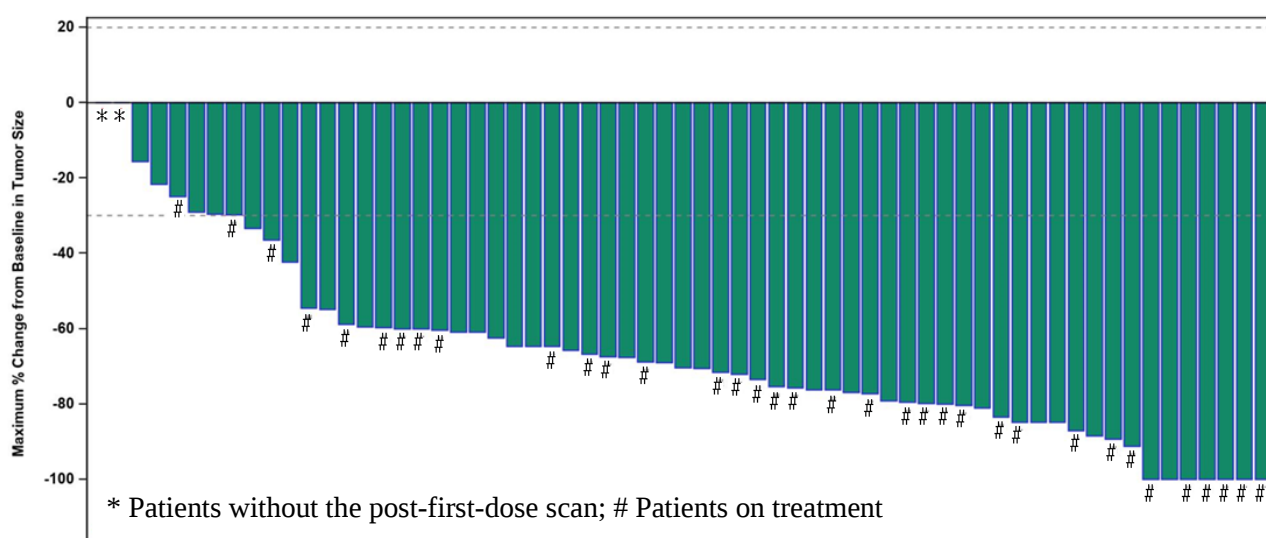


Figure 1. Maximum percent change in total tumor size (target lesion)
(EXP-1, efficacy analysis population, independent and central assessment, data cut-off on December 19, 2022)

⁵³) Both S1986F and S1986Y were detected.

⁵⁴) Defined as a period from the first response according to RECIST ver.1.1 to progressive disease (PD) or death, whichever came earlier, in patients with confirmed response (complete response [CR] or partial response [PR])

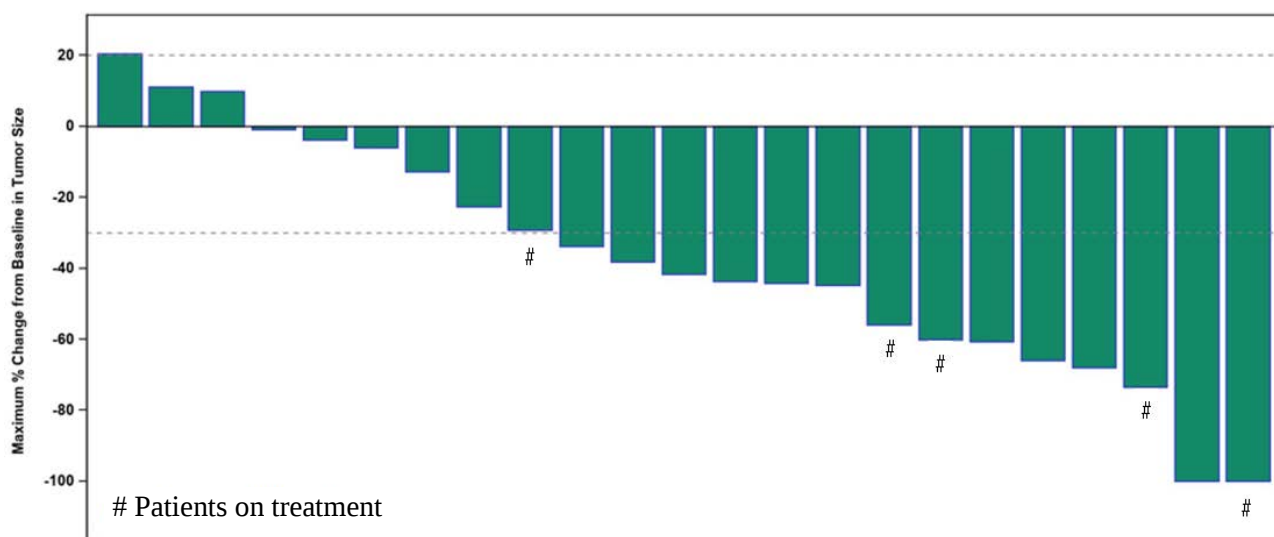


Figure 2. Maximum percent change in total tumor size (target lesion)
(EXP-2, efficacy analysis population, independent and central assessment, data cut-off on December 19, 2022)

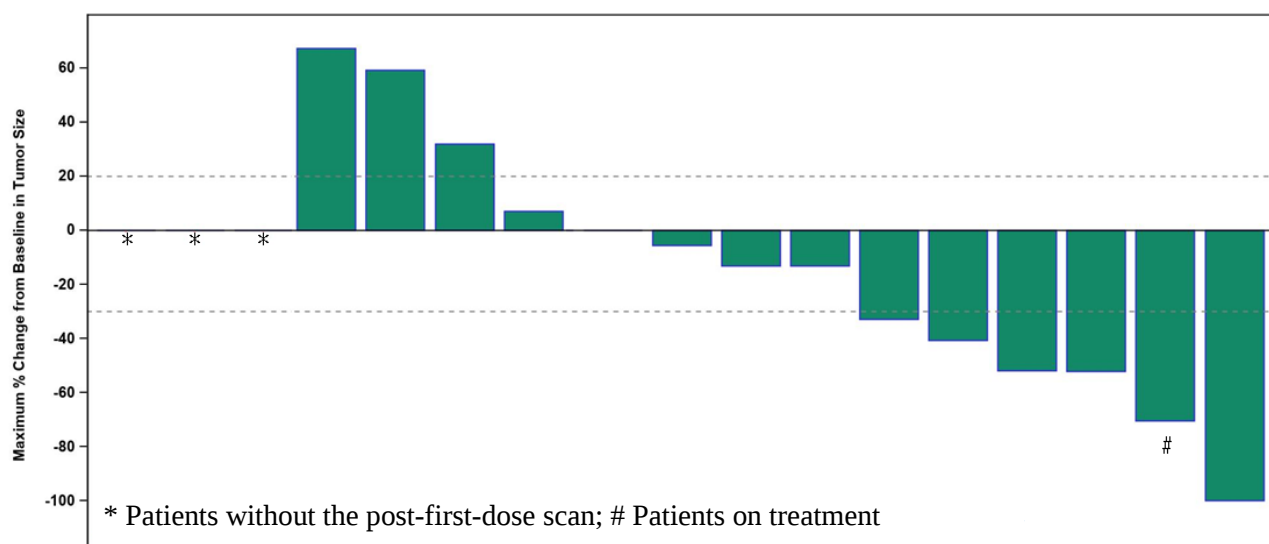


Figure 3. Maximum percent change in total tumor size (target lesion)
(EXP-3, efficacy analysis population, independent and central assessment, data cut-off on December 19, 2022)

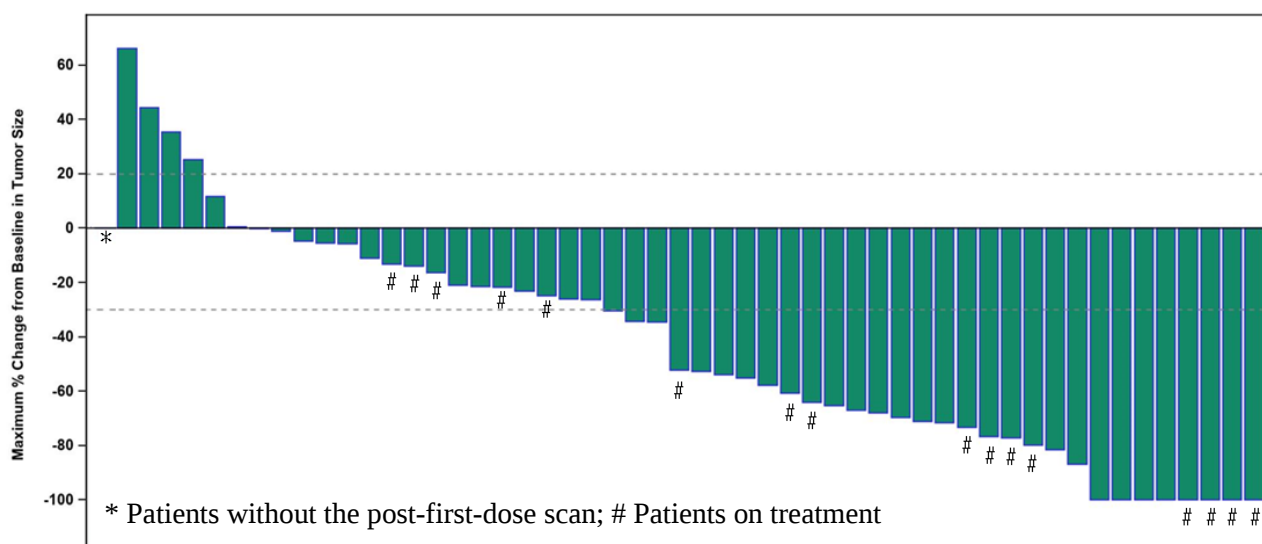


Figure 4. Maximum percent change in total tumor size (target lesion)
(EXP-4, efficacy analysis population, independent and central assessment, data cut-off on December 19, 2022)

In 3 Japanese patients included in the efficacy analysis population in the phase II part of the TRIDENT-1 study, the best overall response was partial response (PR) and stable disease (SD) in 1 patient each in EXP-2 and PR in 1 patient in EXP-3.

In view of the above clinical study results and the following point, repotrectinib was demonstrated to have a certain level of efficacy in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC.

- In *ROS1* fusion gene-positive NSCLC, *ROS1* fusion gene is deemed as an oncogenic driver vital in the onset of NSCLC (*Ann Oncol.* 2018;29:iv192-iv237, *Lung Cancer.* 2019;130:201-7), and repotrectinib is a drug that inhibits *ROS1* kinase [see Section 3.R.1].

PMDA's view:

There were limitations to evaluate the efficacy of repotrectinib in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC based on results from the phase II part of the TRIDENT-1 study, which is handled as the pivotal study, in view of the following points:

- A relationship between overall survival (OS), the true endpoint, and the response rate remains unclear, and evaluating survival benefit of repotrectinib in the concerned patients based on results on the response rate, the primary endpoint in the phase II part of the TRIDENT-1 study, is difficult.
- The efficacy analysis results in the TRIDENT-1 study are difficult to interpret statistically [see Section 7.R.2.1].
- In consideration that the pre-determined sample sizes for EXP-2 to EXP-4 of the TRIDENT-1 study were not reached, possible overestimation cannot be ruled out for results in the concerned cohorts [see Section 7.R.2.1].

In view of the following points, however, repotrectinib was demonstrated to have a certain level of efficacy in patients with *ROS1* fusion gene-mutation-positive unresectable advanced or recurrent NSCLC, including Japanese patients:

- The response rate in EXP-1 of the TRIDENT-1 study is similar to those of conventional therapies in ROS1-TKI-naïve patients, and the concerned result is considered to be clinically meaningful.
- For the response rates in EXP-2 to EXP-4 of the TRIDENT-1 study, possible overestimation cannot be denied, and thus comparisons with conventional therapies have limitations. However, clinical meaningfulness is found in the response observed in patients who had received prior therapy with existing ROS1-TKIs and patients who had resistance mutations to ROS1-TKIs to a certain extent.
- The *ROS1* fusion gene is deemed as an oncogenic driver of *ROS1* fusion gene-positive NSCLC, and repotrectinib is a drug that inhibits ROS1.
- The response was observed in the Japanese patients as well, and no clear differences are observed in PK of repotrectinib between Japanese and non-Japanese patients [see Section 6.2.9].

7.R.3 Safety [for adverse events, see Section “7.3 Adverse events, etc. observed in clinical studies”]

PMDA’s view:

Based on the following review, adverse events requiring particular attention during treatment with repotrectinib in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC are interstitial lung disease (ILD) and central nervous system disorders. Special attention should be paid to these events during use of repotrectinib.

Although the above adverse events require attention during treatment, repotrectinib will be tolerable in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC as well when appropriate measures, such as monitoring of patients, management of adverse events, and dose interruption, dose reduction, and discontinuation of repotrectinib, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

7.R.3.1 Safety profile

The applicant’s explanation about the safety profile of repotrectinib based on the safety information obtained in the TRIDENT-1 study:

Table 35 shows the summary of the safety in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC who were included in the safety analysis in the TRIDENT-1 study and enrolled in the phase II part.

Table 35. Summary of safety (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

	n (%)	
	ROS1-TKI-naïve EXP-1 N = 107	ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205
All adverse events	107 (100)	203 (99.0)
Grade ≥ 3 adverse events	57 (53.3)	93 (45.4)
Adverse events leading to death*	2 (1.9)	10 (4.9)
Serious adverse events	38 (35.5)	61 (29.8)
Adverse events leading to treatment discontinuation	10 (9.3)	11 (5.4)
Adverse events leading to dose interruption	59 (55.1)	94 (45.9)
Adverse events leading to dose reduction	51 (47.7)	58 (28.3)

* Events were death and hypoxia in 1 patient each in EXP-1 as well as death, pneumonia aspiration, and dyspnoea in 2 patients each, and cardiac arrest, cardiac failure, disseminated intravascular coagulation, and sudden death in 1 patient each in EXP-2 to EXP-4.

Table 36 shows adverse events with a high incidence in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC who were included in the safety analysis in the TRIDENT-1 study and enrolled in the phase II part. There were neither adverse events leading to death nor adverse events leading to treatment discontinuation, reported by $\geq 2\%$ of subjects.

Table 36. Adverse events with a high incidence* (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

	n (%)	
	ROS1-TKI-naïve EXP-1 N = 107	ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205
All adverse events		
Dizziness	75 (70.1)	119 (58.0)
Dysgeusia	66 (61.7)	93 (45.4)
Constipation	49 (45.8)	66 (32.2)
Anaemia	45 (42.1)	72 (35.1)
Paraesthesia	45 (42.1)	62 (30.2)
Aspartate aminotransferase increased	31 (29.0)	40 (19.5)
Ataxia	31 (29.0)	34 (16.6)
Muscular weakness	30 (28.0)	39 (19.0)
Dyspnoea	29 (27.1)	53 (25.9)
Alanine aminotransferase increased	27 (25.2)	54 (26.3)
Weight increased	26 (24.3)	24 (11.7)
Blood creatine phosphokinase increased	22 (20.6)	32 (15.6)
Fatigue	19 (17.8)	43 (21.0)
Grade ≥ 3 adverse events		
Blood creatine phosphokinase increased	7 (6.5)	5 (2.4)
Anaemia	5 (4.7)	16 (7.8)
Dyspnoea	4 (3.7)	13 (6.3)
Serious adverse events		
Hypoxia	4 (3.7)	3 (1.5)
Pneumonitis	4 (3.7)	1 (0.5)
Pneumonia	3 (2.8)	8 (3.9)
Dyspnoea	2 (1.9)	6 (2.9)
Pleural effusion	2 (1.9)	9 (4.4)
Adverse events leading to dose interruption		
Blood creatine phosphokinase increased	10 (9.3)	3 (1.5)
Muscular weakness	9 (8.4)	10 (4.9)
Dizziness	7 (6.5)	13 (6.3)
Dyspnoea	7 (6.5)	12 (5.9)
Ataxia	6 (5.6)	5 (2.4)
Adverse events leading to dose reduction		
Muscular weakness	10 (9.3)	6 (2.9)
Dizziness	8 (7.5)	19 (9.3)
Ataxia	7 (6.5)	8 (3.9)
Blood creatine phosphokinase increased	7 (6.5)	2 (1.0)

* The events with the following incidence in either population are listed: All adverse events with $\geq 20\%$; Grade ≥ 3 adverse events with $\geq 5\%$; serious adverse events with $\geq 2\%$; adverse events leading to dose interruption with $\geq 5\%$; adverse events leading to dose reduction with $\geq 5\%$

PMDA's view:

The events listed under all adverse events with the high incidence in the TRIDENT-1 study are likely to occur during the treatment with repotrectinib, and patients should be carefully monitored during the treatment with a relationship to repotrectinib taken into account. However, most of the adverse events including Grade ≥ 3 adverse events and serious adverse events were manageable by dose interruption, dose reduction, and discontinuation of repotrectinib. In view of the above point, repotrectinib will be tolerable when appropriate measures, such as monitoring and management of adverse events, and dose interruption, dose reduction, and discontinuation of repotrectinib, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

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

The applicant's explanation about differences in safety of repotrectinib between Japanese and non-Japanese patients based on the safety information obtained in the TRIDENT-1 study:

Table 37 shows the safety in Japanese and non-Japanese patients with *ROS1* fusion gene-positive NSCLC who were included in the safety analysis in the TRIDENT-1 study and enrolled in the phase II part.

Table 37. Summary of safety in Japanese and non-Japanese patients (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

	n (%)	
	Japanese patients N = 11	Non-Japanese patients N = 301
All adverse events	11 (100)	299 (99.3)
Grade ≥ 3 adverse events	2 (18.2)	148 (49.2)
Adverse events leading to death	0	12 (4.0)
Serious adverse events	1 (9.1)	98 (32.6)
Adverse events leading to treatment discontinuation	0	21 (7.0)
Adverse events leading to dose interruption	6 (54.5)	147 (48.8)
Adverse events leading to dose reduction	7 (63.6)	102 (33.9)

Table 38 shows adverse events with a higher incidence in Japanese patients than in non-Japanese patients, in patient population with *ROS1* fusion gene-positive NSCLC enrolled in the phase II part of the TRIDENT-1 study. There were neither Grade ≥ 3 adverse events nor serious adverse events of which the incidence was $\geq 10\%$ higher in Japanese patients than in non-Japanese patients. Furthermore, neither adverse events leading to death nor adverse events leading to treatment discontinuation occurred in Japanese patients.

Table 38. Adverse events with a higher incidence in Japanese patients than in non-Japanese patients* (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut-off on December 19, 2022)

	n (%)	
	Japanese patients N = 11	Non-Japanese patients N = 301
All adverse events		
Nausea	4 (36.4)	52 (17.3)
Neuralgia	3 (27.3)	36 (12.0)
COVID-19	3 (27.3)	30 (10.0)
White blood cell count decreased	3 (27.3)	30 (10.0)
Oedema peripheral	3 (27.3)	28 (9.3)
Neutrophil count decreased	3 (27.3)	27 (9.0)
Adverse events leading to dose interruption		
Dizziness	2 (18.2)	18 (6.0)
Muscular weakness	2 (18.2)	17 (5.6)
Adverse events leading to dose reduction		
Dizziness	4 (36.4)	23 (7.6)
Muscular weakness	2 (18.2)	14 (4.7)

* The events with the following difference in incidence are listed: $\geq 15\%$ in all adverse events; $\geq 10\%$ in adverse events leading to dose interruption; $\geq 10\%$ in adverse events leading to dose reduction

PMDA's view:

The number of Japanese patients who received repotrectinib is limited, and comparison of the safety profile between Japanese and non-Japanese patients has limitations. The events with a higher incidence

in Japanese patients than in non-Japanese patients were observed in the TRIDENT-1 study, and thus attention should be paid to these events during the treatment with repotrectinib. However, repotrectinib will be tolerable in Japanese patients as well because (1) the incidences of serious adverse events and Grade ≥ 3 adverse events do not tend to be clearly higher in Japanese patients than in non-Japanese patients; and (2) repotrectinib is used by physicians with adequate knowledge and experience in cancer chemotherapy.

In the following sections, PMDA reviewed the safety results in the TRIDENT-1 study with a focus on adverse events with a higher incidence and adverse events requiring attention for use of crizotinib and entrectinibs, approved ROS-TKIs.

7.R.3.3 ILD

The applicant's explanation about ILD associated with repotrectinib:

Events classified into "interstitial lung disease (broad)," preferred terms (PTs) in the Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ), were tabulated as ILD.

Table 39 and Table 40 show incidences of ILD in the population of patients with *ROS1* fusion gene-positive NSCLC in the phase II part in the safety analysis population in the TRIDENT-1 study. The median time to the first onset of ILD (minimum, maximum) (days) in the TRIDENT-1 study was 34 (19, 197) in EXP-1 and 111.5 (29, 356) in EXP-2 to EXP-4.

Table 39. Incidences of ILD (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

PT (MedDRA ver.25.0)	Number of patients (%)			
	ROS1-TKI-naïve EXP-1 n = 107		ROS1-TKI-prior-treated EXP-2 to EXP-4 n = 205	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
ILD*	5 (4.7)	3 (2.8)	6 (2.9)	1 (0.5)
Pneumonitis	4 (3.7)	3 (2.8)	5 (2.4)	1 (0.5)
Bronchiolitis	1 (0.9)	0	0	0
Pulmonary granuloma	0	0	1 (0.5)	0

* Total number of events to be tabulated

Table 40. Incidences of serious ILD (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

PT (MedDRA ver.25.0)	Number of patients (%)	
	ROS1-TKI-naïve EXP-1 n = 107	ROS1-TKI-prior-treated EXP-2 to EXP-4 n = 205
Fatal ILD	0	0
Serious ILD	4 (3.7)	1 (0.5)
Pneumonitis	4 (3.7)	1 (0.5)
Serious ILD for which a causal relationship to repotrectinib could not be ruled out	3 (2.8)	1 (0.5)
Pneumonitis	3 (2.8)	1 (0.5)
ILD leading to treatment discontinuation	2 (1.9)	1 (0.5)
Pneumonitis	2 (1.9)	1 (0.5)
ILD leading to dose interruption	4 (3.7)	2 (1.0)
Pneumonitis	4 (3.7)	2 (1.0)
ILD leading to dose reduction	1 (0.9)	1 (0.5)
Pneumonitis	1 (0.9)	1 (0.5)

Table 41 shows details of the patients with serious ILD for which a causal relationship to repotrectinib could not be ruled out in the TRIDENT-1 study. In clinical studies of repotrectinib and foreign post-marketing use,⁵⁵⁾ no fatal ILD has occurred.

Table 41. List of patients with serious ILD for which a causal relationship to repotrectinib could not be ruled out (TRIDENT-1 study)

Age	Sex	Race	Cancer type	PT (MedDRA ver.26.1)	Grade	Time to onset (Day)	Duration (Day)	Action on repotrectinib	Outcome
5	Male	Non-Japanese	NSCLC	Pneumonitis	2	34	11	Dose interruption	Resolved
7	Male	Non-Japanese	NSCLC	Pneumonitis	3	42	8	Discontinuation	Resolved
4	Male	Non-Japanese	Solid tumor	Pneumonitis	3	34	9	Discontinuation	Resolved
4	Male	Non-Japanese	NSCLC	Pneumonitis	3	29	3	Dose interruption	Resolved
5	Male	Non-Japanese	NSCLC	Pneumonitis	2	48	9	Dose interruption	Resolved

Patients should be instructed to visit medical institutions immediately if they experience initial symptoms of ILD such as shortness of breath and cough associated with repotrectinib. In addition, repotrectinib should be discontinued if ILD occurs. The concerned information will be included in the package insert to raise cautions.

PMDA's view:

For use of repotrectinib, attention should be paid to onset of ILD because (1) serious ILD for which a causal relationship to repotrectinib could not be ruled out occurred in the TRIDENT-1 study; and (2) ILD is a risk known for crizotinib, which is ROS1-TKI as with repotrectinib. The package insert, etc. should include the incidence of ILD in clinical studies and actions to be taken on ILD to raise cautions appropriately among healthcare professionals.

7.R.3.4 Central nervous system disorders

The applicant's explanation about central nervous system disorders associated with repotrectinib:

Adverse events classified into MedDRA SMQ of "convulsions (narrow)," HLGTS of "disturbances in thinking and perception," "cognitive and attention disorders and disturbances," "dementia and amnesic conditions," "neurological disorders NEC," and "delirium (incl confusion)," PTs in HLT of "mental disorders NEC," and PT of "Fall" were tabulated as central nervous system disorders.

Table 42 and Table 43 show incidences of central nervous system disorders in patients with *ROS1* fusion gene-positive NSCLC in the phase II part in the safety analysis population in the TRIDENT-1 study. The median time to the first onset of central nervous system disorder (minimum, maximum) (days) in the TRIDENT-1 study was 3 (1, 281) in EXP-1 and 7 (1, 120) in EXP-2 to EXP-4.

⁵⁵⁾ Based on the safety information in 731 subjects enrolled in clinical studies of repotrectinib and foreign post-marketing use in 9 patients

Table 42. Incidences of central nervous system disorders reported by $\geq 2\%$ of subjects in either population (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

PT (MedDRA ver.25.0)	n (%)			
	ROS1-TKI-naïve EXP-1 N = 107		ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Central nervous system disorders*	99 (92.5)	10 (9.3)	180 (87.8)	11 (5.4)
Dizziness	75 (70.1)	2 (1.9)	119 (58.0)	3 (1.5)
Dysgeusia	66 (61.7)	0	93 (45.4)	0
Paraesthesia	45 (42.1)	2 (1.9)	62 (30.2)	0
Ataxia	31 (29.0)	1 (0.9)	34 (16.6)	0
Memory impairment	19 (17.8)	0	24 (11.7)	1 (0.5)
Neuralgia	12 (11.2)	0	27 (13.2)	0
Disturbance in attention	10 (9.3)	0	25 (12.2)	0
Cognitive disorder	7 (6.5)	0	15 (7.3)	0
Somnolence	6 (5.6)	0	20 (9.8)	0
Hypoaesthesia oral	6 (5.6)	0	10 (4.9)	0
Vertigo	6 (5.6)	0	5 (2.4)	0
Hyperaesthesia	6 (5.6)	0	3 (1.5)	0
Paraesthesia oral	5 (4.7)	0	9 (4.4)	0
Balance disorder	5 (4.7)	0	6 (2.9)	0
Fall	4 (3.7)	2 (1.9)	4 (2.0)	0
Gait disturbance	4 (3.7)	0	12 (5.9)	1 (0.5)
Syncope	3 (2.8)	3 (2.8)	4 (2.0)	4 (2.0)
Taste disorder	3 (2.8)	0	7 (3.4)	0
Dysphonia	3 (2.8)	0	5 (2.4)	0
Ageusia	3 (2.8)	0	0	0
Hypoaesthesia	2 (1.9)	0	9 (4.4)	0
Oral dysaesthesia	2 (1.9)	0	4 (2.0)	0
Dysaesthesia	2 (1.9)	0	4 (2.0)	0

* Total number of events to be tabulated

Table 43. Incidences of serious central nervous system disorders (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

PT (MedDRA ver.25.0)	n (%)	
	ROS1-TKI-naïve EXP-1 N = 107	ROS1-TKI-prior- treated EXP-2 to EXP-4 N = 205
Fatal central nervous system disorders	0	0
Serious central nervous system disorders	2 (1.9)	7 (3.4)
Ataxia	2 (1.9)	0
Fall	1 (0.9)	0
Syncope	0	3 (1.5)
Seizure	0	2 (1.0)
Altered state of consciousness	0	1 (0.5)
Dizziness	0	1 (0.5)
Serious central nervous system disorders for which a causal relationship to repotrectinib could not be ruled out	1 (0.9)	2 (1.0)
Ataxia	1 (0.9)	0
Fall	1 (0.9)	0
Dizziness	0	1 (0.5)
Seizure	0	1 (0.5)
Central nervous system disorders leading to treatment discontinuation	0	2 (1.0)
Depressed level of consciousness	0	1 (0.5)
Balance disorder	0	1 (0.5)
Central nervous system disorders leading to dose interruption*	15 (14.0)	27 (13.2)
Dizziness	7 (6.5)	13 (6.3)
Ataxia	6 (5.6)	5 (2.4)
Paraesthesia	1 (0.9)	2 (1.0)
Confusional state	0	2 (1.0)
Syncope	0	2 (1.0)
Central nervous system disorders leading to dose reduction*	23 (21.5)	33 (16.1)
Dizziness	8 (7.5)	19 (9.3)
Ataxia	7 (6.5)	8 (3.9)
Paraesthesia	2 (1.9)	3 (1.5)
Gait disturbance	2 (1.9)	2 (1.0)
Balance disorder	2 (1.9)	1 (0.5)
Dysgeusia	2 (1.9)	0
Memory impairment	1 (0.9)	2 (1.0)

* Events reported by $\geq 1\%$ of subjects in either population

Table 44 shows details of the patients with serious central nervous system disorders for which a causal relationship to repotrectinib could not be ruled out in clinical studies of repotrectinib and foreign post-marketing use.⁵⁵⁾

Table 44. List of patients with serious central nervous system disorders for which a causal relationship to repotrectinib could not be ruled out

Study	Age	Sex	PT (MedDRA ver.26.1)	Grade	Time to onset (Day)	Duration (Day)	Action on repotrectinib	Outcome
TRIDENT-1	4	Female	Dizziness	3	1,367	3	Dose interruption	Resolved
	7	Female	Dizziness	3	198	4	Dose interruption	Resolved
	3	Male	Seizure	2	1	3	Dose reduction, Dose interruption	Resolved
	6	Male	Dizziness	3	66	3	Dose reduction	Resolved
	5	Female	Syncope	3	27	2	Dose interruption	Resolved
	8	Female	Ataxia	2	200	103	Unchanged	Resolved
			Fall	3	200	1	Unchanged	Resolved
	4	Female	Dizziness	3	2	3	Dose reduction, Dose interruption	Resolved
	7	Male	Depressed level of consciousness	3	20	14	Dose reduction, Dose interruption	Not resolved
	6	Female	Paraesthesia oral	2	37	2	Dose reduction, Dose interruption	Resolved
	6	Female	Dizziness	3	13	16	Dose reduction, Dose interruption	Resolved
CARE	1	Female	Pharyngeal paraesthesia	2	34	2	Unchanged	Resolved
			Dizziness	2	42	6	Unchanged	Resolved

CARE study: Phase I/II study in pediatric or adult patients with malignant tumor harboring *ALK*, *ROS1*, or *NTRK* gene abnormalities

The package insert will include the cautionary statement that if a central nervous system disorder such as dizziness, ataxia, or cognitive disorder occurs after treatment with repotrectinib, repotrectinib should be interrupted, reduced in dose, or discontinued according to the criteria for dose interruption, dose reduction, and discontinuation, which are specified based on the criteria in the TRIDENT-1 study [see Section 7.R.5.2].

PMDA's view:

Considering that serious central nervous system disorders for which a causal relationship to repotrectinib could not be ruled out occurred in clinical studies of repotrectinib, attention should be paid to onset of a central nervous system disorder following administration of repotrectinib. The package insert, etc. should include the incidence of central nervous system disorders in clinical studies and actions to be taken on central nervous system disorders to raise cautions appropriately among healthcare professionals.

7.R.3.5 Others

(a) Hepatic dysfunction

The applicant's explanation about hepatic dysfunction associated with repotrectinib:

Adverse events classified into "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (broad)," "hepatitis, non-infectious (broad)," "liver related investigations, signs and symptoms (broad)," "liver-related coagulation and bleeding disturbances (narrow)," and "cholestasis and jaundice of hepatic origin (narrow)," PTs in MedDRA SMQs, were tabulated as hepatic dysfunction.

Table 45 and Table 46 show incidences of hepatic dysfunction in patients with *ROS1* fusion gene-positive NSCLC in the phase II part in the safety analysis population in the TRIDENT-1 study. The median time to the first onset of hepatic dysfunction (minimum, maximum) (days) in the TRIDENT-1 study was 16 (1, 562) in EXP-1 and 14 (1, 729) in EXP-2 to EXP-4.

Table 45. Incidences of hepatic dysfunction (phase II part of the TRIDENT-1 study, patients with *ROS1* fusion gene-positive NSCLC, data cut-off on December 19, 2022)

PT (MedDRA ver.25.0)	n (%)			
	ROS1-TKI-naïve EXP-1 N = 107		ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic dysfunction*	45 (42.1)	7 (6.5)	70 (34.1)	9 (4.4)
Aspartate aminotransferase increased	31 (29.0)	2 (1.9)	40 (19.5)	3 (1.5)
Alanine aminotransferase increased	27 (25.2)	2 (1.9)	54 (26.3)	4 (2.0)
Gamma-glutamyltransferase increased	8 (7.5)	2 (1.9)	14 (6.8)	1 (0.5)
Blood alkaline phosphatase increased	7 (6.5)	1 (0.9)	15 (7.3)	1 (0.5)
Hypoalbuminaemia	3 (2.8)	0	7 (3.4)	1 (0.5)
Prothrombin time prolonged	3 (2.8)	0	0	0
Hepatic function abnormal	2 (1.9)	1 (0.9)	1 (0.5)	0
Hypertransaminasaemia	2 (1.9)	0	1 (0.5)	0
International normalised ratio increased	2 (1.9)	0	1 (0.5)	0
Hepatic cytolysis	1 (0.9)	1 (0.9)	0	0
Blood fibrinogen decreased	1 (0.9)	0	0	0
Hepatitis	1 (0.9)	0	0	0
Blood bilirubin increased	0	0	3 (1.5)	1 (0.5)
Ascites	0	0	1 (0.5)	1 (0.5)
Bilirubin conjugated increased	0	0	1 (0.5)	0
Blood bilirubin unconjugated increased	0	0	1 (0.5)	0

* Total number of events to be tabulated

Table 46. Incidences of serious hepatic dysfunction (phase II part of the TRIDENT-1 study, patients with *ROS1* fusion gene-positive NSCLC, data cut-off on December 19, 2022)

PT (MedDRA ver.25.0)	n (%)	
	ROS1-TKI-naïve EXP-1 N = 107	ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205
Fatal hepatic dysfunction	0	0
Serious hepatic dysfunction	0	1 (0.5)
Ascites	0	1 (0.5)
Blood bilirubin increased	0	1 (0.5)
Serious hepatic dysfunction for which a causal relationship to repotrectinib could not be ruled out	0	0
Hepatic dysfunction leading to treatment discontinuation	0	1 (0.5)
Blood alkaline phosphatase increased	0	1 (0.5)
Hepatic dysfunction leading to dose interruption	3 (2.8)	9 (4.4)
Alanine aminotransferase increased	2 (1.9)	5 (2.4)
Aspartate aminotransferase increased	2 (1.9)	2 (1.0)
Gamma-glutamyltransferase increased	1 (0.9)	2 (1.0)
Hepatic cytolysis	1 (0.9)	0
Blood bilirubin increased	0	1 (0.5)
Hepatic function abnormal	0	1 (0.5)
Hepatic dysfunction leading to dose reduction	2 (1.9)	1 (0.5)
Alanine aminotransferase increased	2 (1.9)	0
Aspartate aminotransferase increased	1 (0.9)	0
Gamma-glutamyltransferase increased	1 (0.9)	0
Blood bilirubin increased	0	1 (0.5)

Table 47 shows details of the patients with serious hepatic dysfunction for which a causal relationship to repotrectinib could not be ruled out in clinical studies of repotrectinib and foreign post-marketing use.⁵⁵⁾

Table 47. List of patients with serious hepatic dysfunction for which a causal relationship to repotrectinib could not be ruled out

Study	Age	Sex	PT (MedDRA ver.26.1)	Grade	Time to onset (Day)	Duration (Day)	Action on repotrectinib	Outcome
TRIDENT-1	41	Male	Hepatic function abnormal	2	15	2	Unchanged	Not resolved
			Hepatic function abnormal	1	17	4	Unchanged	Not resolved

(b) QT prolonged

The applicant's explanation about QT prolonged associated with repotrectinib:

Adverse events classified into "torsade de pointes/QT prolongation (narrow)," PTs in MedDRA SMQ, were tabulated as QT prolonged.

Table 48 shows incidences of QT prolonged in patients with *ROS1* fusion gene-positive NSCLC in the phase II part in the safety analysis population in the TRIDENT-1 study. The median time to the first onset of QT prolonged (minimum, maximum) (days) in the TRIDENT-1 study was 14 (14, 14) in EXP-1 and 29 (15, 307) in EXP-2 to EXP-4.

Table 48. Incidences of QT prolonged (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

PT (MedDRA ver.25.0)	n (%)			
	ROS1-TKI-naïve EXP-1 N = 107		ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205	
	All Grades	Grade ≥3	All Grades	Grade ≥3
QT prolonged*	1 (0.9)	0	3 (1.5)	0
Electrocardiogram QT prolonged	1 (0.9)	0	3 (1.5)	0

* Total number of events to be tabulated

None of fatal QT prolonged, serious QT prolonged, and QT prolonged leading to treatment discontinuation, dose interruption, or dose reduction occurred in patients with *ROS1* fusion gene-positive NSCLC in the phase II part in the safety analysis population in the TRIDENT-1 study.

Table 49 shows changes in QTcF associated with repotrectinib in patients with *ROS1* fusion gene-positive NSCLC in the phase II part of the TRIDENT-1 study. Of patients with the changed QTcF, none experienced symptoms related to serious QT prolonged.

Table 49. Changes in QTcF associated with repotrectinib (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut-off on December 19, 2022)

	n (%)	
	ROS1-TKI-naïve EXP-1 N = 107	ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205
Maximum		
>480 ms	0	2 (1.0)
>500 ms	0	1 (0.5)
>550 ms	0	0
Increase from baseline (maximum)		
>30 ms	25 (23.4)	30 (14.6)
>60 ms	2 (1.9)	3 (1.5)
>100 ms	0	0
Increase from baseline (mean maximum) [90% CI]	21.9[19.6, 24.2]	19.1[17.4, 20.7]

No serious arrhythmia (torsade de pointes, ventricular tachycardia, ventricular fibrillation or ventricular flutter) occurred in clinical studies of repotrectinib or foreign post-marketing use.⁵⁵⁾

(c) Blood disorders

The applicant's explanation about blood disorders associated with repotrectinib:

Adverse events classified into PTs in MedDRA HLGT of "haemolyses and related conditions" and MedDRA PTs of "anaemia," "blood loss anaemia," "bone marrow failure," "eosinophilia," "febrile neutropenia," "iron deficiency anaemia," "leukocytosis," "leukopenia," "lymphadenopathy," "lymphocytosis," "lymphopenia," "neutropenia," "pancytopenia," "thrombocytopenia," "thrombocytosis," "eosinophil count increased," "haematocrit decreased," "haemoglobin decreased," "lymphocyte count decreased," "mean cell volume increased," "monocyte count increased," "neutrophil count decreased," "neutrophil count increased," "platelet count decreased," "platelet count increased," "red blood cell count decreased," "white blood cell count decreased," "white blood cell count increased," "haemoglobin increased," and "lymphocyte count increased" were tabulated as blood disorder.

Table 50 and Table 51 show incidences of blood disorders in patients with *ROS1* fusion gene-positive NSCLC in the phase II part in the safety analysis population in the TRIDENT-1 study. The median time to the first onset of blood disorder (minimum, maximum) (days) in the TRIDENT-1 study was 42 (1, 925) in EXP-1 and 22 (1, 307) in EXP-2 to EXP-4.

Table 50. Incidences of blood disorders reported by $\geq 1\%$ of subjects in either population (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

PT (MedDRA ver.25.0)	n (%)			
	ROS1-TKI-naïve EXP-1 N = 107		ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Blood disorders*	63 (58.9)	12 (11.2)	87 (42.4)	21 (10.2)
Anaemia	45 (42.1)	5 (4.7)	72 (35.1)	16 (7.8)
Neutrophil count decreased	13 (12.1)	4 (3.7)	17 (8.3)	5 (2.4)
White blood cell count decreased	12 (11.2)	2 (1.9)	21 (10.2)	2 (1.0)
Platelet count increased	9 (8.4)	1 (0.9)	8 (3.9)	0
Lymphocyte count decreased	3 (2.8)	0	9 (4.4)	0
Neutropenia	3 (2.8)	0	2 (1.0)	1 (0.5)
Haemoglobin decreased	2 (1.9)	1 (0.9)	3 (1.5)	0
Thrombocytopenia	1 (0.9)	1 (0.9)	2 (1.0)	0
Thrombocytosis	1 (0.9)	0	4 (2.0)	0
Lymphopenia	1 (0.9)	0	3 (1.5)	0
Neutrophil count increased	1 (0.9)	0	2 (1.0)	0
Platelet count decreased	0	0	3 (1.5)	1 (0.5)

* Total number of events to be tabulated

Table 51. Incidences of serious blood disorders (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

PT (MedDRA ver.25.0)	n (%)	
	ROS1-TKI-naïve EXP-1 N = 107	ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205
Fatal blood disorders	0	0
Serious blood disorders	2 (1.9)	3 (1.5)
Anaemia	1 (0.9)	2 (1.0)
Thrombocytopenia	1 (0.9)	0
Bone marrow failure	0	1 (0.5)
Serious blood disorders for which a causal relationship to repotrectinib could not be ruled out	0	2 (1.0)
Anaemia	0	2 (1.0)
Blood disorders leading to treatment discontinuation	1 (0.9)	0
Neutrophil count decreased	1 (0.9)	0
Blood disorders leading to dose interruption	8 (7.5)	9 (4.4)
Neutrophil count decreased	4 (3.7)	2 (1.0)
Anaemia	2 (1.9)	5 (2.4)
White blood cell count decreased	2 (1.9)	1 (0.5)
Platelet count increased	1 (0.9)	0
Neutropenia	0	1 (0.5)
Thrombocytosis	0	1 (0.5)
Blood disorders leading to dose reduction	2 (1.9)	4 (2.0)
Neutrophil count decreased	1 (0.9)	1 (0.5)
Platelet count increased	1 (0.9)	0
Anaemia	0	2 (1.0)
Neutropenia	0	1 (0.5)

Table 52 shows details of the patients with serious blood disorders for which a causal relationship to repotrectinib could not be ruled out in clinical studies of repotrectinib and foreign post-marketing use.⁵⁵⁾

Table 52. List of patients with serious blood disorders for which a causal relationship to repotrectinib could not be ruled out

Study	Age	Sex	PT (MedDRA ver.26.1)	Grade	Time to onset (Day)	Duration (Day)	Action on repotrectinib	Outcome
TRIDENT-1	5	Female	Anaemia	3	265	3	Unchanged	Resolved
			Anaemia	2	94	2	Not applicable*	Resolved
	4	Female	Anaemia	2	182	3	Unchanged	Resolved
			Anaemia	2	227	2	Unchanged	Resolved
			Anaemia	2	254	3	Unchanged	Resolved
	7	Female	Anaemia	3	43	1	Dose interruption	Not resolved
			Anaemia	2	44	2	Dose reduction	Not resolved
	5	Female	Platelet count increased	2	34	2	Unchanged	Resolved

* Repotrectinib was interrupted before onset of the concerned event.

(d) Blood creatine phosphokinase increased

The applicant's explanation about blood creatine phosphokinase increased associated with repotrectinib: Adverse events classified into PTs in MedDRA SMQ of "rhabdomyolysis/myopathy (broad)" and MedDRA PTs of "blood creatine phosphokinase MB increased," "blood creatine phosphokinase decreased," "blood creatine phosphokinase increased," "hypercreatinemia," "muscle spasms," "muscle tightness," "muscle twitching," "muscular weakness," "musculoskeletal discomfort," "musculoskeletal pain," "myalgia," "myopathy," "myositis," "torticollis," "trismus," and "muscle fatigue" were tabulated as blood creatine phosphokinase increased.

Table 53 and Table 54 show incidences of blood creatine phosphokinase increased in patients with *ROS1* fusion gene-positive NSCLC in the phase II part in the safety analysis population in TRIDENT-1 the study. The median time to the first onset of blood creatine phosphokinase increased (minimum, maximum) (days) in the TRIDENT-1 study was 28 (1, 895) in EXP-1 and 39 (1, 731) in EXP-2 to EXP-4.

Table 53. Incidences of blood creatine phosphokinase increased reported by ≥1% of subjects in either population (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

PT (MedDRA ver.25.0)	n (%)			
	ROS1-TKI-naïve EXP-1 N = 107		ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Blood creatine phosphokinase increased*	57 (53.3)	12 (11.2)	85 (41.5)	13 (6.3)
Muscular weakness	30 (28.0)	3 (2.8)	39 (19.0)	4 (2.0)
Blood creatine phosphokinase increased	22 (20.6)	7 (6.5)	32 (15.6)	5 (2.4)
Myalgia	13 (12.1)	1 (0.9)	15 (7.3)	1 (0.5)
Blood creatinine increased	4 (3.7)	0	6 (2.9)	1 (0.5)
Hypocalcaemia	3 (2.8)	0	5 (2.4)	0
Myopathy	2 (1.9)	0	1 (0.5)	1 (0.5)
Muscle twitching	2 (1.9)	0	1 (0.5)	0
Muscle spasms	1 (0.9)	0	3 (1.5)	1 (0.5)
Musculoskeletal discomfort	1 (0.9)	0	3 (1.5)	0
Musculoskeletal pain	1 (0.9)	0	3 (1.5)	0

* Total number of events to be tabulated

Table 54. Incidences of serious blood creatine phosphokinase increased (phase II part of the TRIDENT-1 study, population of patients with ROS1 fusion gene-positive NSCLC, data cut off on December 19, 2022)

PT (MedDRA ver.25.0)	n (%)	
	ROS1-TKI- naïve EXP-1 N = 107	ROS1-TKI-prior- treated EXP-2 to EXP-4 N = 205
Fatal blood creatine phosphokinase increased	0	0
Serious blood creatine phosphokinase increased	1 (0.9)	3 (1.5)
Muscular weakness	1 (0.9)	2 (1.0)
Renal failure	0	1 (0.5)
Serious blood creatine phosphokinase increased for which a causal relationship to repotrectinib could not be ruled out	1 (0.9)	2 (1.0)
Muscular weakness	1 (0.9)	1 (0.5)
Renal failure	0	1 (0.5)
Blood creatine phosphokinase increased leading to treatment discontinuation	2 (1.9)	1 (0.5)
Muscular weakness	2 (1.9)	1 (0.5)
Blood creatine phosphokinase increased leading to dose interruption	18 (16.8)	18 (8.8)
Blood creatine phosphokinase increased	10 (9.3)	3 (1.5)
Muscular weakness	9 (8.4)	10 (4.9)
Myalgia	1 (0.9)	2 (1.0)
Blood creatinine increased	1 (0.9)	0
Muscle rupture	1 (0.9)	0
Myositis	1 (0.9)	0
Muscle spasms	0	1 (0.5)
Myopathy	0	1 (0.5)
Renal failure	0	1 (0.5)
Blood creatine phosphokinase increased leading to dose reduction	18 (16.8)	11 (5.4)
Muscular weakness	10 (9.3)	6 (2.9)
Blood creatine phosphokinase increased	7 (6.5)	2 (1.0)
Blood creatinine increased	1 (0.9)	2 (1.0)
Myopathy	0	1 (0.5)

Table 55 shows details of the patients with serious blood creatine phosphokinase increased for which a causal relationship to repotrectinib could not be ruled out in clinical studies of repotrectinib and foreign post-marketing use.⁵⁵⁾

Table 55. List of patients with serious blood creatine phosphokinase increased

Study	Age	Sex	PT (MedDRA ver.26.1)	Grade	Time to onset (Day)	Duration (Day)	Action on repotrectinib	Causal relationship	Outcome
TRIDENT -1	61	Female	Muscular weakness	2	60	2	Dose interruption	Related	Resolved
	61	Male	Muscular weakness	2	94	5	Discontinuation	Related	Resolved
	61	Female	Muscular weakness	2	37	2	Dose reduction, dose interruption	Related	Resolved
	61	Male	Muscular weakness	2	45	7	Dose interruption	Related	Resolved
			Muscular weakness	3	75	5	Discontinuation	Related	Resolved
	51	Female	Renal failure	3	288	17	Dose interruption	Related	Resolved

(e) Cardiac disorders (except QT prolonged)

The applicant's explanation about cardiac disorders (except QT prolonged) (hereinafter, "cardiac disorders") associated with repotrectinib:

Adverse events classified into PTs in MedDRA SOC of "cardiac disorders" were tabulated as cardiac disorders.

Table 56 and Table 57 show incidences of cardiac disorders in patients with *ROS1* fusion gene-positive NSCLC in the phase II part in the safety analysis population in the TRIDENT-1 study. The median time to the first onset of cardiac disorder (minimum, maximum) (days) in the TRIDENT-1 study was 57 (1, 481) in EXP-1 and 32.5 (1, 337) in EXP-2 to EXP-4.

Table 56. Incidences of cardiac disorders reported by $\geq 1\%$ of subjects in either population (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

PT (MedDRA ver.25.0)	n (%)			
	ROS1-TKI-naïve EXP-1 N = 107		ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Cardiac disorders*	15 (14.0)	4 (3.7)	20 (9.8)	5 (2.4)
Pericardial effusion	6 (5.6)	3 (2.8)	2 (1.0)	2 (1.0)
Sinus tachycardia	2 (1.9)	0	3 (1.5)	0
Sinus bradycardia	2 (1.9)	0	2 (1.0)	0
Atrial fibrillation	2 (1.9)	0	0	0
Bradycardia	2 (1.9)	0	0	0
Myocardial ischaemia	1 (0.9)	0	2 (1.0)	1 (0.5)
Tachycardia	0	0	5 (2.4)	0
Cardiac failure	0	0	3 (1.5)	2 (1.0)

* Total number of events to be tabulated

Table 57. Incidences of serious cardiac disorders (phase II part of the TRIDENT-1 study, population of patients with *ROS1* fusion gene-positive NSCLC, data cut off on December 19, 2022)

PT (MedDRA ver.25.0)	n (%)	
	ROS1-TKI-naïve EXP-1 N = 107	ROS1-TKI-prior-treated EXP-2 to EXP-4 N = 205
Fatal cardiac disorders	0	2 (1.0)
Cardiac arrest	0	1 (0.5)
Cardiac failure	0	1 (0.5)
Fatal cardiac disorders for which a causal relationship to repotrectinib could not be ruled out	0	0
Serious cardiac disorders	3 (2.8)	5 (2.4)
Pericardial effusion	2 (1.9)	2 (1.0)
Endocarditis noninfective	1 (0.9)	0
Cardiac arrest	0	1 (0.5)
Cardiac failure	0	1 (0.5)
Cardiac tamponade	0	1 (0.5)
Serious cardiac disorders (causally related to the study drug)	1 (0.9)	2 (1.0)
Pericardial effusion	1 (0.9)	2 (1.0)
Cardiac disorders leading to treatment discontinuation	1 (0.9)	1 (0.5)
Pericardial effusion	1 (0.9)	0
Cardiac septal hypertrophy	1 (0.9)	0
Cardiac arrest	0	1 (0.5)
Cardiac disorders leading to dose interruption	2 (1.9)	2 (1.0)
Pericardial effusion	2 (1.9)	1 (0.5)
Cardiac tamponade	0	1 (0.5)
Cardiac disorders leading to dose reduction	1 (0.9)	1 (0.5)
Pericardial effusion	1 (0.9)	1 (0.5)

Table 58 shows details of the patients with serious cardiac disorders for which a causal relationship to repotrectinib could not be ruled out in clinical studies of repotrectinib and foreign post-marketing use.⁵⁵⁾

Table 58. List of patients with serious cardiac disorders for which a causal relationship to repotrectinib could not be ruled out

Study	Age	Sex	PT (MedDRA ver.26.1)	Grade	Time to onset (Day)	Duration (Day)	Action on repotrectinib	Outcome
TRIDENT-1	3	Female	Pericardial effusion	4	57	6	Dose reduction, Dose interruption	Resolved
	6	Male	Pericardial effusion	3	43	7	Dose interruption	Resolved
	7	Female	Pericardial effusion	2	55	7	Not applicable*	Not resolved
			Pericardial effusion	3	62	1	Not applicable*	Resolved
	5	Male	Cardio-respiratory arrest	5	331	2	Unchanged	Death

* Treatment with repotrectinib was discontinued before onset of the concerned event.

PMDA's views on the above (a) to (e):

- (a) Serious events of hepatic dysfunction for which a causal relationship to repotrectinib could not be ruled out occurred in clinical studies of repotrectinib. However, occurrences of the observed serious hepatic dysfunction, Grade ≥ 3 hepatic dysfunction, and hepatic dysfunction leading to treatment discontinuation were limited. In view of this finding, special cautions are unnecessary to raise at the present time, on the premise that the incidences of hepatic dysfunction in clinical studies will be included in the package insert and other materials to provide the information.
- (b) The number of subjects with QT prolonged in the clinical studies in the submitted data was limited, and no serious arrhythmia occurred. Thus, special cautions about QT prolonged are considered unnecessary to raise at the present time.
- (c) Although serious events of blood disorders for which a causal relationship to repotrectinib could not be ruled out occurred in the clinical studies in the submitted data, most of the observed events resolved in the short term, and many of them were at Grade ≤ 2 . In view of these findings, special cautions are unnecessary to raise at the present time, on the premise that the incidences of blood disorders in clinical studies will be included in the package insert and other materials to provide the information.
- (d) Serious events of blood creatine phosphokinase increased for which a causal relationship to repotrectinib could not be ruled out occurred in clinical studies in the submitted data. However, the Grade ≥ 3 events for which a causal relationship to repotrectinib could not be ruled out are limited, and many of the events resolved after dose interruption, dose reduction, or other measures. In view of these findings, special cautions are unnecessary to raise at the present time, on the premise that the incidences of blood creatine phosphokinase increased in clinical studies will be included in the package insert, etc. to provide the information.
- (e) Serious events of cardiac disorders (except QT prolonged) for which a causal relationship to repotrectinib could not be ruled out occurred in clinical studies in the submitted data, but effects of the primary disease, etc. were possibly involved. In view of this point, special cautions are unnecessary to raise at the present time, on the premise that the incidences of cardiac disorders in clinical studies will be included in the package insert and other materials to provide the information.

7.R.4 Clinical positioning and indication

The proposed indication of repotrectinib was “*ROS1* fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer.” The following statements had been proposed for the Precautions Concerning Indications section:

- Repotrectinib should be used in patients who are confirmed to test positive for *ROS1* fusion gene by adequately experienced pathologists or testing at qualified laboratories. The testing should be performed using approved *in vitro* diagnostics or medical devices.
- The efficacy and safety of repotrectinib have not been established for use in adjuvant chemotherapy.

As a result of the review in Sections “7.R.2 Efficacy,” “7.R.3 Safety,” and the following subsections, PMDA has concluded that the indication of repotrectinib should be “*ROS1* fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer” as proposed, with the following cautionary statements included in the Precautions Concerning Indications section:

- Repotrectinib should be used in patients who are confirmed to test positive for *ROS1* fusion gene by adequately experienced pathologists or testing at qualified laboratories. The testing should be performed using approved *in vitro* diagnostics or medical devices.
- The efficacy and safety of repotrectinib have not been established for use in neo-adjuvant and adjuvant chemotherapy.

7.R.4.1 Clinical positioning of repotrectinib and intended population

Japanese clinical practice guidelines and representative textbooks on clinical oncology were found to have no descriptions about use of repotrectinib for treatment of patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC. On the other hand, representative foreign clinical practice guidelines were found to include the following descriptions about use of repotrectinib for the treatment of patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC:

Clinical practice guidelines

- National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer (NCCN guidelines) (v.2.2024):
 - Repotrectinib is recommended as the first-line treatment in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC.
 - Repotrectinib is recommended for patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC who have received prior-therapy with entrectinib, crizotinib, or ceritinib.
- Oncogene-addicted metastatic non-small cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up (European Society for Medical Oncology [ESMO] guideline) (2023):
 - Repotrectinib is one of the first-line treatment options for patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC.
 - Repotrectinib is one of treatment options for patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC who have received prior-therapy with crizotinib.

The applicant's explanation about the intended population and clinical positioning of repotrectinib: In the phase II part of the TRIDENT-1 study, repotrectinib was demonstrated to have clinical usefulness in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC, irrespective of prior-therapy with *ROS1*-TKIs [see Sections 7.R.2 and 7.R.3]. The concerned patients can form the intended population of repotrectinib.

However, repotrectinib is not recommended for adjuvant chemotherapy because no clinical study results for the efficacy and safety of repotrectinib are available for use in adjuvant chemotherapy.

Based on the above, the proposed indication was specified as “*ROS1* fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer,” with the following cautionary statements included in the Precautions Concerning Indications section.

- The efficacy and safety of repotrectinib have not been established for use in adjuvant chemotherapy.

In addition, no clinical study results on the efficacy and safety of repotrectinib in comparison with (1) crizotinib or entrectinib or (2) cytotoxic antineoplastic agents are available. A definite conclusion on the choice between repotrectinib and these drugs for patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC who (1) are *ROS1*-TKI-naïve or (2) have received prior-therapy with *ROS1*-TKI remains unclear at the present time. The choice will be made in consideration of the safety profile and other profiles of each drug.

PMDA's view:

PMDA largely accepted the applicant's explanation. Japanese and foreign clinical practice guidelines recommend neo-adjuvant chemotherapy for NSCLC, but no clinical study results on the efficacy and safety of repotrectinib are available for use in neo-adjuvant chemotherapy. Therefore, the indication of repotrectinib should be “*ROS1* fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer” as proposed, with the following cautionary statements included in the Precautions Concerning Indications section:

- The efficacy and safety of repotrectinib have not been established for use in neo-adjuvant and adjuvant chemotherapy.

7.R.4.2 Testing for *ROS1* fusion gene

The applicant's explanation about testing for *ROS1* fusion gene used to select patients eligible for repotrectinib:

The phase II part of the TRIDENT-1 study included the patients assessed as *ROS1* fusion gene-positive based on the result of a test performed by polymerase chain reaction (PCR) or next generation sequencing (NGS) at CLIA or equivalent testing facilities.

For a companion diagnostic device of repotrectinib, an application of “AmoyDx Pan Lung Cancer PCR Panel” was submitted by Riken Genesis Co., Ltd. An equivalence study using tumor tissue specimens revealed that the assessment results favorably agreed with those obtained by the test method used in the TRIDENT-1 study. This device is thus considered to have an ability to identify the patient population expected to benefit from the efficacy and safety of repotrectinib.

Based on the above, “AmoyDx Pan Lung Cancer PCR Panel” should be used to select patients before the use of repotrectinib. The Precautions Concerning Indications section should include the following instruction to raise cautions.

- Repotrectinib should be used in patients who are confirmed to test positive for *ROS1* fusion gene by adequately experienced pathologists or testing at qualified laboratories. The testing should be performed using approved *in vitro* diagnostics or medical devices.

PMDA accepted the applicant’s explanation.

7.R.5 Dosage and administration

The proposed dosage and administration of repotrectinib was “The usual adult dosage is 160 mg of repotrectinib orally administered once daily for 14 days, followed by 160 mg of repotrectinib orally administered twice daily. The dose may be reduced according to the patient’s condition.” The following statements were proposed for the Precautions Concerning Dosage and Administration section:

- The efficacy and safety of repotrectinib have not been established for use in combination with other antineoplastic agents.
- Guide for treatment dose interruption, dose reduction, and discontinuation of repotrectinib in response to onset of adverse drug reactions

As a result of the review in Sections “7.R.2 Efficacy,” “7.R.3 Safety,” and the following subsections, PMDA has concluded that the “Dosage and Administration” should be as proposed, with the following cautionary statements included in the Precautions Concerning Dosage and Administration section.

- The efficacy and safety of repotrectinib have not been established for use in combination with other antineoplastic agents.
- The dose should not be increased to BID if tolerability is not confirmed over 14 days after the first dose.
- Guide for treatment dose interruption, dose reduction, and discontinuation of repotrectinib in response to onset of adverse drug reactions

7.R.5.1 Dosage and administration of repotrectinib

The applicant’s explanation about the rationale for the proposed dosage and administration of repotrectinib:

The most commonly reported adverse event in the phase I part of the TRIDENT-1 study was dizziness, and 2 subjects experienced this event as DLT (1 subject each in the 160 mg BID group and the 240 mg QD group). In view of the following results in the phase I part of the TRIDENT-1 study, the 160 mg QD regimen for the first 14 days followed by the 160 mg BID regimen, which would lead to the dose increase, was expected to be well tolerated.

- In the phase Ic part in which repotrectinib 160 mg was administered QD for the first 7 days, and then the dose was increased to 160 mg BID, no DLT was observed.
- Dizziness mostly occurred within 14 days after the first dose.

In addition to the above findings, results in the phase I part of the TRIDENT-1 study indicated that the effect of food on the PK of repotrectinib is minor, and thus the dosage regimen for the phase II part was specified as follows: Repotrectinib 160 mg should be administered QD for the first 14 days without regard to meals, and then if the initial regimen is tolerable,⁵⁶⁾ the dose may be increased to 160 mg BID. In the phase II part of the TRIDENT-1 study, most of the patients⁵⁷⁾ had their dose increased to 160 mg BID based on the tolerability for the first 14 days. Repotrectinib was demonstrated to have clinical usefulness in the treatment of *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC [see Sections 7.R.2 and 7.R.3]. The proposed dosage and administration of repotrectinib was thus chosen based on the regimen employed in the phase II part of the TRIDENT-1 study.

No clinical study results on repotrectinib used concomitantly with the other antineoplastic agents are obtained in the TRIDENT-1 study. Therefore, the following statements will be included in the Precautions Concerning Dosage and Administration section.

- The efficacy and safety of repotrectinib have not been established for use in combination with other antineoplastic agents.

PMDA's view:

PMDA largely accepted the applicant's explanation. However, cautions should be raised to advise physicians that the dose should not be increased if tolerability is not confirmed over 14 days after the first dose because the dose increase to 160 mg BID was allowed only when tolerability was confirmed over this period in the phase II part of the TRIDENT-1 study.

Based on the above, the Dosage and Administration should be specified as proposed, with the following statements included in the Precautions Concerning Dosage and Administration section:

- The efficacy and safety of repotrectinib have not been established for use in combination with other antineoplastic agents.
- The dose should not be increased to BID if tolerability is not confirmed over 14 days after the first dose.

7.R.5.2 Dose adjustment of repotrectinib

The applicant's explanation about dose adjustment of repotrectinib:

In the phase II part of the TRIDENT-1 study, criteria for dose adjustment of repotrectinib were specified, and repotrectinib used in accordance with the concerned criteria was demonstrated to have clinical usefulness. The Precautions Concerning Dosage and Administration section included the criteria for dose interruption, dose reduction, and discontinuation, which were established based on the criteria in the phase II part of the TRIDENT-1 study by making the following changes:

⁵⁶⁾ When none of the following events occur, the regimen is considered tolerable:

- Grade ≥ 3 adverse events related to repotrectinib
- Unmanageable and Grade ≥ 2 dizziness, ataxia, or paraesthesia
- Clinically important Grade ≥ 3 abnormal laboratory values

⁵⁷⁾ Of 312 patients with *ROS1* fusion gene-positive tumor corresponding to the safety analysis population in the phase II part, 271 patients increased the dose to repotrectinib 160 mg BID. A total of 41 patients did not increase the dose to 160 mg BID mostly because of the adverse events that had occurred during a period of 14 days after the first dose, except patient's will and unknown reason in 2 patients each, and death within 14 days after the first dose, physician's decision, disease progression, and treatment period shorter than 14 days as of data cut-off date in 1 patient each.

- (a) In the phase II part of the TRIDENT-1 study, the criteria allowed continuation or resumption of the treatment after occurrence of Grade 1 or 2 events of ILD, but more careful management of ILD will be required in actual clinical practice. A criterion will be in place to discontinue treatment in response to ILD at any grade.
- (b) In the phase II part of the TRIDENT-1 study, the criteria specified treatment interruption or dose reduction for Grade 2 events of dizziness, ataxia, or paraesthesia, but 32 patients actually continued repotrectinib without dose reduction after experiencing the concerned event, indicating that continued repotrectinib was tolerable in these patients.⁵⁸⁾ A criterion will be in place to interrupt treatment in response to Grade 2 dizziness, ataxia, or paraesthesia only when the regimen is not tolerable, as specified for the other central nervous system disorders.
- (c) In the phase II part of the TRIDENT-1 study, the criteria allowed resumption of the treatment after occurrence of Grade 4 events of central nervous system disorders, but actual clinical practices are considered to require more careful management. A criterion will be in place to discontinue treatment in response to Grade 4 central nervous system disorders.
- (d) In the phase II part of the TRIDENT-1 study, the criteria specified dose interruption for Grade 3 events of QT prolonged and subsequent resumption at a 1-level reduced dose in the Grade 3 event that resolved within 4 weeks, and treatment discontinuation for Grade 4 events. However, no Grade ≥ 3 QT prolonged actually occurred, and thus a risk of QT prolonged was not identified for repotrectinib [see Section 7.R.3.5]. Criteria will be in place to allow resumption at the same dose after occurrence of Grade 3 QT prolonged and also allow resumption even after occurrence of Grade 4 QT prolonged as specified for adverse drug reactions other than central nervous system disorders and ILD.
- (e) In the phase II part of the TRIDENT-1 study, the criteria specified dose interruption for Grade 3 events of non-hematological toxicity (except ILD and central nervous system disorders) and subsequent resumption at a 1-level reduced dose in the Grade 3 event that resolved within 4 week, and treatment discontinuation or dose interruption for Grade 4 events and subsequent resumption at a 1-level reduced dose in the Grade 4 event that resolved within 4 weeks. But the concerned events may include events not requiring dose reduction, such as abnormal laboratory values. A criterion will be in place to allow resumption at the same dose after occurrence of Grade 3 or Grade 4 non-hematological toxicity (except ILD and central nervous system disorders).

In the phase II part of the TRIDENT-1 study, when events requiring dose reduction occurred during the BID treatment with repotrectinib, dose reduction to 120 mg BID (1-level dose reduction) or 80 mg BID (2-level dose reduction) was recommended. However, dose reduction by changing the regimen from BID to QD was not recommended. In view of this practice and the following point, the dose should be reduced as recommended in the phase II part of the TRIDENT-1 study.

- By an exposure-response analysis, the response rates to 160 mg QD and 120 mg BID regimens in ROS1-TKI-naïve patients were estimated to be 76% and 80%, respectively. Thus, the dose reduction to 120 mg BID is expected to provide higher efficacy than that to the 160 mg QD regimen.

⁵⁸⁾ In the phase II part of the TRIDENT-1 study, Grade 2 dizziness, ataxia, or paraesthesia occurred in 108 patients, of whom 76 patients reduced the dose of, interrupted, or discontinued repotrectinib, and 32 patients continued it without dose reduction or interruption. The median treatment period to onset of the Grade 2 events (minimum, maximum) in the above 32 patients was 140 (1, 1,007) days.

Among patients with *ROS1* fusion gene-positive NSCLC who increased the dose to 160 mg BID in the phase II part and were included in the safety analysis population in the TRIDENT-1 study, the following populations were identified: (i) Patients in whom the dose was reduced to 120 mg without changing the BID regimen (BID dose reduction population); and (ii) patients in whom the dose was reduced by changing to the QD regimen without changing the dosage of 160 mg (QD dose reduction population). The BID dose reduction population was compared with the QD dose reduction population. The BID dose reduction population tended to experience more adverse events and continue repotrectinib for a shorter period than the QD dose reduction population (Table 59). However, since the comparison between the populations with different patient characteristics, follow-up period, and other factors had limitations, it is considered inappropriate to recommend the regimen change from BID to QD with the dosage unchanged for dose reduction based on the concerned trends.

**Table 59. Incidences of adverse events and duration of treatment in BID or QD dose reduction patient population*
(phase II part of the TRIDENT-1 study, patients with *ROS1* fusion gene-positive NSCLC who increased the dose to 160 mg BID, data cut-off on December 19, 2022)**

	(i) BID dose reduction population n = 69	(ii) QD dose reduction population n = 23
Number of patients with Grade ≥ 3 adverse events (%)	31 (44.9)	6 (26.1)
Number of patients with adverse events leading to death (%)	4 (5.8)	0
Number of patients with serious adverse events (%)	20 (29.0)	3 (13.0)
Median duration of treatment [minimum, maximum] (days)	167 [3, 1,008]	267 [8, 1,014]

* Adverse events occurring after the first dose reduction and duration of treatment after the first dose reduction were tabulated.

PMDA's view:

PMDA largely accepted the applicant's explanation. Although the change in the above (b) is understandable to a certain extent, adopting dose reduction or dose interruption as a potential measure should be considered because in the phase II part of the TRIDENT-1 study, even tolerable events led to dose reduction or dose interruption according to the patient's condition as specified for the study. In addition, the change in the above (e) is considered to have an unknown potential impact on the safety, and the criterion should be specified as done in the phase II part of the TRIDENT-1 study. Based on the above, the following criteria for dose adjustment of repotrectinib should be specified in the Precautions Concerning Dosage and Administration section. The incidences of adverse events in patients in whom the dose was increased to 160 mg BID and then was reduced without changing the BID regimen or was reduced by changing to the QD regimen in the phase II part of the TRIDENT-1 study should be presented in materials for healthcare professionals to provide information.

- If any adverse drug reaction occurs, repotrectinib should be interrupted, reduced in dose, or discontinued with reference to the following criteria.

Regimens available for dose reduction

Dose reduction level	Dose	
Usual dose	160 mg once daily	160 mg twice daily
1-level reduced dose	120 mg once daily	120 mg twice daily
2-level reduced dose	80 mg once daily	80 mg twice daily

Criteria for dose interruption, dose reduction, and discontinuation

Adverse drug reaction	Severity*	Action
Central nervous system disorders	Grade 2 dizziness, ataxia, or paraesthesia	Consider the 1-level reduced dose or dose interruption until the symptom resolves to Grade ≤ 1 or baseline. If repotrectinib is interrupted, resume repotrectinib at the same dose after resolution.
	Intolerable Grade 2 (except dizziness, ataxia, and paraesthesia) Grade 3	Interrupt repotrectinib until the symptom resolves to Grade ≤ 1 or baseline. After resolution, resume repotrectinib at the 1-level reduced dose.
	Grade 4	Discontinue repotrectinib.
ILD	Any grade	Discontinue repotrectinib.
Adverse drug reactions other than the above	Grade 3	Interrupt repotrectinib until the symptom resolves to Grade ≤ 1 or baseline. After resolution, resume repotrectinib at the 1-level reduced dose.
	Grade 4	Discontinue or interrupt repotrectinib until the symptom resolves to Grade ≤ 1 or baseline. After resolution, resume repotrectinib at the 1-level reduced dose. If the symptom recurs, discontinue repotrectinib.

* Graded according to NCI-CTCAE v4.03

7.R.6 Post-marketing investigations

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

The applicant plans to conduct a post-marketing surveillance in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC to investigate the safety of repotrectinib in post-marketing clinical practice.

The safety specification in the surveillance was effects on the central nervous system and ILD in view of the safety profile of repotrectinib [see Section 7.R.3].

The target sample size and observation period were 100 patients and 52 weeks, respectively, in view of the incidences in the TRIDENT-1 study for each of the events listed in the safety specification in the surveillance.

PMDA's view:

In view of the points presented below, there is little need to conduct post-marketing surveillance in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC immediately after approval, on the premise that the following actions are in place: Through the early post-marketing phase vigilance and regular pharmacovigilance activities, information about adverse events requiring special attention during use of repotrectinib (ILD and central nervous system disorders) is provided to healthcare professionals and the safety information about repotrectinib is collected; and appropriate safety measures based on information that are available to date and are to become available in the future are taken.

- The safety profile of repotrectinib is clarified to a certain degree by the clinical study results of repotrectinib.

- The adverse events requiring special attention during use of repotrectinib [see Section 7.R.3] are all known risks for the approved ROS1-TKIs,⁵⁹⁾ and no safety concerns specific to repotrectinib are identified at the present time.
- For the approved ROS1-TKIs (crizotinib and entrectinib), post-marketing use results are available to a certain extent,⁶⁰⁾ and no additional safety concerns in Japanese patients are considered to be identified.

However, if an additional investigation item is identified in post-marketing clinical use of repotrectinib, post-marketing surveillance, etc. should be immediately conducted as an additional pharmacovigilance activity.

7.3 Adverse events, etc. observed in clinical studies

Deaths reported in the safety evaluation data were detailed in Sections “7.1 Evaluation data” and “7.2 Reference data.” The following subsections summarize major adverse events other than the deaths.

7.3.1 Global phase I/II study (TRIDENT-1 study)

7.3.1.1 Phase Ia to Ic part

Adverse events occurred in all patients. Adverse events for which a causal relationship to repotrectinib could not be ruled out occurred in 10 of 13 patients (76.9%) in the repotrectinib 40 mg QD group, 11 of 12 patients (91.7%) in the 80 mg QD group, 17 of 23 patients (73.9%) in the 160 mg QD group, all the patients in the 240 mg QD group, 160 mg BID group, 200 mg BID group, 120 mg QD (fed state) group, and 160 mg QD (fed state) group, and 11 of 12 patients (91.7%) in the 160 mg QD/BID (fed state) group.

Adverse events with an incidence of $\geq 30\%$ and reported by ≥ 2 patients were anaemia in 7 patients (53.8%), dizziness and pyrexia in 6 patients (46.2%) each, nausea and cough in 5 patients (38.5%) each, dysgeusia, constipation, and fatigue in 4 patients (30.8%) each in the repotrectinib 40 mg QD group, dizziness in 7 patients (58.3%), dysgeusia and paraesthesia in 6 patients (50.0%) each, constipation and pyrexia in 5 patients (41.7%) each, fatigue in 4 patients (33.3%) in the 80 mg QD group, dizziness in 14 patients (60.9%), dyspnoea in 11 patients (47.8%), dysgeusia in 10 patients (43.5%), constipation and anaemia in 9 patients (39.1%) each in the 160 mg QD group, dizziness in 7 patients (70.0%), dysgeusia and paraesthesia in 5 patients (50.0%) each, fatigue in 4 patients (40.0%), ataxia, constipation, vomiting, hypoaesthesia oral, dyspnoea, and anaemia in 3 patients (30.0%) each in the 240 mg QD group, dizziness and dysgeusia in 7 patients (58.3%) each, dyspnoea in 6 patients (50.0%), headache, gastroesophageal reflux disease, muscular weakness, and upper respiratory tract infection in 4 patients (33.3%) each in the 160 mg BID group, dizziness, dysgeusia, paraesthesia, and fatigue in 2 patients (100%) each in the

⁵⁹⁾ Adverse events requiring special attention during use of (a) crizotinib and (b) entrectinib are (a) ILD, visual disturbance (diplopia, photopsia, vision blurred, visual field defect, visual impairment, vitreous floaters, etc.), hepatic dysfunction, blood disorders, neuropathy, QTc prolonged, bradycardia, thromboembolism, photosensitivity and complicated renal cyst) and cardiac failure; and (b) cognitive disorder, ataxia, syncope, ILD, QT prolonged and cardiac disorders (except QT prolonged) (see the “Review Report on Xalkori Capsules 200 mg, Xalkori Capsules 250 mg, dated April 7, 2017” and “Review Report on Rozlytrek Capsules 100 mg, Rozlytrek Capsules 200 mg, dated February 12, 2020”).

⁶⁰⁾ Crizotinib was approved for the indication of *ALK* fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer in March 2012, and the indication of *ROS1* fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer was approved in May 2017. The surveillance result report of the post-marketing surveillance in all patients treated with crizotinib (2,028 patients in the safety analysis population) was submitted, and the re-examination result on the indication of *ALK* fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer was notified in June 2023.

Entrectinib was approved for the indication of *NTRK* fusion gene-positive advanced or recurrent solid tumor in June 2019, and the indication of *ROS1* fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer was approved in February 2020.

200 mg BID group, dysgeusia, headache, and nausea in 2 patients (66.7%) each in the 120 mg QD (fed state) group, dizziness and dysgeusia in 5 patients (83.3%) each, nausea, fatigue, and anaemia in 3 patients (50.0%) each, peripheral sensory neuropathy, dyspnoea, arthralgia, alanine aminotransferase increased, aspartate aminotransferase increased, alopecia, rash maculo-papular, and embolism in 2 patients (33.3%) each in the 160 mg QD (fed state) group, and dizziness in 8 patients (66.7%), constipation and dyspnoea in 6 patients (50.0%) each, dysgeusia in 5 patients (41.7%), productive cough, and pneumonia in 4 patients (33.3%) each in the 160 mg QD/BID (fed state) group.

Serious adverse events occurred in 5 of 13 patients (38.5%) in the repotrectinib 40 mg QD group, 3 of 12 patients (25.0%) in the 80 mg QD group, 11 of 23 patients (47.8%) in the 160 mg QD group, 4 of 10 patients (40.0%) in the 240 mg QD group, 5 of 12 patients (41.7%) in the 160 mg BID group, 1 of 2 patients (50.0%) in the 200 mg BID group, 1 of 3 patients (33.3%) in the 120 mg QD (fed state) group, 5 of 6 patients (83.3%) in the 160 mg QD (fed state) group, and 8 of 12 patients (66.7%) in the 160 mg QD/BID (fed state) group. Serious adverse events reported by ≥ 2 patients in any group were pneumonia in 2 patients (16.7%) in the 80 mg QD group, hemiparesis and urinary tract infection in 2 patients (8.7%) each in the 160 mg QD group, and pneumonia in 4 patients (33.3%) in the 160 mg QD/BID (fed state) group, a causal relationship to repotrectinib was ruled out for all events.

Adverse events leading to treatment discontinuation of repotrectinib occurred in 1 of 13 patients (7.7%) in the repotrectinib 40 mg QD group, 1 of 12 patients (8.3%) in the 80 mg QD group, 4 of 23 patients (17.4%) in the 160 mg QD group, 2 of 10 patients (20.0%) in the 240 mg QD group, 1 of 12 patients (8.3%) in the 160 mg BID group, 1 of 2 patients (50.0%) in the 200 mg BID group, 1 of 3 patients (33.3%) in the 120 mg QD (fed state) group, 1 of 6 patients (16.7%) in the 160 mg QD (fed state) group, and 2 of 12 patients (16.7%) in the 160 mg QD/BID (fed state) group. There were no adverse events leading to treatment discontinuation of repotrectinib reported ≥ 2 patients in any group.

7.3.1.2 Sub-study

Adverse events occurred in all patients. Adverse events for which a causal relationship to repotrectinib could not be ruled out occurred in 9 of 10 patients (90.0%). Adverse events with an incidence of $\geq 30\%$ were dyspnoea in 6 patients (60.0%), dysgeusia in 5 patients (50.0%), dizziness in 4 patients (40.0%), and hypoxia, constipation, gastrooesophageal reflux disease, peripheral sensory neuropathy, and muscular weakness in 3 patients (30.0%) each.

Serious adverse events occurred in 7 of 10 patients (70.0%). Serious adverse events reported by ≥ 2 patients were dyspnoea and hypoxia in 3 patients (30.0%) each, a causal relationship to repotrectinib was ruled out for all events.

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

7.3.1.3 Phase II part (EXP-1 to EXP-4)

Adverse events occurred in all patients in EXP-1, EXP-2, and EXP-3 and 100 of 102 patients (98.0%) in EXP-4. Adverse events for which a causal relationship to repotrectinib could not be ruled out occurred

in 106 of 107 patients (99.1%) in EXP-1, 44 of 46 patients (95.7%) in EXP-2, 53 of 57 patients (93.0%) in EXP-3, and 96 of 102 patients (94.1%) in EXP-4. Table 60 shows adverse events with an incidence of $\geq 20\%$ in any cohort.

Table 60. Adverse events with an incidence of $\geq 20\%$ in any cohort (EXP-1 to EXP-4)

SOC PT (MedDRA ver.25.0)	n (%)							
	EXP-1 N= 107		EXP-2 N = 46		EXP-3 N = 57		EXP-4 N= 102	
	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
All adverse events	107 (100)	57 (53.3)	46 (100)	20 (43.5)	57 (100)	32 (56.1)	100 (98.0)	41 (40.2)
Nervous system disorders								
Dizziness	75 (70.1)	2 (1.9)	27 (58.7)	0	34 (59.6)	1 (1.8)	58 (56.9)	2 (2.0)
Dysgeusia	66 (61.7)	0	20 (43.5)	0	21 (36.8)	0	52 (51.0)	0
Paraesthesia	45 (42.1)	2 (1.9)	14 (30.4)	0	13 (22.8)	0	35 (34.3)	0
Ataxia	31 (29.0)	1 (0.9)	10 (21.7)	0	7 (12.3)	0	17 (16.7)	0
Headache	20 (18.7)	0	10 (21.7)	0	5 (8.8)	0	23 (22.5)	0
Gastrointestinal disorders								
Constipation	49 (45.8)	0	12 (26.1)	0	19 (33.3)	0	35 (34.3)	0
Nausea	17 (15.9)	0	11 (23.9)	0	12 (21.1)	0	16 (15.7)	2 (2.0)
Investigations								
Alanine aminotransferase increased	27 (25.2)	2 (1.9)	12 (26.1)	2 (4.3)	11 (19.3)	1 (1.8)	31 (30.4)	1 (1.0)
Aspartate aminotransferase increased	31 (29.0)	2 (1.9)	11 (23.9)	2 (4.3)	10 (17.5)	1 (1.8)	19 (18.6)	0
Blood creatine phosphokinase increased	22 (20.6)	7 (6.5)	12 (26.1)	1 (2.2)	4 (7.0)	1 (1.8)	16 (15.7)	3 (2.9)
Weight increased	26 (24.3)	5 (4.7)	6 (13.0)	1 (2.2)	3 (5.3)	2 (3.5)	15 (14.7)	2 (2.0)
General disorders and administration site conditions								
Fatigue	19 (17.8)	2 (1.9)	7 (15.2)	0	14 (24.6)	0	22 (21.6)	0
Musculoskeletal and connective tissue disorders								
Muscular weakness	30 (28.0)	3 (2.8)	9 (19.6)	1 (2.2)	9 (15.8)	1 (1.8)	21 (20.6)	2 (2.0)
Respiratory, thoracic and mediastinal disorders								
Dyspnoea	29 (27.1)	4 (3.7)	8 (17.4)	1 (2.2)	20 (35.1)	7 (12.3)	25 (24.5)	5 (4.9)
Blood and lymphatic system disorders								
Anaemia	45 (42.1)	5 (4.7)	16 (34.8)	4 (8.7)	18 (31.6)	7 (12.3)	38 (37.3)	5 (4.9)

Serious adverse events occurred in 38 of 107 patients (35.5%) in EXP-1, 13 of 46 patients (28.3%) in EXP-2, 19 of 57 patients (33.3%) in EXP-3, and 29 of 102 patients (28.4%) in EXP-4. Serious adverse events reported by ≥ 2 patients in any cohort were hypoxia and pneumonitis in 4 patients (3.7%) each, pneumonia in 3 patients (2.8%), ataxia, dyspnoea, pericardial effusion, pleural effusion, and pulmonary embolism in 2 patients (1.9%) each in EXP-1, pleural effusion and pneumonia in 2 patients (4.3%) each in EXP-2, dyspnoea and pneumonia in 3 patients (5.3%) each in EXP-3, and pleural effusion in 5 patients (4.9%), dyspnoea and pneumonia in 3 patients (2.9%) each, and anaemia, hypoxia, pneumonia aspiration, seizure, and syncope in 2 patients (2.0%) each in EXP-4. A causal relationship to repotrectinib could not be ruled out for pneumonitis in 3 patients, pleural effusion in 2 patients, pneumonia, ataxia, dyspnoea, pericardial effusion, and pulmonary embolism in 1 patient each in EXP-1, and anaemia in 2 patients, hypoxia and seizure in 1 patient each in EXP-4.

Adverse events leading to treatment discontinuation of repotrectinib occurred in 10 of 107 patients (9.3%) in EXP-1, 1 of 46 patients (2.2%) in EXP-2, 3 of 57 patients (5.3%) in EXP-3, and 7 of 102 patients (6.9%) in EXP-4. Adverse events leading to treatment discontinuation of repotrectinib reported by ≥ 2 patients in any cohort were muscular weakness and pneumonitis in 2 patients each in EXP-1, and a causal relationship to repotrectinib could not be ruled out for all events.

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 inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. 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 5.3.5.2-4) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA confirmed that the studies were generally conducted in accordance with GCP and thus concluded that there were no obstacles to conducting its review based on the application documents submitted. However, the following finding in the sponsor was noted although it would not have a considerable impact on evaluation of the studies overall. It was notified to the sponsor as a finding requiring corrective action.

Finding requiring corrective action

Sponsor

- There were some audits implemented without preparation of the protocols and procedures for audits.

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

On the basis of the data submitted, PMDA has concluded that repotrectinib has a certain level of efficacy in the treatment of *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC, and that repotrectinib has acceptable safety in view of its benefits. Repotrectinib is a drug with a new active ingredient expected to inhibit tyrosine kinases such as *ROS1* and *TRK* and is clinically meaningful as an option for the treatment of *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC. PMDA considers that the clinical positioning and post-marketing investigations should be further discussed.

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

Review Report (2)

August 13, 2024

Product Submitted for Approval

Brand Name	Augtyro Capsules 40 mg
Non-proprietary Name	Repotrectinib
Applicant	Bristol-Myers Squibb K.K.
Date of Application	October 25, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

In the phase II part of the global phase I/II study in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC (TRIDENT-1 study), the response rate [95% CI], the primary endpoint, was 77.8% [65.5%, 87.3%] in EXP-1, 43.5% [23.2%, 65.5%] in EXP-2, 29.4% [10.3%, 56.0%] in EXP-3, and 37.7% [24.8%, 52.1%] in EXP-4 according to RECIST ver 1.1 as assessed by independent central review.

As a result of the review in Section “7.R.2 Efficacy” in the Review Report (1), the *ROS1* fusion gene is deemed as an oncogenic driver of *ROS1* fusion gene-positive NSCLC, and the above results in the phase II part of the TRIDENT-1 study are considered clinically meaningful in view of the following points. PMDA has concluded that repotrectinib is demonstrated to have a certain level of efficacy in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC:

- The response rate in EXP-1, which included *ROS1*-TKI-naïve patients, was similar to those of existing *ROS1*-TKIs.
- For the response rates in EXP-2 to EXP-4, because the pre-determined sample sizes were not reached, possible overestimation cannot be denied for results in the concerned cohorts, and thus comparisons with conventional therapies have limitations. However, the response to a certain extent was observed in patients who had received prior therapy with existing *ROS1*-TKIs and patients who had resistance mutations to *ROS1*-TKIs.

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

1.2 Safety

As a result of the review in Section “7.R.3 Safety” in the Review Report (1), PMDA has concluded that adverse events requiring particular attention during treatment with repotrectinib in patients with *ROS1* fusion gene-positive unresectable advanced or recurrent NSCLC are ILD and central nervous system disorders.

PMDA has concluded that although attention should be paid to the above adverse events during the treatment of repotrectinib, repotrectinib is tolerable as long as physicians with adequate knowledge and experience in cancer chemotherapy take appropriate measures, such as monitoring of patients, management of adverse events, dose interruption, and dose reduction of repotrectinib.

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

1.3 Clinical positioning and indication

As a result of the review in Section “7.R.4 Clinical positioning and indication” in the Review Report (1), PMDA has concluded that the Indication of repotrectinib should be “*ROS1* fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer” as proposed, with the following cautionary statements included in the Precautions Concerning Indications section.

Precautions Concerning Indications

- Repotrectinib should be used in patients who are confirmed to test positive for *ROS1* fusion gene by adequately experienced pathologists or testing at qualified laboratories. The testing should be performed using approved *in vitro* diagnostics or medical devices.
- The efficacy and safety of repotrectinib have not been established for use in neo-adjuvant and adjuvant chemotherapy.

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

PMDA instructed the applicant to specify the Indications and the Precautions Concerning Indications section as described above. The applicant agreed.

1.4 Dosage and administration

As a result of the review in Section “7.R.5 Dosage and administration” in the Review Report (1), PMDA has concluded that the Dosage and Administration of repotrectinib should be “The usual adult dosage is 160 mg of repotrectinib orally administered once daily for 14 days, followed by 160 mg of repotrectinib orally administered twice daily. The dose may be reduced according to the patient’s condition.” as proposed, with the following cautionary statements included in the Precautions Concerning Dosage and Administration section.

Precautions Concerning Dosage and Administration

- The efficacy and safety of repotrectinib have not been established for use in combination with other antineoplastic agents.
- The dosing frequency should not be switched from QD to BID if tolerability is not confirmed over 14 days after the first dose.
- If any adverse drug reaction occurs following administration of repotrectinib, repotrectinib should be interrupted, reduced in dose, or discontinued with reference to the following criteria.

Regimens available for dose reduction

Dose reduction level	Dose	
Usual regimen	160 mg once daily	160 mg twice daily
1-level reduced dose	120 mg once daily	120 mg twice daily
2-level reduced dose	80 mg once daily	80 mg twice daily

Criteria for dose interruption, dose reduction, and discontinuation

Adverse drug reaction	Severity*	Action
Central nervous system disorders	Grade 2 dizziness, ataxia, or paraesthesia	Consider the 1-level reduced dose or dose interruption until the symptom resolves to Grade ≤ 1 or baseline. If repotrectinib is interrupted, resume repotrectinib at the same dose after recovery.
	Intolerable Grade 2 (except dizziness, ataxia, and paraesthesia) Grade 3	Interrupt repotrectinib until the symptom resolves to Grade ≤ 1 or baseline. After recovery, resume repotrectinib at the 1-level reduced dose.
	Grade 4	Discontinue repotrectinib.
ILD	Any Grade	Discontinue repotrectinib.
Adverse drug reactions other than the above	Grade 3	Interrupt repotrectinib until the symptom resolves to Grade ≤ 1 or baseline. After recovery, resume repotrectinib at the 1-level reduced dose.
	Grade 4	Discontinue or interrupt repotrectinib until the symptom resolves to Grade ≤ 1 or baseline. After recovery, resume repotrectinib at the 1-level reduced dose. If the symptom recurs, discontinue repotrectinib.

*, Graded according to NCI-CTCAE v4.03

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

PMDA instructed the applicant to specify the Dosage and Administration and the Precautions Concerning Dosage and Administration section as described above. The applicant agreed.

1.5 Risk management plan (draft)

As a result of the review in Section “7.R.6 Post-marketing investigations” in the Review Report (1), PMDA has concluded that there is little need to immediately conduct post-marketing surveillance to investigate the safety of repotrectinib in patients with ROS1 fusion gene-positive unresectable advanced or recurrent NSCLC after the approval as long as the applicant ensures that the following actions are in place: Through the early post-marketing phase vigilance and regular pharmacovigilance activities, information about adverse events requiring special attention during use of repotrectinib (ILD and central nervous system disorders) is provided to healthcare professionals and the safety information about repotrectinib is collected; and appropriate safety measures based on information that are available to date and are to become available in the future are taken.

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

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for repotrectinib should include the safety specification presented in Table 61, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 62.

Table 61. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Interstitial lung disease • Central nervous system disorders	• Embryo-foetal toxicity	• Use in patients with hepatic impairment
Efficacy specification		
Not applicable		

Table 62. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance	Not applicable	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate materials for healthcare professionals • Organize and disseminate materials for patients

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following approval condition, provided that the package insert includes appropriate cautionary statements; information about proper use is appropriately disseminated in post-marketing settings; and repotrectinib is properly used by physicians with adequate knowledge and experience in cancer chemotherapy at medical institutions capable of emergency response. The product is a drug with a new active ingredient, and the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

ROS1 fusion gene-positive unresectable advanced or recurrent non-small cell lung cancer

Dosage and Administration

The usual adult dosage is 160 mg of repotrectinib orally administered once daily for 14 days, followed by 160 mg of repotrectinib orally administered twice daily. The dose may be reduced according to the patient's condition.

Approval Condition

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

Warnings

1. The product should be administered only to patients considered to be eligible for the therapy with the product by physicians with adequate knowledge and experience in cancer chemotherapy at medical institutions capable of emergency response. Prior to treatment, the benefits and risks of the therapy should be thoroughly explained to the patient or their family member, and consent should be obtained.
2. Interstitial lung disease may occur following administration of the product. Patients should be carefully monitored for initial symptoms (shortness of breath, cough, pyrexia, etc.) and by chest computed tomography (CT) or other examinations. If any abnormalities are observed, treatment with the product should be discontinued and appropriate measures should be taken. The initial treatment should be provided after hospitalization or under equivalent management to ensure adequate monitoring for clinically significant adverse drug reactions such as interstitial lung disease.

Contraindication

Patients with a history of hypersensitivity to any of the ingredients contained in this drug

Precautions Concerning Indications

1. Repotrectinib should be used in patients who are confirmed to test positive for *ROS1* fusion gene by adequately experienced pathologists or testing at qualified laboratories. The testing should be performed using approved *in vitro* diagnostics or medical devices.
2. The efficacy and safety of repotrectinib have not been established for use in neo-adjuvant and adjuvant chemotherapy.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of repotrectinib have not been established for use in combination with other antineoplastic agents.
2. The dosing frequency should not be switched from once-daily dosing to twice-daily dosing if tolerability is not confirmed over 14 days after the first dose.
3. If any adverse drug reaction occurs following administration of repotrectinib, repotrectinib should be interrupted, reduced in dose, or discontinued with reference to the following criteria.

Regimens available for dose reduction

Dose reduction level	Dose	
Usual dose	160 mg once daily	160 mg twice daily
1-level reduced dose	120 mg once daily	120 mg twice daily
2-level reduced dose	80 mg once daily	80 mg twice daily

Criteria for interruption, dose reduction, and discontinuation

Adverse drug reaction	Severity*	Action
Central nervous system disorders	Grade 2 dizziness, ataxia, or paraesthesia	Consider the 1-level reduced dose or dose interruption until the symptom resolves to Grade ≤ 1 or baseline. If repotrectinib is interrupted, resume repotrectinib at the same dose after recovery.
	Intolerable Grade 2 (except dizziness, ataxia, and paraesthesia) Grade 3	Interrupt repotrectinib until the symptom resolves to Grade ≤ 1 or baseline. After recovery, resume repotrectinib at the 1-level reduced dose.
	Grade 4	Discontinue repotrectinib.
ILD	Any Grade	Discontinue repotrectinib.
Adverse drug reactions other than the above	Grade 3	Interrupt repotrectinib until the symptom resolves to Grade ≤ 1 or baseline. After recovery, resume repotrectinib at the 1-level reduced dose.
	Grade 4	Discontinue or interrupt repotrectinib until the symptom resolves to Grade ≤ 1 or baseline. After recovery, resume repotrectinib at the 1-level reduced dose. If the symptom recurs, discontinue repotrectinib.

*, Graded according to NCI-CTCAE v4.03.

List of Abbreviations

A/G	albumin/globulin
AKT	protein kinase B
Alectinib	Alectinib hydrochloride
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Application	Application for marketing approval
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BA	bioavailability
BCRP	breast cancer resistance protein
BID	bis in die
BSEP	bile salt export pump
C1156Y	Cysteine at position 1,156 substituted by tyrosine
Cabozantinib	Cabozantinib malate
CHO cell line	Chinese hamster ovary cell line
CI	confidence interval
CK	creatine phosphokinase
CL	clearance
CLMAX	maximum induced clearance
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CYP	cytochrome P450
¹⁴ C-repotrectinib	¹⁴ C-labeled repotrectinib
D2033N	Aspartate at position 2,033 substituted by asparagine
DDI	drug-drug interaction
DLT	dose limited toxicity
DMSO	dimethylsulfoxide
Docetaxel	Docetaxel hydrate
DOR	duration of response
DRDI	dose reduction or dose interruption due to adverse events
efflux ratio	Ratio of secretion permeability coefficient in the secretive direction to that in the absorptive direction
EMA	European Medical Agency
ERK	extracellular signal-regulated kinase
ESMO	European Society for Medical Oncology
ESMO guideline	Oncogene-addicted metastatic non-small cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up
EXP	expansion cohort
F1	bioavailability
F1174C	Phenylalanine at position 1,174 substituted by cysteine
F1174L	Phenylalanine at position 1,174 substituted by leucine
F1174S	Phenylalanine at position 1,174 substituted by serine
F2004I	Phenylalanine at position 2,004 substituted by isoleucine
G595R	Glycine at position 595 substituted by arginine
G623R	Glycine at position 623 substituted by arginine
G639R	Glycine at position 639 substituted by arginine
G1202R	Glycine at position 1,202 substituted by arginine
G1269A	Glycine at position 1,269 substituted by alanine

G1269S	Glycine at position 1,269 substituted by serine
G2032R	Glycine at position 2,032 substituted by arginine
GC	gas chromatography
GGT	gamma-glutamyltransferase
HEK	human embryonic kidney
hERG	human <i>ether-a-go-go</i> -related gene
HPLC	High performance liquid chromatography
IC ₅₀	concentration that results in 50% inhibition
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use
ICH Q1A (R2) guideline	“Revision of the Guidelines on Stability Testing of New Drug Substances and Products” (PFSB/ELD Notification No. 0603001 dated June 3, 2003)
ICH Q1E guideline	“Guideline on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
IHC	immunohistochemistry
ILD	interstitial lung disease
IR	infrared absorption spectroscopy
JAK	janus kinase
KA	first-order absorption rate constant
L1152P	Leucine at position 1,152 substituted by proline
L1152R	Leucine at position 1,152 substituted by arginine
L1196M	Leucine at position 1,196 substituted by methionine
L2026M	Leucine at position 2,026 substituted by methionine
L2086F	Leucine at position 2,086 substituted by phenylalanine
Larotrectinib	Larotrectinib sulfate
LCK	lymphocyte-specific protein tyrosine kinase
LC-MS/MS	liquid chromatography-tandem mass spectrometry
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
MS	mass spectrometry
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Small Cell Lung Cancer
NE	not evaluable
NGS	next generation sequencing
NMR	nuclear magnetic resonance spectroscopy
NSCLC	non-small cell lung cancer
NTRK	neurotrophic receptor tyrosine kinase
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
P _{app A→B}	apparent permeability in apical to basal direction
P _{app B→A}	apparent permeability in basolateral to apical direction
PCR	polymerase chain reaction
PD	progressive disease
Pemetrexed	Pemetrexed sodium hydrate
PFS	progression free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics

PR	partial response
PT	preferred term
PTP	press through packaging
Q	intercompartmental clearance
QD	quaque die
QD/BID	QD for the first 14 days followed by BID for dose increase
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected by Fridericia method
Δ QTcF	Change in QTcF from baseline
R1275Q	Arginine at position 1,275 substituted by glutamine
Ramucirumab	Ramucirumab (genetical recombination)
RDW	red blood cell distribution width
RECIST	Response Evaluation Criteria in Solid Tumors
Repotrectinib	Repotrectinib
ROS1	c-ros oncogene 1
ROS1-TKI	c-ros oncogene 1-tyrosine kinase inhibitor
RP2D	recommended Phase 2 dose
S1206R	Serine at position 1,206 substituted by arginine
S1986F	Serine at position 1,986 substituted by phenylalanine
S1986Y	Serine at position 1,986 substituted by tyrosine
SCID-beige mouse	severe combined immunodeficiency beige mouse
SD	stable disease
SFM	solvent front mutation
SLS	sodium laurilsulfate
STAT3	signal transducer and activator of transcription 3
Study 09	Study TPX-0005-09
Study 10	Study TPX-0005-10
Study 11	Study TPX-0005-11
Study 14	Study TPX-0005-14
T1151M	Threonine at position 1,151 substituted by methionine
1151Tins	Insertion of threonine at position 1,151
TKI	tyrosine kinase inhibitor
TRIDENT-1 study	Study TPX-0005-01
TRK	tropomyosin receptor kinase
TRK-TKI	tropomyosin receptor kinase-tyrosine kinase inhibitor
UDPGA	uridine diphosphate glucuronic acid
UGT	uridine 5'-diphosphoglucuronosyltransferase
USPI	United States Prescribing Information
UVA	ultraviolet light A
UVB	ultraviolet light B
UV-VIS	ultraviolet-visible spectroscopy
Vc	central volume of distribution
Vp	peripheral volume of distribution