Report on the Deliberation Results

May 14, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Jaypirca Tablets 50 mg Jaypirca Tablets 100 mg
Non-proprietary Name	Pirtobrutinib (JAN*)
Applicant	Eli Lilly Japan K.K.
Date of Application	June 30, 2023

Results of Deliberation

In its meeting held on May 9, 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 Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

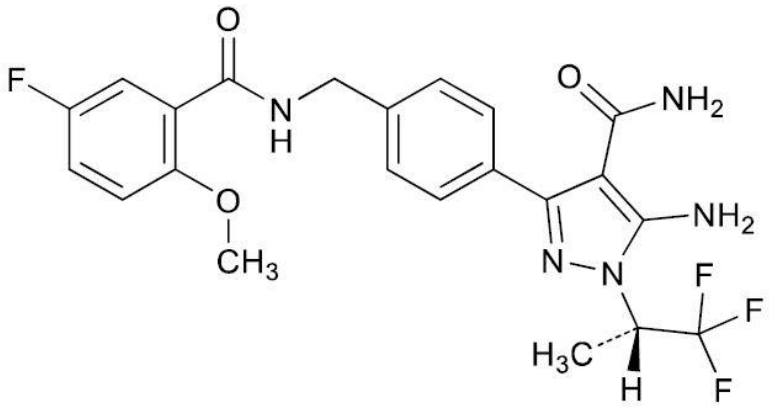
Review Report

April 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	Jaypirca Tablets 50 mg Jaypirca Tablets 100 mg
Non-proprietary Name	Pirtobrutinib
Applicant	Eli Lilly Japan K.K.
Date of Application	June 30, 2023
Dosage Form/Strength	Tablets, each containing 50 mg or 100 mg of pirtobrutinib
Application Classification	Prescription drug (1), Drugs with a new active ingredient

Chemical Structure



Molecular formula:	$C_{22}H_{21}F_4N_5O_3$
Molecular weight:	479.43
Chemical name:	5-Amino-3-{4-[(5-fluoro-2-methoxybenzamido)methyl]phenyl}-1-[(2*S*)-1,1,1-trifluoropropan-2-yl]-1*H*-pyrazole-4-carboxamide

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in the treatment of relapsed or refractory mantle cell lymphoma resistant or intolerant to other Bruton's tyrosine kinase (BTK) inhibitors, 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 condition. Arrhythmia and second primary malignancies should be further evaluated in the post-marketing surveillance.

Indication

Relapsed or refractory mantle cell lymphoma in patients who are resistant or intolerant to other BTK inhibitors

Dosage and Administration

The usual adult dosage is 200 mg of pirtobrutinib administered orally once daily. The dose should be reduced according to the patient's condition.

Approval Conditions

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

Attachment

Review Report (1)

February 26, 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	Jaypirca Tablets 50 mg Jaypirca Tablets 100 mg
Non-proprietary Name	Pirtobrutinib
Applicant	Eli Lilly Japan K.K.
Date of Application	June 30, 2023
Dosage Form/Strength	Tablets, each containing 50 mg or 100 mg of pirtobrutinib
Proposed Indication	Relapsed or refractory mantle cell lymphoma in patients who are resistant or intolerant to BTK inhibitors
Proposed Dosage and Administration	The usual adult dosage is 200 mg of pirtobrutinib administered orally once daily. The dose should be reduced according to the patient's condition.

Table of Contents

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information 2
2. Quality and Outline of the Review Conducted by PMDA 3
3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA 5
4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA 12
5. Toxicity and Outline of the Review Conducted by PMDA 20
6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA 26
7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA 38
8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA 72
9. Overall Evaluation during Preparation of the Review Report (1) 72

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

Bruton's tyrosine kinase (BTK) is a signaling pathway downstream of the B cell receptor (BCR), which is expressed mainly in B cells (e.g., *J Clin Oncol.* 2014;32:1830-9). The BCR signaling pathway is involved in the initiation, growth, and progression of various B cell malignancies such as mantle cell lymphoma (MCL) (e.g., *Int Rev Immunol.* 2012;31:119-32).

Pirtobrutinib is a low molecular compound inhibiting BTK developed by Loxo Oncology, Inc., a US-based company. Pirtobrutinib binds non-covalently to an active site of BTK in B cell malignancies harboring resistance mutations such as BTK C481S (cysteine to serine substitution at position 481), which confer resistance to existing BTK inhibitors.[1)] This binding action of pirtobrutinib is thought to inhibit BTK kinase activity, thereby suppressing tumor growth.

1.2 Development history, etc.

Outside Japan, a phase I/II study (Study 18001) was initiated in [redacted] 20[redacted] by the US-based Loxo Oncology, Inc. in patients with non-Hodgkin lymphoma (NHL) and patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

In May 2022, applications for approval of pirtobrutinib were filed in the US and EU based on data from Study 18001 as pivotal data in patients with relapsed or refractory mantle cell lymphoma (MCL) who are resistant or intolerant to BTK inhibitors. In January 2023, pirtobrutinib was approved in the US under the accelerated approval program with the following indication: "JAYPIRCA is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial." In October 2023, pirtobrutinib was approved in the EU with the following indication: "Jaypirca as monotherapy is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL) who have been previously treated with a Bruton's tyrosine kinase (BTK) inhibitor."

As of January 2024, pirtobrutinib has been approved in 38 countries and regions for the treatment of relapsed or refractory MCL in patients who are resistant or intolerant to BTK inhibitors.

In Japan, the applicant initiated enrolling patients in Study 18001 in [redacted] 20[redacted].

Recently, the applicant has filed an application for marketing approval of pirtobrutinib with the results from Study 18001 as pivotal data.

[1)] Ibrutinib is a BTK inhibitor approved in Japan for the treatment of MCL.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white, yellow, to brown solid. Its description, solubility, acid dissociation constant, crystal form, hygroscopicity, melting point, and optical rotation have been evaluated. Three crystal forms (Forms A, B, and C) of the drug substance have been identified. Among these forms, only Form A is produced commercially, and the stability study demonstrated that the crystal form remained unchanged.

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

2.1.2 Manufacturing process

The drug substance is synthesized using Compound A[2)] and Compound B[3)] as the starting materials.

The quality control strategy has been formulated based on the following assessments (Table 1).

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) based on the quality risk assessment and determination of the proven acceptable range (PAR) for manufacturing process parameters

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

CQA	Control method
Content	Manufacturing process, specifications
Description	Manufacturing process, specifications
Identification	Manufacturing process, specifications
Related substances	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
Residual solvents	Manufacturing process, specifications
Water content	Manufacturing process, specifications
Inorganic impurities	Manufacturing process, specifications
[redacted] and [redacted]	Manufacturing process, specifications
[redacted]	Manufacturing process
Elemental impurities	Manufacturing process
Crystal form	Manufacturing process

The [redacted] of [redacted][4)] and the [redacted] of [redacted] have been defined as critical steps. Process control items and process control parameters have been established for the [redacted] steps. [redacted] is controlled as a critical intermediate.

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

2.1.3 Control of drug substance

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

2.1.4 Stability of drug substance

Table 2 summarizes the main stability studies for the drug substance. The results showed that the drug substance is stable. The results of a photostability study showed that the drug substance is photostable.

Table 2. Stability studies for the drug substance

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial scale batches	30°C	65% RH	Linear low-density polyethylene bag + laminated aluminum bag	36 months
Accelerated		40°C	75% RH		6 months

Based on the above results, a retest period of [redacted] months was proposed for the drug substance when placed in linear low-density polyethylene bags and stored in a laminated aluminum bag at room temperature.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an immediate-release film-coated tablet, with each tablet containing 50 or 100 mg of the drug substance. The drug product contains hypromellose acetate succinate, crystalline cellulose, lactose hydrate, croscarmellose sodium, hydrated silicon dioxide, magnesium stearate, and [redacted] as excipients.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising the following steps: [redacted], coating suspension preparation, coating, and packaging/labeling/testing. Process control items and process control parameters have been established for the [redacted] steps. [redacted] is controlled as a critical intermediate.

The quality control strategy has been formulated based on the following assessments (Table 3).

- Identification of CQAs
- Identification of CPPs based on the risk evaluation and determination of the PAR for manufacturing process parameters
- Formulation of the control strategy for impurities using models

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

CQA	Control method
Description	Manufacturing process, specifications
Identification	Specifications
Strength	Manufacturing process, specifications
Related substances	Manufacturing process, specifications
Residual solvents	Manufacturing process
Elemental impurities	Manufacturing process
Content uniformity	Manufacturing process, specifications
Solubility	Manufacturing process, specifications
Microbial limit	Manufacturing process

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description, identification (LC), purity (LC), uniformity of dosage units (content uniformity [LC]), solubility (LC), and assay (LC).

2.2.4 Stability of drug product

Table 4 summarizes the main stability studies for the drug product. The results showed that the drug product is stable. The results of a photostability study showed that the drug product is photostable.

Table 4. Stability studies for the drug product

Study	Primary batch	Temperature	Humidity	Storage package	Storage period
Long-term	3 commercial scale batches	30°C	65% RH	Blister pack (polyvinyl chloride/ polychlorotrifluoroethylene and aluminum foil)	24 months
Accelerated		40°C	75% RH		6 months

Based on the above results, a shelf life of 36 months was proposed for the drug product when packaged in a blister pack (polyvinyl chloride/polychlorotrifluoroethylene and aluminum foil) and stored at room temperature in accordance with the ICH Q1E guidelines. Long-term testing will be continued up to [redacted] months.

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA concluded that the quality of the drug substance and drug product is adequately controlled.

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

3.1 Primary pharmacodynamics

3.1.1 Binding to BTK (CTD 4.2.1.1.2, 4.2.1.1.4, 4.2.1.1.5, 4.2.1.1.13)

The binding affinity of pirtobrutinib for wild type BTK as well as human BTK (recombinant protein) harboring 3 types of resistance mutations[5)] was evaluated using surface plasmon resonance. Table 5 shows the values of dissociation constant (K_D) for pirtobrutinib.

[5)] There have been reports of acquired mutations emerging in the BTK tyrosine kinase domain, such as C481S, occurred in patients who received existing covalent BTK inhibitors (e.g., ibrutinib and acalabrutinib) (*J Clin Oncol.* 2017;35:1437-43, *Blood.* 2019;134:504).

Table 5. The binding affinity of pirtobrutinib for wild type BTK or BTK harboring resistance mutations

Resistance mutation	N	K_D (nmol/L)
None	3	1.0 ± 0.3
C481S*	3	1.7 ± 0.8
C481R*	1	0.4
C481T*	1	0.2

Mean ± standard deviation; individual value when N = 1; * substitution of cysteine (C) at position 481 with serine (S), arginine (R), or threonine (T)

The inhibitory effect of pirtobrutinib on adenosine triphosphate (ATP) binding to wild-type BTK or human BTK (recombinant protein) harboring the C481S mutation was investigated by homogeneous time-resolved fluorescence (HTRF) assay. The IC_{50} values (N = 1) of pirtobrutinib against kinase activity of wild-type and C481S mutant BTKs were 5.5 and 2.6 nmol/L, respectively. The results suggest that pirtobrutinib competitively binds to the ATP binding site of BTK, inhibiting BTK.

Bruton's tyrosine kinase occupancy by pirtobrutinib in human peripheral blood mononuclear cells (PBMCs) was assessed based on a mobility shift assay using fluorescently labeled substrates. The EC_{50} value[6)] of pirtobrutinib (mean ± standard deviation; N = 3) was 3.82 ± 1.35 nmol/L, and the BTK occupancy[7)] by pirtobrutinib at 1,000 nmol/L was >97%.

3.1.2 Inhibitory effects on BTK kinase activity (CTD 4.2.1.1.1, 4.2.1.1.3, 4.2.1.1.6, 4.2.1.1.7, 4.2.1.1.8, 4.2.1.1.9)

The inhibitory effects of pirtobrutinib on the kinase activity of wild-type and C481S mutant BTKs were investigated at ATP concentrations[8)] equivalent to the K_m value using the substrate uptake of ^{33}P-labeled ATP as an indicator. The IC_{50} values of pirtobrutinib (mean ± standard deviation; N = 12) were 3.15 ± 1.32 and 1.42 ± 0.60 nmol/L for the wild type BTK and C481S mutant BTK, respectively.

The inhibitory effects of pirtobrutinib, ibrutinib, and acalabrutinib on BTK autophosphorylation were investigated by western blotting or electrochemiluminescence (ECL) using human fetal kidney HEK293 cells expressing wild-type BTK or BTK harboring one of the 4 types of resistance mutations. Table 6 shows the IC_{50} values of pirtobrutinib, ibrutinib, and acalabrutinib.

Table 6. Inhibitory effects of pirtobrutinib, ibrutinib, and acalabrutinib on the autophosphorylation of wild-type BTK or BTK harboring resistance mutations

Resistance mutation	IC_{50} (nmol/L)					
	N	Pirtobrutinib	N	Ibrutinib	N	Acalabrutinib
None*1	3	3.9 ± 1.6	2	1.9, 2.0	2	9.3, 15
C481S*1,3	2	9.0, 7.2	1	120	2	>300, >300
C481T*1,3	2	4.8, 9.5	2	146, >300	2	270, >300
C481G*2,3	2	17, 11	1	>300	1	>300
C481R*2,3	2	9.0, 16	1	>300	1	>300

Mean ± standard deviation; individual value when N = 1 or 2; *1, measured by western blotting; *2, measured by ECL; *3, substitution of cysteine (C) at position 481 with serine (S), threonine (T), glycine (G), or arginine (R)

6) Concentration at which 50% of BTK is occupied
7) Occupancy (%) = 100 − (percentage of unoccupied BTK relative to vehicle control [dimethylsulfoxide (DMSO)])
8) Inhibitory effects were studied at 50 μmol/L for wild-type BTK and at 15 μmol/L (N = 10) or 50 μmol/L (N = 2) for C481S mutant BTK.

The inhibitory effects of pirtobrutinib and ibrutinib on BTK autophosphorylation were investigated by western blotting using HEK293 cells stably expressing wild-type or C481S mutant BTK. Table 7 shows the IC_{50} values of pirtobrutinib and ibrutinib.

Table 7. Inhibitory effects of pirtobrutinib and ibrutinib on the autophosphorylation of wild-type or C481S mutant BTK

Resistance mutation	IC_{50} (nmol/L)	
	Pirtobrutinib	Ibrutinib
None	8.8 ± 1.2	6.2 ± 1.0
C481S	9.8 ± 4.3	>300

Mean ± standard deviation; N = 3

The inhibitory effects of pirtobrutinib on BTK autophosphorylation were investigated using the TMD8 cell line derived from human activated B cell subtype diffuse large B-cell lymphoma (ABC-DLBCL) and the Ramos RA1 cell line derived from human Burkitt lymphoma by western blotting. The IC_{50} values were 0.9 and 5.5 nmol/L (individual values; N = 2) for TMD8 cells, and 3.3 ± 0.8 nmol/L (mean ± standard deviation; N = 3) for Ramos RA1 cells.

The inhibitory effects of M1 (ring opening of pyrazole ring), a metabolite of pirtobrutinib, on the kinase activity of human BTK (recombinant protein) were investigated using the substrate uptake of ^{33}P-labeled ATP as an indicator. The results showed no inhibition.

3.1.3 Inhibitory effects on BTK-mediated downstream signaling (CTD 4.2.1.1.8)

The inhibitory effects of pirtobrutinib on phosphorylation of PLCγ2, a signaling pathway downstream of BTK, were investigated by western blotting using the Ramos RA1 cell line. The IC_{50} value of pirtobrutinib was 9.1 ± 4.1 nmol/L (mean ± standard deviation; N = 3).

3.1.4 Inhibitory effects on proliferation of malignant tumor cell lines

3.1.4.1 Mantle cell lymphoma cell lines

3.1.4.1.1 *In vitro* (CTD 4.2.1.1.10)

The inhibitory effects of pirtobrutinib on the proliferation of the human MCL REC-1 cell line were investigated using live cell ATP levels as an indicator. The IC_{50} value of pirtobrutinib was 3.13 ± 0.54 nmol/L (mean ± standard deviation; N = 3).

3.1.4.1.2 *In vivo* (CTD 4.2.1.1.16)

The inhibitory effects of pirtobrutinib on tumor growth were investigated using nude mice (N = 6 or 10/group) implanted with subcutaneous xenografts of REC-1 cells. The day of xenograft was considered as Day 0, which was the starting date of the study. Pirtobrutinib 10, 30, or 50 mg/kg was orally administered BID for 21 days from the next day after the mean tumor volume reached 150 mm^3 (Day 19), and tumor volume was calculated. On Day 39, statistically significant tumor growth inhibition was observed in all pirtobrutinib treatment groups compared to the control group (0.6% methylcellulose and 0.5%Tween 80) (Figure 1).

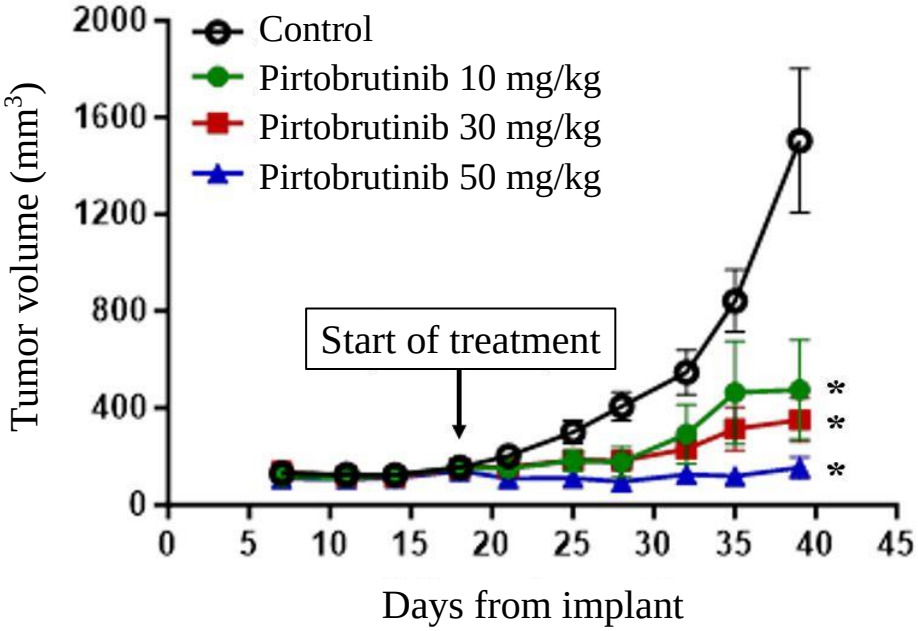


Figure 1. Inhibition of tumor growth by pirtobrutinib in nude mice implanted with subcutaneous xenografts of REC-1 cells

N = 6 or 10; mean ± standard error; * *P*-values compared to the control group were *P* = 0.0007 (pirtobrutinib 10 mg/kg), *P* = 0.0002 (pirtobrutinib 30 mg/kg), and *P* <0.0001 (pirtobrutinib 50 mg/kg) (two-way repeated measures analysis of variance [ANOVA] with Bonferroni's multiple comparison test was used for all comparisons)

3.1.4.2 Malignant tumor cell lines other than MCL

3.1.4.2.1 *In vitro* (CTD 4.2.1.1.9)

The inhibitory effects of pirtobrutinib on the cell proliferation of TMD8 cells were investigated by measuring cell numbers. The IC_{50} value of pirtobrutinib was 2.33 nmol/L (N = 1).

3.1.4.2.2 *In vivo* (CTD 4.2.1.1.14, 4.2.1.1.15, 4.2.1.1.17)

The inhibitory effect of pirtobrutinib on the growth of tumor cells were investigated in non-obese diabetic (NOD)/severe combined immunodeficiency (SCID) mice (N = 10 or 12/group) implanted with subcutaneous xenografts of human ABC-DLBCL OCI-Ly10 cells. The day when the tumor volume reached 150 to 200 mm^3 (the day of randomization) was considered as the start of the study (Day 0). From Day 0, pirtobrutinib 10 or 50 mg/kg was orally administered BID for 28 days, and tumor volume was calculated. On Day 28, statistically significant tumor growth inhibition was observed in all pirtobrutinib treatment groups as compared to the control group (0.5% hydroxypropyl methylcellulose) (both were *P* <0.0001; Dunnett's multiple comparison test).

The inhibitory effects of pirtobrutinib on the growth of tumor cells were investigated in SCID mice (N = 10/group) implanted with subcutaneous xenografts of TMD8 cells. The day of xenograft was considered as Day 0. Pirtobrutinib 15 or 30 mg/kg was orally administered BID for 18 days (14 days for control) from the next day after the mean tumor volume reached 400 mm^3 (Day 20), and tumor volume was calculated. On Day 33, statistically significant tumor growth inhibition was observed in all pirtobrutinib treatment groups compared to the control group (0.6% methylcellulose and 0.5% Tween 80) (*P* <0.0001 for all; Dunnett's multiple comparison test).

The inhibitory effects of pirtobrutinib on the growth of tumor cells were investigated in SCID mice (N = 10 or 14/group) implanted with subcutaneous xenografts of TMD8 cells stably expressing C481S mutant BTK. The day of xenograft was considered as Day 0. From the next day (Day 13) after the mean tumor volume reached 150 mm^3 (the day of randomization), the following study drug was orally administered BID for 14 days and tumor volume was calculated: (1) pirtobrutinib 3, 10, or 30 mg/kg monotherapy; (2) ibrutinib 50 mg/kg monotherapy; or (3) pirtobrutinib (3, 10, or 30 mg/kg) in combination with ibrutinib (50 mg/kg). On Day 27, statistically significant tumor growth inhibition was observed in the pirtobrutinib monotherapy 10 and 30 mg/kg groups and all combination therapy groups compared to the control group (0.6% methylcellulose and 0.5% Tween 80) (P <0.0001 for all; Dunnett's multiple comparison test).

3.2 Secondary pharmacodynamics

3.2.1 Effects on kinases other than BTK (CTD 4.2.1.2.1, 4.2.1.2.2, 4.2.1.2.3, 4.2.1.2.4)

The inhibitory effects of pirtobrutinib on 371 types of kinases (recombinant proteins) were investigated using the substrate uptake of ^{33}P-labeled ATP as an indicator. Kinases inhibited by 1 μmol/L of pirtobrutinib at ≥50% were human epidermal growth factor receptor (HER)4, breast tumor kinase (BRK), mitogen-activated protein kinase/extracellular signal-regulated kinase (MEK)2, MEK1, Yamaguchi sarcoma viral oncogene homolog (YES), tyrosine protein kinase (TXK), C-terminal Src kinase (CSK), and tyrosine-protein kinase Fyn (FYN).

The inhibitory effects of pirtobrutinib on BTK, the 8 kinases above, and TEC[9)] were investigated using the substrate uptake of ^{33}P-labeled ATP as an indicator. Table 8 shows the IC_{50} values of pirtobrutinib.

Table 8. Inhibitory effects of pirtobrutinib on kinases

Kinase	N	IC_{50} (nmol/L)	Kinase	N	IC_{50} (nmol/L)
BTK	12	3.2 ± 1.3	YES	2	160, 154
HER4/ERBB4	2	12, 15	TXK	2	200, 218
BRK	2	52, 56	CSK	2	517, 587
MEK2	2	87, 79	FYN	2	1,580, 1,840
MEK1	2	143, 151	TEC	12	1,230 ± 256

Mean ± standard deviation; individual values when N = 2

The inhibitory effects of pirtobrutinib and ibrutinib on kinases were investigated by bioluminescence resonance energy transfer (BRET) using HEK293 cells expressing fusion protein of 7 kinases including BTK and luciferase. Table 9 shows the IC_{50} values of pirtobrutinib and ibrutinib.

Table 9. Inhibitory effects of pirtobrutinib and ibrutinib on kinases

Kinase	IC_{50} (nmol/L)	
	Pirtobrutinib	Ibrutinib
BTK	0.66 ± 0.34	0.33 ± 0.13
TEC	70.46 ± 20.30	0.37 ± 0.18
BRK	360.47 ± 198.56	6.29 ± 2.65
YES	>5,000	207.79 ± 116.77
TXK	>5,000	0.26 ± 0.01

9) In a study of inhibition of kinases by ibrutinib, TEC is identified as an off-target molecule inhibited by ibrutinib (*Front Cell Dev Biol.* 2021;9:630942).

CSK	>5,000	544.60 ± 269.24
FYN	>5,000	3,439.00 ± 2,703.73

Mean ± standard deviation, N = 3

The inhibitory effects of pirtobrutinib on HER4 dimerization were investigated using human osteosarcoma U2OS cells co-expressing HER4 fused with a β-galactosidase fragment and SH2 domain fused with a β-galactosidase fragment.[10)] The results of the assay showed that the IC_{50} values of pirtobrutinib were >10,000 nmol/L (N = 2; individual values).

Using the HCT116 human colorectal cancer cell line and the A375 human melanoma cell line, the inhibitory effects of pirtobrutinib on MEK1 and MEK2 were investigated by fluorometric assay with antibodies against phosphorylated ERK1/2, a signaling pathway downstream of MEK. The IC_{50} values of pirtobrutinib against the HCT116 and A375 cell lines were 12,600 ± 2,400 nmol/L and 3,790 ± 1,310 nmol/L, respectively (mean ± standard deviation; N = 3).

The above results showed that the IC_{50} value of pirtobrutinib for BRK (0.36 μmol/L) was <0.57 μmol/L,[11)] the C_{max} of the unbound form in plasma at the recommended clinical dose (200 mg QD). However, given such factors as the extremely low expression level of BRK in normal tissue (*Theranostics.* 2021;11:1115-28), the applicant explained that it is unlikely that safety-related issues will emerge as a result of inhibition of the kinases by pirtobrutinib.

3.2.2 Effects on receptors, ion channels, transporters, and enzymes (CTD 4.2.1.2.5)

The effects of pirtobrutinib on a total of 44 targets including receptors, ion channels, transporters, and enzymes were investigated by assays such as those using radiolabeled ligands. None of the targets tested showed ≥50% inhibition at pirtobrutinib 1 μmol/L.

3.3 Safety pharmacology

3.3.1 Effects on the central nervous system

In a 28-day repeated toxicity study in rats [see Section 5.2], pirtobrutinib 50, 150, or 500 mg/kg (for males) or pirtobrutinib 20, 60, or 175 mg/kg (for females) was administered orally BID, and the effects of pirtobrutinib on the central nervous system were evaluated by functional observational battery and spontaneous motor activity. The results showed no effects of pirtobrutinib.

3.3.2 Effects on the cardiovascular system

3.3.2.1 Effects on hERG potassium current (CTD 4.2.1.3.1)

The effects of pirtobrutinib 3, 10, 30, or 100 μmol/L on the human *ether-a-go-go*-related gene (hERG) potassium current were assessed using the HEK293 cell line transfected with hERG. The percentage inhibition

[10)] When HER4 fused with a β-galactosidase fragment and the SH2 domain fused with a β-galactosidase fragment that is complementing the β-galactosidase fragment fused with HER4 are brought in a close proximity to each other, active β-galactosidase forms. The resulting enzyme hydrolyzes substrate, generating a chemiluminescent light signal, which was measured to evaluate the inhibitory effect of pirtobrutinib.

[11)] The value was calculated based on the C_{max} (6,460 ng/mL) of pirtobrutinib at steady state from the PPK analysis when pirtobrutinib 200 mg was administered QD to patients with MCL and other conditions in global phase I/II study (Study 18001) and the unbound fraction of plasma protein binding (0.04207) [see Section 4.2.2].

of hERG potassium current (mean ± standard error; N = 3) was 8.5% ± 1.1% (3 μmol/L), 21.9% ± 0.3% (10 μmol/L), 48.6% ± 1.3% (30 μmol/L), and 76.7% ± 0.9% (100 μmol/L), with an IC_{50} of 32.1 μmol/L. Statistically significant inhibition was observed in all pirtobrutinib treatment groups compared to the control group (HEPES buffered saline solution containing 0.3% DMSO) (P <0.05 for all; Dunnett's multiple comparison test).

3.3.2.2 Effects on blood pressure, heart rate, and electrocardiogram (CTD 4.2.1.3.2)

Dogs (N = 4) were treated with a single oral dose of pirtobrutinib 5, 20, or 60 mg/kg, with each animal assigned to treatments in a sequence. The effects of pirtobrutinib on blood pressure (systolic blood pressure, diastolic blood pressure, and mean blood pressure), heart rate, and electrocardiogram (PR, RR, QRS, QT interval [QT], and QT interval corrected [QTc]) were assessed. Compared to the control group (0.5% hydroxypropyl methylcellulose), statistically significant QRS interval shortening was observed in the pirtobrutinib 5 and 20 mg/kg groups, and statistically significant QRS interval prolongation observed in the pirtobrutinib 60 mg/kg group.

The applicant explained that it is unlikely that safety-related issues in terms of the effect on QRS interval will emerge when pirtobrutinib is used in clinical settings given the following factors: the assessment described above showed no correlation between the C_{max} of pirtobrutinib and QRS interval; the above findings were not noted in the 28-day repeated dose toxicity study in dogs [see Section 5.2]; in the foreign phase I study (Study 20011), which was conducted to assess the effect of pirtobrutinib on QTc interval, change from baseline in QTc interval was not clearly correlated with plasma pirtobrutinib concentration [see Section 6.2.6].

3.3.3 Effects on the respiratory system

In the 28-day repeated dose toxicity study in dogs [see Section 5.2], pirtobrutinib 10, 30, or 90 mg/kg was administered orally BID, and the effects of pirtobrutinib on the respiratory rate were assessed. No effects of pirtobrutinib were noted.

3.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the non-clinical pharmacology of pirtobrutinib is acceptable except for the points raised in the following sections.

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

The applicant's explanation about the mechanism of action of pirtobrutinib and its efficacy in the treatment of MCL resistant to existing BTK inhibitors (e.g., ibrutinib):

Bruton's tyrosine kinase, a signaling pathway downstream of BCR expressed mainly in B cells, is activated by BCR engagement and plays a significant role in B-cell survival, proliferation, and other processes (e.g., *J Clin Oncol.* 2014;32:1830-9). There have been reports that the BCR signaling pathway is constantly activated in MCL, a B cell malignancy (e.g., *Int Rev Immunol.* 2012;31:119-32).

Acquired resistance to existing BTK inhibitors is commonly mediated by resistance mutation at the covalent binding site (C481) between a BTK inhibitor and BTK (*J Clin Oncol.* 2017;35:1437-43, *Blood.* 2019;134:504). This mutation has also been reported in patients with MCL resistant to ibrutinib (e.g., *Blood.* 2016;127:1559-63, *Br J Haematol.* 2018;183:578-87). Furthermore, mutation of genes involved in the BCR signaling pathway (e.g., caspase recruitment domain family member 11 [CARD11]) in the mechanism of acquired resistance to ibrutinib in patients with MCL has been reported (e.g., *Oncotarget.* 2016;7:38180-90).

Pirtobrutinib inhibits BTK kinase activation as existing covalent BTK inhibitors do, but it binds to BTK non-covalently, unlike existing BTK inhibitors (*Front Cell Dev Biol.* 2021;9:630942). Pirtobrutinib is thought to inhibit BTK kinase activation reversibly even where the C481 mutation is present [see Section 3.1.1], inhibiting BTK-mediated downstream signaling pathway [see Sections 3.1.2 and 3.1.3] and inhibiting tumor growth.

In addition, given that pirtobrutinib showed tumor growth inhibition in mice implanted with human MCL REC-1 cells and TMD8 cells derived from human ABC-DLBCL expressing C481S mutant BTK [see Sections 3.1.4.1.2 and 3.1.4.2.2], pirtobrutinib is expected to be effective in the treatment of MCL resistant to existing BTK inhibitors.

PMDA's view:
The applicant's explanation is generally acceptable. However, the efficacy of pirtobrutinib in the treatment of MCL that became resistant to existing BTK inhibitors by a mechanism of acquired resistance other than BTK C481 mutation remains unclear at this time. It is likely that this will become important information in predicting the efficacy or selecting eligible patients for pirtobrutinib in clinical use; therefore, the evaluation should be continued and if new information becomes available, the applicant should provide such information to health professionals in an appropriate manner.

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

The pharmacokinetics (PK) of pirtobrutinib in animals was evaluated in rats and dogs. The plasma protein binding, drug metabolizing enzymes, transporters, and other pharmacokinetic properties of pirtobrutinib were investigated using biological samples derived from humans or animals.

Pirtobrutinib in rat or dog plasma was determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS) (lower limit of quantitation, 20 ng/mL). Radioactivity levels in rat tissues were determined by quantitative whole-body autoradiography (lower limit of quantitation, 178 ng Eq./g).

4.1 Absorption

4.1.1 Single-dose studies

A single oral dose of pirtobrutinib 300 mg was administered to male and female dogs under non-fasting or fasting conditions, and plasma pirtobrutinib concentrations were evaluated (Table 10). No clear differences in PK of pirtobrutinib were observed between the sexes. No food effects on the PK of pirtobrutinib were noted.

Table 10. PK parameters of pirtobrutinib (male and female dogs; single oral dose)

Feed condition	Sex	N	C_{max} (ng/mL)	t_{max}* (h)	AUC_t (ng·h/mL)
Non-fasting	M	4	12,800 ± 5,260	1.00 (1.00, 4.00)	122,000 ± 25,700
	F	4	20,200 ± 9,290	0.75 (0.50, 4.00)	144,000 ± 26,600
Fasting	M	4	14,500 ± 4,350	3.00 (1.00, 4.00)	161,000 ± 57,600
	F	4	11,300 ± 1,090	2.00 (2.00, 2.00)	110,000 ± 24,800

Mean ± standard deviation; * median (Min, Max)

4.1.2 Repeated-dose studies

Oral doses of pirtobrutinib 50, 150, or 500 mg/kg (male rats), pirtobrutinib 20, 60, or 175 mg/kg (female rats) were administered BID for 28 days, and plasma pirtobrutinib concentrations were evaluated (Table 11). The C_{max} and $AUC_{0\text{-}24h}$ of pirtobrutinib increased less than the dose ratio within the dose range studied. The applicant's explanation for these results was that the absorption of pirtobrutinib may have been saturated because the dissolution of pirtobrutinib reached its limit in the digestive tract at the high dose.

Table 11. PK parameters of pirtobrutinib* (male and female rats; 28-day repeated oral dose administration)

Measured (Day)	Sex	Dose (mg/kg)	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-}24h}$ (ng·h/mL)
1	Male	50	1,480	13	16,200
		150	2,750	16	44,300
		500	1,860	4.0	27,000
	Female	20	1,440	4.0	18,000
		60	9,330	13	164,000
		175	14,100	13	260,000
28	Male	50	1,550	13	19,500
		150	2,420	4.0	38,600
		500	2,820	16	48,200
	Female	20	5,410	13	80,700
		60	9,680	4.0	172,000
		175	17,500	16	300,000

* PK parameters were calculate based on the mean (N = 6) of plasma pirtobrutinib concentrations at each measuring timepoint.

4.1.3 *In vitro* membrane permeability

The membrane permeability of pirtobrutinib was investigated in Madin-Darby canine kidney (MDCK) cells expressing human P-glycoprotein (P-gp). The apparent permeability in the apical to basal direction ($P_{app\ A\rightarrow B}$) for pirtobrutinib 5 μmol/L was 48.8×10^{-6} cm/sec in the presence of a P-gp inhibitor (LSN335984 2.5 μmol/L). In addition, the $P_{app\ A\rightarrow B}$ for propranolol, a compound with high permeability, was 36.5×10^{-6} cm/sec. The applicant explained that these results and other factors indicate pirtobrutinib has a high permeability.

4.2 Distribution

4.2.1 Tissue distribution

A single oral dose of carbon-14 radiolabeled (^{14}C-labeled) pirtobrutinib 35 mg/kg was administered to male pigmented rats to investigate the tissue distribution of radioactivity. Radioactivity was widely distributed across the tissues. Tissue radioactivity levels reached their maximum within 2 hours post-dose in the majority of tissues. Compared with the maximum radioactivity levels in blood (10,200 ng Eq./g), the maximum tissue radioactivity level was particularly high in the liver (55,700 ng Eq./g), small intestine (18,600 ng Eq./g),

bladder (18,200 ng Eq./g), and stomach (16,100 ng Eq./g). The radioactivity levels fell below the limit of quantitation at 168 hours post-dose in the majority of tissues; conversely, radioactivity was detected after 168 hours post-dose in the uvea (294 ng Eq./g) and liver (262 ng Eq./g).

The applicant explained that although the above results suggest that pirtobrutinib and its metabolites bind to melanin, no abnormalities or findings suggestive of toxicity in the eye (other than the cornea), skin, or nervous system were noted in the repeated-dose toxicity studies in rats and dogs [see Section 5.2]; and no safety concerns were identified in melanin-containing tissues (eye and skin) in the clinical studies.

4.2.2 Plasma protein binding

Rat, dog, and human plasma was incubated with pirtobrutinib (50-5,000 ng/mL) at 37°C for 6 hours, and plasma protein binding of pirtobrutinib was investigated using equilibrium dialysis. Plasma protein binding was 86.8% to 87.6% in rats, 82.0% to 83.0% in dogs, and 94.8% to 95.9% in humans.

Male human plasma, female human plasma, human serum albumin (40 mg/mL), or human α1-acid glycoprotein (0.5 or 2 mg/mL) was incubated with pirtobrutinib (0.5-50 μmol/L) or M1 (ring opening of pyrazole ring; 0.5-50 μmol/L) at 37°C for 6 hours, and binding of pirtobrutinib and M1 with human plasma, human serum albumin, or human α1-acid glycoprotein was investigated using equilibrium dialysis. Table 12 shows the percentage binding of pirtobrutinib and M1 to male human plasma, female human plasma, human serum albumin, and human α1-acid glycoprotein.

Table 12. Percentage binding of pirtobrutinib and M1 to human plasma, human serum albumin, and human α1-acid glycoprotein

	Pirtobrutinib	M1
Male human plasma	95.34%-96.21%	99.87%-99.91%
Female human plasma	95.19%-96.61%	99.83%-99.90%
Human serum albumin	97.78%-98.04%	99.72%-99.78%
Human α1-acid glycoprotein (0.5 mg/mL)	21.02%-31.04%	30.69%-59.54%
Human α1-acid glycoprotein (2 mg/mL)	47.05%-55.32%	73.08%-91.93%

4.2.3 Distribution in blood cells

Rat, dog, and human blood was incubated with pirtobrutinib (1 μmol/L) at 37°C for 1 hour and the distribution of pirtobrutinib in blood cells was investigated. The blood-to-plasma concentration ratio for pirtobrutinib was 0.84 (rat), 0.88 (dog), and 0.79 (human), and the blood cell-to-plasma concentration ratio was 0.64 (rat), 0.74 (dog), and 0.51 (human). The applicant explained that the results indicated that in humans, pirtobrutinib is primarily distributed in plasma.

4.2.4 Placental and fetal transfer

Neither the placental nor fetal transfer of pirtobrutinib has been studied. The applicant explained that pirtobrutinib may cross the placental barrier and reach the fetus because embryo-fetal toxicities and teratogenicity have been noted in an embryo-fetal development study in rats [see Section 5.5].

4.3 Metabolism

4.3.1 *In vitro*

Rat, dog, monkey, and human hepatocytes were incubated with pirtobrutinib (2 μmol/L) at 37°C for 24 hours or 168 hours in the presence or absence of a non-selective inhibitor of cytochrome P450 (CYP) isoform (1-aminobenzotriazole, 1 mmol/L), and metabolites of pirtobrutinib were investigated. No human-specific metabolites were detected. Main metabolites detected in human hepatocytes were Metabolite A (*N*-glucuronide), Metabolite B (metabolite formed by glucuronidation following hydroxylation), Metabolite C (metabolite formed by glucuronidation following *O*-demethylation), Metabolites E and H (metabolites formed by hydroxylation). The amounts of Metabolites B, C, E, and H produced decreased in the presence of the non-selective inhibitor of CYP isoform.

Recombinant human CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP2J2, CYP3A4, and CYP3A5) were incubated with pirtobrutinib (30 and 60 nmol/L) at 37°C for 2 hours in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), and CYP isoforms involved in the metabolism of pirtobrutinib were investigated. The proportion of unchanged pirtobrutinib was approximately 50% when incubated in the presence of CYP3A4 and ≥85% when incubated in the presence of other CYP isoforms.

The applicant explained that the above results indicate that CYP3A4 is primarily involved in the metabolism of pirtobrutinib in humans. The pharmacokinetic interactions of pirtobrutinib with CYP3A inhibitors and inducers will be discussed in Sections "6.2.3.1 Drug interaction study with itraconazole or rifampin" and "6.R.2 Pharmacokinetic interactions with CYP3A inhibitors and inducers."

4.3.2 *In vivo*

A single oral dose of ^{14}C-labeled pirtobrutinib 35 mg/kg was administered to bile duct-intact or bile duct-cannulated male and female rats. Metabolites in plasma, urine, feces, and bile were analyzed and the following results were obtained:

- In plasma samples collected from bile duct-intact rats up to 24 hours post-dose, the main compounds detected in male rat samples were M1, M5 (metabolite formed by oxidation of M1), and unchanged pirtobrutinib, representing 33.9%, 20.1%, and 17.9% of plasma total radioactivity, respectively, while the main metabolite detected in female rat samples was unchanged pirtobrutinib, representing 74.2% of plasma total radioactivity.
- In urine samples collected from bile duct-intact rats up to 24 hours post-dose, the main compounds detected in male rat samples were unchanged pirtobrutinib, M2 (*N*-glucuronide), M4 (*N*-glucuronide), and M12 (*O*-desmethyl glucuronide), each representing 0.1% of the administered radioactivity, while the main compounds detected in female rat samples were M12, M2, unchanged pirtobrutinib, and M11 (*O*-desmethyl pirtobrutinib), representing 0.6%, 0.5%, 0.4%, and 0.2% of the administered radioactivity, respectively.

- In fecal samples collected from bile duct-intact rats up to 48 hours post-dose, the main compounds detected in male and female rat samples were unchanged pirtobrutinib (representing 57.7% [M] and 72.9% [F] of the administered radioactivity), M10 (sulfate conjugate; 12.3% [M] and 1.8% [F]), and M11 (5.7% [M] and 10.3% [F]).
- In bile samples collected from bile-duct cannulated rats up to 48 hours post-dose, the main compounds detected in male and female rat samples were M4 (16.8% [M] and 11.8% [F]), unchanged pirtobrutinib (14.8% [M] and 9.7% [F]), M3 (monooxy glucuronide; 10.5% [M] and 6.2% [F]), and M2 (3.8% [M] and 5.9% [F]).

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

A single oral dose of ^{14}C-labeled pirtobrutinib 35 mg/kg was administered to bile duct-intact male and female rats, and urinary and fecal excretion (percentage of the administered radioactivity) was investigated. Up to 120 hours post-dose, 1.72% (male rats) and 3.64% (female rats) were excreted in urine and 95.7% (male rats) and 94.9% (female rats) were excreted in feces.

A single oral dose of ^{14}C-labeled pirtobrutinib 35 mg/kg was administered to bile duct-cannulated male and female rats, and urinary, fecal, and biliary excretion (percentage of the administered radioactivity) was investigated. Up to 120 hours post-dose, 1.40% (male) and 3.04% (female) were excreted in urine, 41.6% (male) and 53.7% (female) were excreted in feces, and 52.2% (male) and 39.4% (female) were excreted in bile.

The applicant explained that the above results indicate that pirtobrutinib and its metabolite are primarily excreted in feces.

4.4.2 Excretion in milk

The excretion of pirtobrutinib in milk has not been investigated. Given that pirtobrutinib has high membrane permeability [see Section 4.1.3] and is a substrate for breast cancer resistance protein (BCRP) [see Section 4.5.3], pirtobrutinib may be excreted in milk.

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

Based on the plasma protein binding of pirtobrutinib [see Section 4.2.2] and the C_{max} of pirtobrutinib (13.5 μmol/L[12)]) after treatment according to the proposed dosage regimen of pirtobrutinib, in addition to the investigation results shown below, the applicant explained that pirtobrutinib may cause pharmacokinetic interactions through inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A during clinical use. The pharmacokinetic interactions between pirtobrutinib and the substrates for CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP3A are described in Sections "6.2.3.2 Drug interaction study with

[12)] The C_{max} of pirtobrutinib at steady state (6,460 ng/mL) based on the PPK analysis when pirtobrutinib 200 mg was administered QD to patients with MCL and other conditions in the global phase I/II study (Study 18001).

midazolam," "6.2.3.3 Drug interaction study with repaglinide," and "6.2.3.4 Drug interaction study with caffein, *S*-warfarin, and omeprazole."

- Human liver microsomes were incubated with pirtobrutinib (0.06-60 μmol/L) in the presence of substrates for CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A)[13] and NADPH to investigate the inhibitory effects of pirtobrutinib on the CYP isoforms. Pirtobrutinib inhibited the metabolism of the substrates for CYP2C8 (IC_{50} = 12 μmol/L), CYP2C9 (IC_{50} = 27 μmol/L), and CYP3A (IC_{50} = 38 μmol/L[14]). Pirtobrutinib also inhibited the metabolism of the substrates for CYP2B6, CYP2C19, and CYP2D6, with an inhibition percentage of 30%, 51%, and 22%, respectively, at the maximum concentration studied. Pirtobrutinib did not show clear inhibitory effects on the metabolism of the substrates for the other CYP isoforms studied.
- Human liver microsomes were incubated with pirtobrutinib (0.06-60 μmol/L) in the presence of NADPH, and then incubated with the substrates for CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A)[15] to investigate the time-dependent inhibitory effects of pirtobrutinib on the CYP isoforms. Pirtobrutinib inhibited the metabolism of the substrates for CYP3A in a time-dependent manner with an IC_{50} of 8.0 μmol/L.[16] Pirtobrutinib did not show clear time-dependent inhibitory effects on the metabolism of the substrates for the other CYP isoforms studied.
- Complementary deoxyribonucleic acid (cDNA)-expressed enzyme or human liver microsomes[17] were incubated with pirtobrutinib (0.1-180 μmol/L) in the presence of the substrates for uridine diphosphate glucuronosyl transferase (UGT) isoforms (UGT1A1, UGT1A8, UGT1A9, and UGT2B7)[18] and uridine diphosphate glucuronic acid (UDPGA) to investigate the inhibitory effects of pirtobrutinib on the UGT isoforms. Pirtobrutinib inhibited the metabolism of the substrates for UGT1A1 (IC_{50} = 18 μmol/L), UGT1A9 (IC_{50} = 57 μmol/L), and UGT2B7 (IC_{50} = 170 μmol/L). Pirtobrutinib did not show a clear inhibitory effect on the metabolism of the substrate for UGT1A8.

4.5.2 Enzyme induction

Primary human hepatocytes were incubated in the presence of pirtobrutinib (0.1-75 μmol/L) for 2 days to determine the messenger ribonucleic acid (mRNA) expression and enzyme activity of CYP1A2, CYP2B6, CYP2C19, CYP3A4, and CYP3A5, and the mRNA expression of CYP2C8, CYP2C9, and CYP2D6. Pirtobrutinib induced the mRNA expression of CYP2B6, CYP2C19, and CYP3A4, at a maximum of 21.3% to

[13] The following compounds were used as substrates for the CYP isoforms: phenacetin (CYP1A2), efavirenz (CYP2B6), amodiaquine (CYP2C8), diclofenac (CYP2C9), *S*-mephenytoin (CYP2C19), and dextromethorphan (CYP2D6). As substrates for CYP3A, testosterone and midazolam were used.

[14] The IC_{50} values obtained when testosterone was used as the substrate for CYP3A. The IC_{50} value was 59 μmol/L when midazolam was used as a substrate.

[15] The following compounds were used as substrates for the CYP isoforms: phenacetin (CYP1A2), efavirenz (CYP2B6), amodiaquine (CYP2C8), diclofenac (CYP2C9), *S*-mephenytoin (CYP2C19), and dextromethorphan (CYP2D6). As substrates for CYP3A, testosterone and midazolam were used.

[16] The IC_{50} value obtained when testosterone was used as the substrate for CYP3A. The IC_{50} value was 9.7 μmol/L when midazolam was used as a substrate.

[17] Complementary DNA-expressed enzyme was used to study UGT1A8, while human liver microsomes were used to study UGT1A1, UGT1A9, and UGT2B7.

[18] The following compounds were used as substrates for the UGT isoforms: 17β-estradiol (UGT1A1), propofol (UGT1A8 and UGT1A9), and zidovudine (UGT2B7).

288%,[19] 122%, and 111% of that of the respective positive control,[20] respectively, and the mRNA expression of CYP3A5 at a maximum of ≥20% of that of the positive control. Pirtobrutinib also induced enzyme activity of CYP2B6 and CYP2C19 at a maximum of 35.9%[21] and 43.6% to 104% of that of the respective positive control, respectively. Conversely, pirtobrutinib did not show a clear inductive effect on the mRNA expression or enzyme activity of the other CYP isoforms.

Based on the plasma protein binding of pirtobrutinib [see Section 4.2.2] and the C_{max} of pirtobrutinib (13.5 μmol/L[12]) after treatment according to the proposed dosage regimen of pirtobrutinib, in addition to the investigation results above, the applicant explained that pirtobrutinib may cause pharmacokinetic interactions through induction of CYP2B6, CYP2C19, and CYP3A in clinical use. The pharmacokinetic interactions between pirtobrutinib and the substrates for CYP2C19 and CYP3A are described in Sections "6.2.3.2 Drug interaction study with midazolam," and "6.2.3.4 Drug interaction study with caffein, *S*-warfarin, and omeprazole."

4.5.3 Transporters

Based on the following study results and other data, pirtobrutinib was shown to be a substrate for P-gp and BCRP. The pharmacokinetic interactions of pirtobrutinib with P-gp inhibitors are discussed in Section "6.2.3.1 Drug interaction study with itraconazole or rifampin."

- Using MDCK cells expressing human P-gp, P-gp-mediated transport of pirtobrutinib (1-10 μmol/L[22]) was investigated. The ratio of the efflux ratio of pirtobrutinib in the cells expressing the transporter to that in the cells not expressing the transporter was 17.6 to 22.3, while the ratio was 1.17 in the presence of P-gp inhibitor (elacridar, 3 μmol/L).
- Using MDCK II cells expressing human BCRP, BCRP-mediated transport of pirtobrutinib (1-10 μmol/L[22]) was investigated. The ratio of the efflux ratio of pirtobrutinib in the cells expressing the transporter to that in the cells not expressing the transporter was 5.65 to 9.79, while the ratio was 0.963 in the presence of BCRP inhibitor (Ko143, 1 μmol/L).
- Using MDCK II cells expressing human organic anion transporting polypeptide (OATP)1B1, OATP1B3, or organic cation transporter (OCT)1, each transporter-mediated transport of pirtobrutinib (1-10 μmol/L) was investigated. The ratio of the uptake rate of pirtobrutinib in the cells expressing the transporter to that in the cells not expressing the transporter was <2 for all the transporters.
- Using membrane vesicles prepared from insect ovarian Sf9 cells expressing human bile salt export pump (BSEP), BSEP-mediated transport of pirtobrutinib (1-10 μmol/L) was investigated. The ratio of the uptake amount of pirtobrutinib in the presence of ATP to that in the absence of ATP was <2.

[19] The percentages are based on the values when 6-(4-chlorophenyl)imidazo[2,1-b][1,3]thiazole-5-carbaldehyde O-(3,4-dichlorobenzyl)oxim (CITCO) was used as a positive control. When phenobarbital was used, a maximum of 20.1% to 27.1% was obtained.
[20] As positive controls, rifampicin (20 μmol/L; for CYP2C8, CYP2C9, CYP2C19, and CYP3A4) and phenobarbital (1,000 μmol/L; for CYP3A5) were used. As positive controls for CYP2B6, CITCO (100 nmol/L) and phenobarbital (1,000 μmol/L) were used.
[21] The percentage is based on the value when CITCO was used as a positive control. When phenobarbital was used, a maximum of 19.2% was obtained.
[22] The assays in the presence of P-gp or BCRP inhibitor were performed at 3 μmol/L.

Based on the plasma protein binding of pirtobrutinib [see Section 4.2.2], the C_{max} of pirtobrutinib (13.5 μmol/L[12)]) after treatment according to the proposed dosage regimen of pirtobrutinib, and estimated concentration of pirtobrutinib (1,670 μmol/L) in the digestive tract after treatment according to the proposed dosage regimen of pirtobrutinib, in addition to the investigation results shown below, the applicant explained that pirtobrutinib may cause pharmacokinetic interactions through inhibition of P-gp and BCRP in clinical use. The pharmacokinetic interactions of pirtobrutinib with the substrates for P-gp and BCRP are described in Sections "6.2.3.5 Drug interaction study with digoxin" and "6.2.3.6 Drug interaction study with rosuvastatin."

- The inhibitory effects of pirtobrutinib (0.274-200 μmol/L) on the transport of the substrate for P-gp (^{3}H-labeled vinblastine, 0.1 μmol/L) using HEK293 cells expressing human P-gp. Pirtobrutinib inhibited the transport of the substrate for P-gp with an IC_{50} of 6.01 μmol/L.
- The inhibitory effects of pirtobrutinib (0.3-100 μmol/L) on the transport of the substrates for the transporters[23)] were investigated using MDCK II cells expressing human BCRP, organic anion transporter (OAT)1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, multidrug and toxin extrusion (MATE)1 or MATE2-K, and membrane vesicles prepared from Sf9 cells expressing BSEP. Pirtobrutinib inhibited the transport of the substrates for BCRP (IC_{50} = 18.1 μmol/L), OAT3 (IC_{50} = 11.8 μmol/L), OCT2 (IC_{50} = 26.1 μmol/L), OATP1B1 (IC_{50} = 21.0 μmol/L), OATP1B3 (IC_{50} = 18.5 μmol/L), MATE1 (IC_{50} = 11.8 μmol/L), and MATE2-K (IC_{50} = 22.7 μmol/L). Pirtobrutinib did not show a clear inhibitory effect on the transport of the substrate for OAT1 or OCT1.
- The inhibitory effects of pirtobrutinib (0.005-100 μmol/L) on the transport of the substrate for OATP2B1 (rosuvastatin, 10 μmol/L) using HEK293 cells expressing human OATP2B1. Pirtobrutinib inhibited the transport of the substrate for OATP2B1 with an IC_{50} of 2.73 μmol/L.

4.R Outline of the review conducted by PMDA

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

4.R.1 Pharmacokinetic interactions

The applicant's explanation about the pharmacokinetic interaction of pirtobrutinib:

The *in vitro* study results suggest that when pirtobrutinib is co-administered with a CYP2B6 or CYP2D6 substrate, or a BCRP inhibitor, pharmacokinetic interactions may occur [see Sections 4.5.1, 4.5.2, and 4.5.3]. However, taking into account the following and other aspects, such interactions are unlikely to cause problems in the clinical use of pirtobrutinib.

- In the global phase I/II study (Study 18001), although the limited number of patients who received pirtobrutinib in combination with a CYP2B6 or CYP2D6 substrate, or a BCRP inhibitor precludes strict evaluation, no particular safety-related concerns were noted in the patients concerned.

[23)] The following compounds were used as substrates for the transporters: prazosin (2 μmol/L) for BCRP, *p*-aminohippuric acid (2 μmol/L) for OAT1, estrone 3-sulfate (0.1 μmol/L) for OAT3, 1-methyl-4-phenylpyridinium (2 μmol/L) for OCT1, estradiol-17β-glucuronide (2 μmol/L) for OATP1B1, cholecystokinin octapeptide (2 μmol/L) for OATP1B3, and taurocholic acid (1 μmol/L) for BSEP. Metformin (10 μmol/L) was used as substrates for OCT2, MATE1, and MATE2-K.

PMDA's view:

The applicant's explanation is generally acceptable. However, information on the pharmacokinetic interactions of pirtobrutinib when co-administered with a CYP2B6 or CYP2D6 substrate, or a BCRP inhibitor is important for proper use of pirtobrutinib. Therefore, currently available information should be provided to health professionals in an appropriate manner using the package insert while gathering relevant information. When useful information becomes available, such information should be provided to health professionals in an appropriate manner.

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

No single-dose toxicity studies of pirtobrutinib have been conducted. Based on the results following administration of the initial dose in the repeated oral dose toxicity studies in rats and dogs, as well as the results from the *in vivo* micronucleus study in rats, the acute toxicity and approximate lethal dose of pirtobrutinib were evaluated. Acute symptoms in rats included unkempt fur and piloerection observed in the *in vivo* micronucleus study in rats, while no acute symptoms were noted in dogs. Based on the above, the approximate lethal dose for oral administration was determined to be >2,000 mg/kg for rats and >90 mg/kg for dogs.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies in rats (28 days) and dogs (3 months) were conducted (Table 13). Main abnormal findings noted in both rats and dogs included decreased lymphocytes in lymphoid organ and tissue, decreased T-cell dependent antibody response (TDAR), and low red blood cell count. Findings reported in rats included pancreatic hemorrhage, inflammation, and acinar atrophy while findings reported in dogs included inflammation/bleeding in the digestive tract and the lung, corneal opacity, erosion, and ulceration.

In the 3-month repeated-dose toxicity study in rats, the no-observed adverse effect level (NOAEL) was determined to be 100 mg/kg/day in male rats and 600 mg/kg/day in female rats. The exposure of pirtobrutinib ($AUC_{0\text{-}24h}$) after repeated-dose administration at the above dose levels was 19,100 ng·h/mL (<1 times the clinical exposure[24)]) for male rats and 369,000 ng·h/mL (4 times the clinical exposure) for female rats. In the 3-month repeated-dose toxicity study in dogs, the NOAEL was determined to be 5 mg/kg/day. The exposure of pirtobrutinib ($AUC_{0\text{-}24h}$) after repeated-dose administration at the above dose level was 15,600 ng·h/mL (<1 times the clinical exposure).

Findings of the pancreas reported in rats have high similarities with those reported in the toxicity studies of other BTK inhibitors; in addition, it is reported that the findings are likely to be class effects of BTK inhibitors occurring only in rats (*J Pharmacol Exp Ther*. 2017;360:226-38). Given these and other factors, the applicant explained that these findings are unlikely to cause problems in the clinical use of pirtobrutinib.

[24)] The $AUC_{0\text{-}24h}$ at steady state of pirtobrutinib (91,300 ng·h/mL) based on the PPK analysis when pirtobrutinib 200 mg was administered QD to patients with MCL and other conditions in the global phase I/II study (Study 18001).

The applicant explained that the findings of the lung reported in dogs are likely to be inflammatory changes secondary to opportunistic infections caused by the immunosuppressive effect of pirtobrutinib. It is possible that the findings of the digestive tract reported in dogs are direct toxicity of pirtobrutinib, since there were no findings suggestive of infections; however, given that there was only a small number of reports of bloody stool and diarrhoea haemorrhagic in the clinical studies of pirtobrutinib, with a lower degree of seriousness, such events are unlikely to cause safety-related problems in the clinical use of pirtobrutinib.

Table 13. Repeated-dose toxicity studies

Test system	Route of administration	Dosing duration	Dose (mg/kg/day)	Key findings	NOAEL	CTD
Male/female rats (Sprague Dawley)	Oral	28 days + 28-day recovery period	Male: 0,[*1] 100, 300, 1,000 Female: 0,[*1] 40, 120, 350	At ≥100 (male), 40 (female): (Males/females) low blood potassium, high blood ALT, low spleen weight, mesenteric lymph node erythrophagocytosis/sinus erythrocytes, pancreatic hemorrhage/mixed cell inflammation/acinar atrophy/fibrosis/pigment; (Males) low body weight gain; At ≥300 (male), 120 (female): (Males/females) decreased lymphocytes in spleen white pulp; (Males) low body weight; (Females) high blood chlorine, low total protein in blood At 1,000 (male), 350 (female): (Males) low food intake; (Females) low red blood cell count, low white blood cell count, low neutrophil count, low lymphocyte count, low eosinophil count, decreased lymphocytes in mesenteric lymph node Post-recovery period: findings were reversible	Male: 1,000 Female: 350	4.2.3.2.2
Male/female rats (Sprague Dawley)	Oral	3 months	Male: 0,[*1] 100, 1,000 Female: 0,[*1] 120, 600	At ≥100 (male), 120 (female): (Males/females) low blood creatine kinase/low blood potassium, low spleen weight, low lymphocyte count, decreased cellularity, low relative proportion of B cells in blood/spleen, high relative proportion of T cells in blood/spleen, decreased TDAR, lymph node erythrophagocytosis, pancreatic hemorrhage, acinar/islet of Langerhans inflammation, acinar atrophy, fibrosis, pigment; (Females) low blood globulin, high A/G ratio, pancreatic acinar mixed cell inflammation At 1,000 (male), 600 (female): (Males/females) high total bilirubin in blood; (Males) low body weight, low body weight gain, low blood globulin, decreased spleen size, pancreatic vascular/perivascular inflammation; (Females) blood low urea nitrogen/low total protein	Male: 100 Female: 600	4.2.3.2.3

Male/female dogs (Beagle)	Oral	28 days + 28-day recovery period	Male/female: 0,[*1] 20/10,[*2] 60/20,[*2] 180/120[*3]	<u>Animals that died or were sacrificed</u> At 180, 5/5 males, 5/5 females (Males/females) dehydration, elevated body temperature, mucous feces, reddish feces, low body weight, low body weight gain, low food intake, low white blood cell count, low platelet count, low blood albumin, decreased lymphocytes in mesenteric lymph node, red discoloration of the lung/mixed cell inflammation/hemorrhage, rectal mixed cell inflammation; (Males) cecum red discoloration, mixed cell inflammation/necrosis/hemorrhage, decreased marrow cellularity, rectal hemorrhage; (Females) hypoactivity, lung raised area, colon mixed cell inflammation/necrosis/hemorrhage/intussusception <u>Animals that survived</u> At ≥20 (Males/females) high blood fibrinogen, high blood cholesterol, low lymphocyte count, decreased spleen white pulp, decreased lymphocytes in gut-associated lymphoid tissue, lymph node erythrophagocytosis/sinus erythrocytes, mixed cell infiltration; (Males) low red blood cell count, decreased thymus lymphocytes; At ≥60 (Males/females) vomiting, non-formed feces, low neutrophil count, low monocyte count; (Males) hypoactivity; (Females) low red blood cell count, low eosinophil count, decreased thymus lymphocytes Post-recovery period: findings were reversible	20/10[*2]	4.2.3.2.5
Male/female dogs (Beagle)	Oral	3 months	0,[*1] 1, 5, 10	At ≥1 (Males/females) low absolute B cell count in blood, low relative proportion of B cells in blood, high absolute T cell count in blood, high relative proportion of T cells in blood, decreased TDAR, decreased lymphoid cellularity in gut-associated lymphoid tissue; (Males) low inorganic phosphorus in blood At ≥5 (Females) low red blood cell count, low hemoglobin, low hematocrit, decreased lymphoid cellularity in mesenteric lymph node At 10 (Males) decreased lymphoid cellularity in mesenteric lymph node, corneal opacity, increased corneal epithelial mitosis, corneal hyperplasia, single cell necrosis in corneal epithelium, corneal epithelial erosion, corneal ulceration, corneal stromal fibrosis, stromal mixed cell infiltration; (Females) low blood albumin, low total protein in blood	5	4.2.3.2.6

*1, 0.5% hydroxypropyl methylcellulose (HPMC) solution; *2, Given that the dose in the 60 mg/kg group was decreased to 20 mg/kg/day from Day 12 due to worsened clinical observations, the dose for the 20 mg/kg group was decreased to 10 mg/kg/day from Day 11; *3, The dose was decreased to 120 mg/kg/day from Day 6 due to worsened clinical observations; however, the dose was not tolerated and all animals were sacrificed on Day 13.

5.3 Genotoxicity

Genotoxicity studies consisted of a bacterial reverse mutation assay (Ames test), an *in vitro* micronucleus assay using human peripheral blood lymphocytes, and an *in vivo* rat micronucleus assay (Table 14). In the *in vitro* micronucleus assay using human peripheral blood lymphocytes, micronuclei were induced via an aneugenic mechanism, while the *in vivo* rat micronucleus assay produced negative results. Based on this, etc., the applicant explained that pirtobrutinib is unlikely to be genotoxic.

Table 14. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentration of dose	Test result	CTD
In vitro	Bacterial reverse mutation assay (Ames)	*Salmonella* Typhimurium: TA98, TA100, TA1535, TA1537 *E. coli* WP2*uvrA*	S9−	0,[*1] 33.3, 100, 333, 1,000, 3,333, 5,000 μg/plate	Negative	4.2.3.3.1.1
			S9+	0,[*1] 33.3, 100, 333, 1,000, 3,333, 5,000 μg/plate		
	Micronucleus study	Human peripheral blood lymphocytes	S9− (4 hours)	0,[*1] 50, 120, 150 μg/mL	Positive	4.2.3.3.1.3
			S9− (24 hours)	0,[*1] 5, 12, 16 μg/mL	Positive	
			S9+ (4 hours)	0,[*1] 50, 100, 225 μg/mL	Positive	
			S9− (24 hours)	0,[*1] 1.25, 2.5, 5.0, 12, 16 μg/mL	Positive [*3]	4.2.3.3.1.4
In vivo	Micronucleus study	Male/female rats (Sprague Dawley), single oral dose, bone marrow		0,[*2] 250, 500, 1,000, 2,000 mg/kg	Negative	4.2.3.3.2.1

*1, DMSO; *2, 0.5% HPMC solution; 3, Centromere-positive micronuclei were noted at a high frequency in the fluorescence *in situ* hybridization (FISH) method.

5.4 Carcinogenicity

No carcinogenicity studies were conducted because pirtobrutinib is an antineoplastic agent intended to be used for the treatment of patients with advanced cancer.

5.5 Reproductive and developmental toxicity

In repeated-dose toxicity studies in rats and dogs, no effects on male or female reproductive organs were noted.

A preliminary study on embryo fetal development was performed in rats (Table 15). Fetal toxicity-related findings include malformations in the kidney, urinary tract, ovary, uterus, and bone, and variations in the kidney, urinary tract, and bone. The NOAEL in the preliminary study on rat embryo fetal development was determined to be 150 mg/kg/day. When repeated-doses of pirtobrutinib of 150 mg/kg/day were administered, the exposure of pirtobrutinib ($AUC_{0\text{-}24h}$) was 106,000 ng·h/mL, 1.2 times the clinical exposure.[24)]

The exposure at the NOAEL in the preliminary study on rat embryo fetal development is similar to the clinical exposure. Because of this and other reasons, the applicant plans to provide advice for healthcare professionals in an appropriate manner using the package insert with the following statements to the effect that (1) it is not advisable to administer pirtobrutinib to women who are or may be pregnant; and (2) women of childbearing potential should be instructed to use effective contraception during and for 1 month after the last dose of pirtobrutinib treatment.[25)]

[25)] Following the "Guidance on the need for contraception related to use of pharmaceuticals" (PSEHB/PED Notification No. 0216-1 and PSEHB/PSD Notification No. 0216-1, dated on February 16, 2023), the duration was established based on the recommended period of >5 times of the half-life (geometric mean, 11.1 hours) of pirtobrutinib in humans [see Section 6.2.1.1].

Table 15. Reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Dosing duration	Dose (mg/kg/day)	Key findings	NOAEL	CTD
Preliminary embryo-fetal development study	Female rats (Sprague Dawley)	Oral	Gestation days 6-17	0,[*1] 50, 150, 750, 1,000	Dams At 1,000, none Embryos/fetuses At ≥750, low fetal body weight, kidney malformations[*2]/decreased size[*2]/renal papilla absent[*3]/small renal papilla,[*3] ureter dilatation[*3] At 750, malpositioned kidney[*2] At 1,000, total resorption of embryos, increased number of early resorptions/late resorptions/resorptions/postimplantation loss, absent kidney,[*2] absent ureter,[*2] malpositioned ovary,[*2] misshapen uterus,[*2] misshapen sternebra,[*2] isolated ossification site in lumbar arch[*3]	Dams (general toxicity): 1,000 Embryos/ fetuses: 150	4.2.3.5.2.1

*1, 0.5% HPMC solution; *2, malformation finding; *3, variation finding

5.6 Other toxicity studies

5.6.1 Photosafety

A phototoxicity study was conducted using mouse fibroblasts (Table 16). The applicant explained that based on the study result, pirtobrutinib did not show phototoxicity potential.

Table 16. Photosafety studies

Test system	Test method	Result	CTD
Mouse fibroblasts (Balb/c 3T3)	After being treated with 0,* 0.100, 0.316, 1.00, 3.16, 10.0, 31.6, 100, 178 μg/mL for 90 minutes, cells were irradiated with UVA (5 J/cm^2) and UVB (25 J/cm^2) for 30 minutes	PIF, not calculable MPE, −0.04, 0.013 Not phototoxic	4.2.3.7.7.1

* DMSO

5.6.2 Safety evaluation of impurities

Impurity A, an impurity in the drug substance, the specification limit of which is set above the qualification threshold according to the ICH Q3A guidelines, is [redacted] of pirtobrutinib, and thus its genotoxicity is expected to be similar to that of pirtobrutinib. Therefore, no genotoxicity studies were conducted for the impurity. The amount of the impurity[26)] per dose based on the body surface area conversion at the NOAEL in the 28-day repeated-dose toxicity studies of pirtobrutinib in rats and dogs [see Section 5.2] is greater than the amount of impurity at the recommended clinical dose (200 mg QD). The applicant explained that given this, the impurity of the drug substance is unlikely to raise safety-related concerns.

A 2-week repeated-dose toxicity study was conducted in rats to qualify Impurity B and Impurity C, impurities in the drug product, the specification limits of which are set at higher than the qualification threshold according to the ICH Q3B guidelines (Table 17). No impurity exposure-related toxicities were noted. Bacterial reverse

[26)] 17 mg/m^2 (male rats), 6.1 mg/m^2 (female rats), and 1.2 mg/m^2 (dogs).

mutation (Ames) studies were performed with Impurity B and Impurity C. The results indicated no immunogenicity. The applicant explained that given the structural similarities between pirtobrutinib and these impurities, it is unlikely that these impurities have a significantly greater ability to induce chromosome aberrations compared to pirtobrutinib. Therefore, the risk of induction of chromosome aberrations from these impurities in the clinical use of pirtobrutinib is low, and the impurities of the drug product is not likely to cause safety-related concerns.

Table 17. General toxicity studies with impurities

Test system	Route of administration	Dosing duration	Dose (mg/kg/day)	Key findings	CTD
Male/female rats (Sprague Dawley)	Oral	2 weeks	0, 600,[*1] 600[*2]	Drug substance containing impurities[*1] Pancreatic hemorrhage/mixed cell inflammation/acinar atrophy/fibrosis, lymph node plasma cells/hemorrhage Drug substance not containing impurities[*2] Pancreatic hemorrhage/mixed cell inflammation/acinar atrophy/fibrosis, lymph node plasma cells/hemorrhage	4.2.3.7.7.2

*1, the drug substance containing 0.51% of Impurity B and 0.52% of Impurity C; *2, the drug substance containing no impurities

5.R Outline of the review conducted by PMDA

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

5.R.1 Effects on the cornea

The applicant's explanation about the corneal toxicity findings in dogs:

Although the mechanism underlying the effect on the cornea reported in dogs is unknown, corneal toxicity has not been reported consistently in association with other BTK inhibitors, and therefore, it is unlikely that these findings can be attributed to BTK inhibition. In addition, effects on the cornea are only observed in the 3-month repeated-dose toxicity study in dogs. Although the reversibility of corneal findings has not been evaluated, given that the corneal epithelium is capable of regenerating, and corneal stroma injury demonstrates repairability (*Wound Repair Regen.* 2001;9:483-94, *Exp Eye Res.* 2020;197:108089), it is considered that the corneal findings are reversible after dose interruption. Furthermore, the incidence of ocular adverse events was low in the clinical studies of pirtobrutinib, with the majority being non-serious and a causal relationship to pirtobrutinib was ruled out.[27)] Based on the above, it is unlikely that safety-related problems will arise in the clinical use of pirtobrutinib. However, information on the effects on the cornea observed in dogs will be provided using the package insert. The applicant plans to continue to gather information, and provide any new information to healthcare professionals in an appropriate manner.

PMDA accepted the applicant's explanation.

[27)] In the global phase I/II study (Study 18001), eye disorders were reported in 29 of 164 subjects (17.7%) in the MSAS (see Table 26). Serious eye disorders were blindness and eyelid ptosis (1 subject each, 0.3%), and a causal relationship to pirtobrutinib was ruled out for both events.

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

The oral formulations of pirtobrutinib are available in liquid and tablets. These formulations were used to investigate the PK and other aspects of pirtobrutinib (Table 18). The proposed commercial formulation is the T2 formulation, 50 and 100 mg tablets. The bioequivalence of the T2 formulations (between 50 mg and 100 mg tablets; between 25 mg and 50 mg tablets) was demonstrated by a solubility study, which was conducted in accordance with the "Guidelines on Bioequivalence for Different Oral Solid Dosage Forms" (PMSB/ELD Notification No. 64, dated on February 14, 2000).

Table 18. Formulations used in clinical studies

Formulation		Study
Oral liquid formulations containing ^{14}C-pirtobrutinib		Foreign phase I (Study 20007[*1])
Tablets	T1 (25 and 100 mg)	Global phase I/II study (Study 18001), foreign phase I study (Study 20014[*2])
	T2 (25 and 100 mg)	Global phase I/II study (Study 18001), foreign phase I studies (Studies 20006,[*2] 20007,[*2] 20008,[*2] 20009,[*2] 20010,[*2] 20011, 20012,[*2] 20013,[*2] 20016,[*2] 20017, 20021,[*2] 21050,[*2] JZNW[*2])

*1, Injectable formulations were also used to assess absolute BA; *2, Only 100 mg-tablets were used.

Pirtobrutinib in human plasma was determined by LC-MS/MS (lower limit of quantitation, 20.0 ng/mL[28]).

6.1.1 Foreign clinical studies

6.1.1.1 Foreign phase I study (CTD 5.3.1.1.2, Study 20014 [February to March 2020])

A 2-treatment, 3-period crossover study was conducted in 10 healthy adults (10 subjects were included in PK analysis) to evaluate the effect of food or omeprazole (proton pump inhibitor) on the PK of pirtobrutinib (T1 formulation). A single oral dose of pirtobrutinib (T1 formulation) 200 mg was administered under fasting conditions[29] or 30 minutes after standard meal intake on Days 1 and 8. On Days 15 to 17, omeprazole 40 mg was orally administered QD, and on Day 18, a single dose of pirtobrutinib 200 mg (T1 formulation) and omeprazole 40 mg were administered orally under fasting conditions.[29]

The geometric mean ratio of pirtobrutinib plus omeprazole to pirtobrutinib alone under fasting conditions [90% confidence interval (CI)] was 1.01 [0.858, 1.18] (C_{max}) and 1.11 [1.02, 1.22] (AUC_{inf}). Based on the above, the applicant explained that it is unlikely that an increase in stomach pH resulting from administration of a proton pump inhibitor or other factors will have a marked effect on the PK of pirtobrutinib.

The geometric mean ratio of the fed state to the fasting state after a standard meal [90% CI] was 0.796 [0.678, 0.935] (C_{max}) and 0.954 [0.874, 1.04] (AUC_{inf}). The applicant's discussion on the food effect on the PK of pirtobrutinib is provided in Section 6.1.1.3.

[28] Plasma specimens used in the early stage of Study 18001 were determined by a method, which has a lower limit of quantitation of 1.0 ng/mL.
[29] Subjects received the study drug after ≥10 hours of fasting, and underwent fasting for 4 hours after dosing.

6.1.1.2 Foreign phase I study (CTD 5.3.1.1.1, Study 20007 Part 2 [September to November 2020])

An open-label, uncontrolled study was conducted in 9 healthy adults (9 subjects were included in PK analysis)[30] to investigate the mass balance (Part 1) and absolute bioavailability (BA) (Part 2). In Part 2, subjects were to receive a single intravenous dose of <100 μg of ^{14}C-labeled pirtobrutinib 2 hours after receiving a single oral dose of pirtobrutinib 200 mg. The details of Part 1 are described in Section 6.2.2.1.

The geometric mean absolute BA calculated from the AUC_{inf} of pirtobrutinib was 85.5%.

6.1.1.3 Foreign phase I study (CTD 5.3.1.1.3, Study 20009 [January to March 2021])

A 2-treatment, 2-period crossover study was conducted in 20 healthy adults (20 subjects were included in PK analysis) to investigate the effects of food on the PK of pirtobrutinib (proposed commercial formulation). Subjects were to receive a single oral dose of pirtobrutinib (proposed commercial formulation) 200 mg under fasting conditions[29] or 30 minutes after having a high-fat meal.[31] There was a 7-day washout period between pirtobrutinib treatments.

The geometric mean ratio [90% CI] (fed state after a high-fat meal/fasting state) was 0.775 [0.672, 0.893] (C_{max}) and 0.929 [0.805, 1.07] (AUC_{inf}). The median t_{max} was 3.00 hours under fasting conditions and 4.00 hours under fed conditions after a high-fat meal. Based on the above results, etc., the applicant explains that the food effect on the PK of pirtobrutinib is limited,[32] and that pirtobrutinib can be administered regardless of food intake.

6.1.1.4 Foreign phase I study (CTD 5.3.1.2.1, Study 21050 [September to December 2021])

A 2-treatments, 2-period crossover study was conducted in 28 healthy adults (28 subjects were included in PK analysis) to compare the PK of the formulations produced using different manufacturing processes[33] (both are 100 mg tablets of the T2 formulations). Subjects were to receive a single oral dose of pirtobrutinib 200 mg under fasting conditions.[29] There was a 7-day washout period between pirtobrutinib treatments.

The geometric mean ratio [90% CI] (post-change formulation/pre-change formulation) was 1.01 [0.928, 1.09] (C_{max}) and 1.03 [0.963, 1.10] (AUC_t). The applicant explained that the change in the manufacturing process for the T2 formulation is unlikely to affect the PK of pirtobrutinib.

6.2 Clinical pharmacology

The PK of pirtobrutinib in healthy adults and patients with cancer following administration of pirtobrutinib alone and in combination with itraconazole or rifampicin was investigated. The effects of pirtobrutinib on the PK of midazolam, repaglinide, caffein, *S*-warfarin, omeprazole, digoxin, and rosuvastatin were investigated.

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[30] Four subjects and 5 subjects were studied in Part 1 and Part 2, respectively (4 and 5 subjects, respectively, were included in the PK analysis).
[31] The meal has approximately 800 to 1,000 kcal, which contains approximately 500 to 600 kcal of fat.
[32] The applicant considers the possibility that a decrease in the gastric emptying rate due to intake of a high-fat meal may have led to delayed t_{max} and decreased C_{max}.
[33] In the process of optimization of the manufacturing process of the proposed commercial formulation, formulations with different dissolution profiles were confirmed.

6.2.1 Global clinical study

6.2.1.1 Global phase I/II study (CTD 5.3.5.2.3, Study 18001 phase I and II parts [ongoing since [redacted] 20[redacted], data cut-off on [redacted] [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted in 725 patients with relapsed or refractory B cell malignancy (595 subjects[34)] were included in PK analysis) to investigate the PK and other aspects of pirtobrutinib. In the phase I dose escalation part, subjects were to receive pirtobrutinib (T1 or T2 formulation) 25, 50, 100, 150, 200, 250, or 300 mg, while in the phase I dose expansion part and the phase II part, subjects were to receive pirtobrutinib (T1 or T2 formulation) 200 mg QD orally.

Table 19 shows the PK parameters of pirtobrutinib. The exposure of pirtobrutinib increased roughly dose proportionally within the dose range studied.

Table 19. PK parameters of pirtobrutinib

Formulation	Dose (mg)	Timepoint (Day)	N	C_{max} (ng/mL)	t_{max}[*1] (h)	$AUC_{0\text{-}8h}$ (ng·h/mL)	$AUC_{0\text{-}24h}$ (ng·h/mL)	$t_{1/2}$ (h)
T1	25	1	5	655 (21.3)	1.05 (1.00, 2.07)	2,930 (17.1)	–	–
		8	5	734 (11.0)	1.97 (1.00, 7.52)	4,240 (12.4)	9,330 (26.9)	–
	50	1	6	1,180 (23.7)	1.93 (1.15, 4.10)	5,910 (20.3)[*2]	–	–
		8	6	1,420 (19.2)	1.48 (0.883, 4.02)	8,650 (24.8)	20,000 (35.1)	–
	100	1	9	1,950 (26.8)	2.17 (1.02, 7.65)	11,000 (30.1)[*2]	–	–
		8	8	3,700 (33.3)	1.99 (1.08, 4.08)	20,500 (32.4)	48,400 (34.9)	–
	150	1	20	3,140 (25.8)	2.02 (0.950, 7.50)	16,800 (29.4)[*3]	–	–
		8	20	4,680 (29.1)	2.01 (0.783, 8.00)	28,000 (29.8)	62,200 (38.6)[*4]	9.76 (21.7)[*2]
	200	1	89	4,240 (34.5)	2.05 (0.817, 7.67)	24,300 (27.2)[*5]	–	–
		8	100	5,940 (48.4)	2.04 (0.00, 7.82)	37,900 (41.2)[*6]	98,700 (39.1)[*7]	11.1 (23.5)[*8]
	250	1	24	5,450 (18.9)	2.04 (0.817, 7.53)	29,900 (20.1)[*9]	–	–
		8	25	8,100 (28.1)	2.00 (0.800, 5.77)	48,500 (34.8)	111,000 (38.7)	9.55 (28.9)[*10]
	300	1	20	5,300 (22.9)	2.06 (0.933, 7.62)	30,800 (26.3)[*11]	–	–
		8	17	10,700 (26.6)	1.98 (0.750, 3.83)	65,800 (36.3)	158,000 (50.0)	5.54, 12.6[*12]
T2	200	1	12	4,440 (23.7)	2.00 (0.833, 4.15)	25,000 (27.0)[*13]	–	–
		8	373	3,670 (89.5)	0.00 (0.00, 8.17)	25,400 (80.7)	81,800 (66.6)[*14]	11.1 (18.7)[*15]

Geometric mean (coefficient of variation, %) (individual value, when N = 2); *1, median (Min, Max); *2, N = 5; *3, N = 18; *4, N = 19; *5, N = 63; *6, N = 98; *7, N = 74; *8, N = 17; *9, N = 20; *10, N = 4; *11, N = 14; *12, N = 2; *13, N = 8; *14, N = 180; *15, N = 37; "–," not calculated

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I study (CTD 5.3.1.1.1, Study 20007 Part 1 [September to November 2020])

An open-label, uncontrolled study was conducted in 9 healthy adults (9 subjects were included in PK analysis)[30)] to investigate the mass balance (Part 1), absolute BA (Part 2), and other aspects. In Part 1, subjects were to receive a single oral dose of approximately 200 mg of ^{14}C-labeled pirtobrutinib and radioactivity levels in plasma, urine, and feces were evaluated.

Up to 96 hours post-dose, unchanged pirtobrutinib was mainly detected in plasma (the $AUC_{0\text{-}96h}$ represents 86.7% of the $AUC_{0\text{-}96h}$ for the total radioactivity).

[34)] The number of patients who had at least 1 evaluable set of blood samples and information on the administration for PK evaluation following administration of pirtobrutinib. Non-compartment analysis was performed based on data from the 559 subjects whose time-course blood samples were collected for PK evaluation.

Up to 360 hours post-dose, 57.0% and 37.3% of the administered radioactivity were excreted in urine and feces, respectively. Up to 96 hours post-dose, M2 (glucuronide) and unchanged pirtobrutinib were the main compounds excreted in urine, representing 22.8% and 10.0% of the administered radioactivity, respectively. Up to 168 hours post-dose, mainly, unchanged pirtobrutinib was excreted in feces, representing 18.2% of the administered radioactivity.

6.2.3 Drug interactions

6.2.3.1 Drug interaction study with itraconazole or rifampin (CTD 5.3.3.4.1, Study 20006 [February to October 2020])

An open-label, uncontrolled study was conducted in 27 healthy adults (27 subjects were included in PK analysis)[35] to investigate the effects of itraconazole (strong CYP3A and P-gp inhibitor) or rifampicin (P-gp inhibitor after single dose administration[36]; strong CYP3A inducer after repeated-dose administration) on pirtobrutinib PK (evaluation of pirtobrutinib as a victim drug). The dosage regimens were as follows:

Part 1: A single oral dose of pirtobrutinib 200 mg was administered on Days 1 and 12. Itraconazole 200 mg was administered orally BID on Day 8, and QD on Days 9 to 18.

Part 2: A single oral dose of pirtobrutinib 200 mg was administered orally on Days 1, 8, and 17. Rifampicin 600 mg was administered orally QD on Days 8 to 23.

The geometric mean ratio [90% CI] of pirtobrutinib C_{max} and AUC_{inf} (co-administered with multiple doses of itraconazole/pirtobrutinib monotherapy) was 1.04 [0.951, 1.13] (C_{max}) and 1.49 [1.40, 1.58] (AUC_{inf}), the geometric mean ratio [90% CI] (co-administered with a single dose of rifampicin [Day 8 in Part 2]/pirtobrutinib monotherapy) was 0.929 [0.867, 0.996] (C_{max}) and 0.968 [0.935, 1.00] (AUC_{inf}),[37] and the geometric mean ratio [90% CI] (co-administered with multiple doses of rifampicin [Day 17 on Part 2]/pirtobrutinib monotherapy) was 0.576 [0.537, 0.617] (C_{max}) and 0.293 [0.271, 0.316] (AUC_{inf}).

The co-administered single dose of rifampicin had no significant effect on pirtobrutinib's PK, and the applicant explains that no cautionary statement is necessary on the co-administration with P-gp inhibitors. Cautionary advice related to pharmacokinetic interactions between pirtobrutinib and CYP3A inhibitors or inducers will be discussed in Section "6.R.2 Pharmacokinetic interactions with CYP3A inhibitors and inducers."

6.2.3.2 Drug interaction study with midazolam (CTD 5.3.3.4.2, Study 20008 [September to October 2020])

An open-label, uncontrolled study was conducted in 15 healthy adults (15 subjects were included in PK analysis) to investigate the effects of pirtobrutinib on the PK of midazolam (CYP3A substrate) (evaluation of pirtobrutinib as a perpetrator). Subjects were to receive a single intravenous dose of midazolam 250 μg on Day

[35] In Parts 1 and 2, 15 and 12 subjects (15 and 12 subjects for PK analysis), respectively, were analyzed.
[36] Inhibition of P-gp by single-dose rifampicin has been reported (*Clin Drug Investig.* 2014;34:651-9).
[37] Geometric least-squares mean ratio was calculated for co-administration with a single dose of rifampicin using $AUC_{0\text{-}24h}$.

1, and a single oral dose of midazolam 500 μg on Day 3. On Days 5 to 17, subjects were to receive oral doses of pirtobrutinib 200 mg QD. On Day 15, a single intravenous dose of midazolam 250 μg was to be administered 2 hours after administration of pirtobrutinib, and on Day 17, a single oral dose of midazolam 500 μg was to be administered immediately after administration of pirtobrutinib.

The geometric least-squares mean ratio [90% CI] of midazolam exposure (co-administered with pirtobrutinib/midazolam monotherapy) was 0.993 [0.834, 1.18] (C_{max}) and 1.12 [1.04, 1.21] (AUC_{inf}) for intravenous midazolam and 1.58 [1.40, 1.78] (C_{max}) and 1.70 [1.55, 1.86] (AUC_{inf}) for oral midazolam.

The applicant's explanation about the effects of pirtobrutinib on the PK of CYP3A substrates based on the above results:
While midazolam exposure increased when an oral dose of midazolam is co-administered with pirtobrutinib, the exposure remained similar when an intravenous dose of midazolam is co-administered with pirtobrutinib; therefore, it is considered pirtobrutinib mainly inhibits CYP3A in the digestive tract. Therefore, caution should be exercised when pirtobrutinib is co-administered with CYP3A substrates (oral formulation) and a cautionary statement to this effect will be included.

6.2.3.3 Drug interaction study with repaglinide (CTD 5.3.3.4.4, Study 20016 [November to December 2020])

An open-label, uncontrolled study was conducted in 16 healthy adults (16 subjects were included in PK analysis) to investigate the effects of pirtobrutinib on the PK of repaglinide (a CYP2C8 substrate) (evaluation of pirtobrutinib as a perpetrator). Subjects were to receive a single oral dose of repaglinide 0.5 mg on Days 1 and 12, and pirtobrutinib 200 mg orally QD on Days 2 to 12.

The geometric least-squares mean ratio [90% CI] of repaglinide exposure (co-administered with pirtobrutinib/repaglinide monotherapy) was 1.98 [1.62, 2.43] (C_{max}) and 2.30 [1.86, 2.84] (AUC_{inf}).

Repaglinide exposure increased when repaglinide is co-administered with pirtobrutinib. Based on the results, the applicant explained that caution should be exercised when pirtobrutinib is co-administered with CYP2C8 substrates, and a cautionary statement to this effect will be included.

6.2.3.4 Drug interaction study with caffein, *S*-warfarin, and omeprazole (CTD 5.3.3.4.3, Study 20010 [January to April 2021])

An open-label, uncontrolled study was conducted in 16 healthy adults (16 subjects were included in PK analysis) to investigate the effects of pirtobrutinib on the PK of CYP isoform substrates (evaluation of pirtobrutinib as a perpetrator). On Days 1 and 15, subjects were to receive a single oral dose of a cocktail of the following probe substrates: caffein (a CYP1A2 substrate) 200 mg, *S*-warfarin (a CYP2C9 substrate) 10 mg, and omeprazole (a CYP2C19 substrate) 40 mg. Subjects were to receive oral doses of pirtobrutinib 200 mg QD on Days 6 to 19.

Table 20 shows the geometric mean ratios for C_{max} and AUC_{inf} of CYP isoform substrates when co-administered with pirtobrutinib to probe substrate cocktail alone.

Table 20. Effects of pirtobrutinib treatment on PK of each CYP isoform substrate

Analyte	N	Geometric mean ratio [90% CI]	
		C_{max}	AUC_{inf}
Caffein (CYP1A2 substrate)	16	0.986 [0.926, 1.05]	0.940 [0.905, 0.976]
S-warfarin (CYP2C9 substrate)	16	1.02 [0.974, 1.06]	1.11 [1.08, 1.14]
Omeprazole (CYP2C19 substrate)	16	1.49 [1.31, 1.70]	1.56 [1.35, 1.80]

The applicant's explanation about the pharmacokinetic interaction mediated by CYP1A2, CYP2C9, or CYP2C19 substrates:
Omeprazole exposure was increased following co-administration with pirtobrutinib; therefore, caution should be exercised when pirtobrutinib is co-administered with CYP2C19 substrates, and a cautionary statement to this effect will be provided. In contrast, co-administration with pirtobrutinib did not significantly increase caffein or *S*-warfarin exposure, and therefore, cautionary advice is not necessary regarding co-administration with CYP1A2 and CYP2C9 substrates.

6.2.3.5 Drug interaction study with digoxin (CTD 5.3.3.4.5, Study 20021 [March to June 2021])

An open-label, uncontrolled study was conducted in 16 healthy adults (16 subjects were included in PK analysis) to investigate the effects of pirtobrutinib on the PK of digoxin (P-gp substrate) (evaluation of pirtobrutinib as a perpetrator). On Day 1, subjects were to receive oral doses of digoxin 0.25 mg BID, and on Days 2 to 16, oral doses of digoxin 0.25 mg QD. Subjects were to receive oral doses of pirtobrutinib 200 mg QD on Days 8 to 16.

The geometric mean ratio [90% CI] of digoxin exposure (co-administered with pirtobrutinib [single or multiple doses]/digoxin monotherapy) was 1.51 [1.32, 1.73] (C_{max}) and 1.17 [1.11, 1.23] (AUC_{tau}) after single-dose co-administration, and 1.55 [1.35, 1.78] (C_{max}) and 1.35 [1.29, 1.42] (AUC_{tau}) after multiple-dose co-administration.

Digoxin exposure increased when digoxin was co-administered with pirtobrutinib. Based on the results, the applicant explained that caution should be exercised when pirtobrutinib is co-administered with P-gp substrates, and a cautionary statement to this effect will be included.

6.2.3.6 Drug interaction study with rosuvastatin (CTD 5.3.3.4.6, Study JZNW [January to [redacted] 2022])

An open-label, uncontrolled study was conducted in 32 healthy adults (32 subjects were included in PK analysis) to investigate the effects of pirtobrutinib on the PK of rosuvastatin (a BCRP substrate) (evaluation of pirtobrutinib as a perpetrator). Subjects were to receive a single oral dose of rosuvastatin 20 mg on Days 1, 6, and 13, and oral doses of pirtobrutinib 200 mg QD on Days 6 to 17.

The geometric mean ratio [90% CI] of rosuvastatin exposure (co-administered with pirtobrutinib [single or multiple doses]/rosuvastatin monotherapy) was 2.43 [2.18, 2.71] (C_{max}) and 2.18 [2.00, 2.37] (AUC_{inf}) after single-dose co-administration, and 2.46 [2.20, 2.75] (C_{max}) and 2.40 [2.21, 2.62] (AUC_{inf}) after multiple-dose co-administration.

Rosuvastatin exposure increased when co-administered with pirtobrutinib. Based on the results, the applicant explained that caution should be exercised when pirtobrutinib is co-administered with BCRP substrates, and a cautionary statement to this effect will be included.

6.2.4 Foreign phase I study to assess the effects of hepatic impairment on pirtobrutinib PK (CTD 5.3.3.3.1, Study 20012 [December 2020 to December 2021])

An open-label, uncontrolled study was conducted in 14 healthy adults (14 subjects were included in PK analysis) and 22 patients with hepatic impairment (22 subjects were included in PK analysis),[38)] which is classified into mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) impairment to investigate the effects of hepatic impairment on pirtobrutinib PK. Subjects were to receive a single oral dose of pirtobrutinib 200 mg, and plasma pirtobrutinib concentrations were evaluated.

The geometric mean ratio [90% CI] of unbound pirtobrutinib exposure (patients with hepatic impairment/healthy adults) was 1.39 [1.10, 1.77] (C_{max}) and 1.16 [0.857, 1.58] (AUC_{inf}) for mild impairment; 1.11 [0.831, 1.48] (C_{max}) and 0.956 [0.725, 1.26] (AUC_{inf}) for moderate impairment; and 1.00 [0.747, 1.35] (C_{max}) and 1.05 [0.793, 1.38] (AUC_{inf}) for severe impairment.

The results showed that hepatic impairment did not have clear effects on the PK of pirtobrutinib. Therefore, the applicant explains that dose adjustment of pirtobrutinib is unnecessary for patients with hepatic impairment.

6.2.5 Foreign phase I study to assess the effects of renal impairment on pirtobrutinib PK (CTD 5.3.3.3.2, Study 20013 [February to June 2021])

An open-label, uncontrolled study was conducted in 8 healthy adults (8 subjects were included in PK analysis) and 8 patients with severe (eGFR <30 mL/min/1.73 m^2) renal impairment (8 subjects were included in PK analysis) to investigate the effects of renal impairment on pirtobrutinib PK. Subjects were to receive a single oral dose of pirtobrutinib 200 mg, and plasma pirtobrutinib concentrations were evaluated.

The geometric mean ratio [90% CI] of unbound pirtobrutinib exposure (patients with severe renal impairment/healthy adults) was 0.825 [0.635, 1.07] (C_{max}) and 1.34 [1.02, 1.77] (AUC_{inf}).

Based on the above results as well as the following points, the applicant explains that dose adjustment of pirtobrutinib is unnecessary for patients with renal impairment.

[38)] Patients with mild, moderate, and severe hepatic impairment, 8, 8, and 6 subjects, respectively, were analyzed (8, 8, and 6 subjects were included in PK analysis, respectively).

- The urinary excretion results for unchanged pirtobrutinib from the foreign phase I study (Study 20007) [see Section 6.2.2.1] suggest that renal excretion plays an insignificant role in pirtobrutinib clearance.
- In the global phase I/II study (Study 18001), the incidences of adverse events in patients with normal renal function (152 subjects) and patients with renal impairment[39] (357, 208, and 8 subjects with mild, moderate, and severe impairment, respectively) were as follows: the incidence of adverse events leading to death was 5.3% (normal), 5.6% (mild impairment), 7.7% (moderate impairment), and 12.5% (severe impairment); the incidence of serious adverse events was 28.9% (normal), 34.7% (mild), 39.9% (moderate), and 50.0% (severe); the incidence of adverse events leading to treatment discontinuation was 4.6% (normal), 5.9% (mild), 7.2% (moderate), and 25.0% (severe); the incidence of adverse events leading to dose interruption was 28.3% (normal), 36.7% (mild), 36.1% (moderate), and 37.5% (severe); and the incidence of adverse events leading to dose reduction was 2.0% (normal), 4.8% (mild), 8.2% (moderate), and 0% (severe). There was no clear correlation between mild/moderate renal impairment and the incidence of adverse events. While the incidence of adverse events tended to be higher in patients with severe renal impairment than in patients with normal renal function, the very small number of patients with severe renal impairment in the evaluation precludes precise evaluation.

6.2.6 Foreign phase I study (CTD 5.3.4.1.1, Study 20011 [December 2020 to March 2021])

A placebo- and positive-controlled (moxifloxacin), 6-treatment, 3-period crossover study[40] was conducted in 31 healthy adults (31 subjects were included in PK analysis) to investigate the effects of pirtobrutinib on QT interval corrected using Fridericia's formula (QTcF). Subjects were to receive a single oral dose of (1) pirtobrutinib 900 mg, (2) moxifloxacin 400 mg, or (3) placebo with a ≥10-day washout period between treatments.

The upper bound for the two-sided 90% confidence interval of the difference versus placebo in change from baseline in QTcF (ΔΔQTcF) at pirtobrutinib 900 mg was <10 milliseconds at all timepoints. The lower bound for the two-sided 90% confidence interval of ΔΔQTcF was >5 milliseconds at 0.75 to 8.5 hours after administration of moxifloxacin, the positive control.

The analysis results of a linear mixed-effects model showed no clear correlation between plasma pirtobrutinib concentration and ΔΔQTcF.

Based on the above, the applicant explained that it is unlikely that prolongation of QT/QTc interval will occur in the clinical use of pirtobrutinib.

[39] The estimated glomerular filtration rate (eGFR) ≥90 (mL/min/1.73 m^2) was classified as normal renal function, eGFR ≥60 and <90 (mL/min/1.73 m^2) as mild renal impairment, eGFR ≥30 and <60 (mL/min/1.73 m^2) as moderate renal impairment, and eGFR <30 (mL/min/1.73 m^2) as severe renal impairment.

[40] The study used a partial double-blind design (double-blind for pirtobrutinib and placebo, and open-label for moxifloxacin).

6.2.7 PPK analysis

Based on the data of pirtobrutinib PK (4,487 measurement timepoints from 595 patients)[41] obtained from the global phase I/II study (Study 18001[42]), a PPK analysis was performed using a nonlinear mixed-effects model (software, NONMEM Version 7.4.2). The PK of pirtobrutinib was described by a 2-compartment model with 4 transit absorption compartments.

In this analysis, a base model that included the effect of body weight on apparent oral clearance (CL/F), apparent volume of distribution of central compartment (V_c/F), apparent volume of distribution of peripheral compartment (V_p/F), and apparent inter-compartmental clearance of apalutamide (Q/F) was used. The following covariates were tested for the effect on the parameters of pirtobrutinib: (1) age, sex, race, ethnicity, serum albumin, renal function (eGFR), hepatic impairment,[43] and cancer type on CL/F; (2) age, sex, serum albumin, and cancer type on V_c/F and V_p/F, (3) age, sex, formulation, and cancer type on absorption rate constant (ka), and (4) formulation on relative bioavailability (F). Renal function (eGFR) and serum albumin were identified as covariates on CL/F, and serum albumin was identified as a covariate on V_c/F.

Body weight, which was included in the final model, renal function (eGFR), and serum albumin did have limited impact[44] on pirtobrutinib exposure. The applicant considers that dose adjustment based on these covariates is unnecessary.

6.2.8 Exposure-efficacy and exposure-safety relationships

6.2.8.1 Exposure-efficacy relationship

Based on the results of Study 18001,[45] the relationship between pirtobrutinib exposure[46] (mean concentration up to the time of best response) and overall response rate was investigated. The results showed no clear relationship between pirtobrutinib exposure and overall response rate.

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[41] The median (Min, Max) and the number of subjects in each category for baseline demographics and disease characteristics of patients analyzed are as follows:
Body weight, 76.6 kg (35.7, 152.5); age, 71 years (50, 87); sex, 394 males and 201 females; race, White (509 subjects), Black or African American (17 subjects), Asian (39 subjects), other (29 subjects), unknown (1 subject); ethnicity, Not Hispanic or Latino (548 subjects), Hispanic (23 subjects), unknown (24 subjects); serum albumin, 41.0 g/L (19.0, 56.5); renal function (eGFR), 72.2 mL/min/1.73 m^2 (22.3, 131.8); hepatic impairment, normal (474 subjects), mild (106 subjects), moderate (13 subjects), severe (1 subject), unknown (1 subject); cancer type, MCL (140 subjects), CLL/SLL (263 subjects), other NHL (192 subjects); formulation, T1 (210 subjects), T2 (385 subjects)

[42] Of the patients who received at least 1 dose of pirtobrutinib monotherapy, patients who had at least 1 evaluable set of blood samples for PK evaluation and sufficient treatment history, regardless of starting dose, were included in the analysis.

[43] Classified according to the National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria.

[44] The time-course of plasma pirtobrutinib concentrations in patients at median, 5th percentile, and 95th percentile body weight were similar. The ratios of patients with 5th and 95th percentiles serum albumin compared to those with the median serum albumin were 1.21 (5th) and 0.90 (95th) for CL/F, and 1.12 (5th) and 0.97 (95th) for V_c/F. The ratios of CL/F in patients with renal impairment to those with normal renal function were 0.88 (mild), 0.78 (moderate), and 0.66 (severe), while the ranges of the values differ between the severity degrees of renal impairment. The eGFR ≥90 (mL/min/1.73 m^2) was classified as normal renal function, eGFR ≥60 and <90 (mL/min/1.73 m^2) as mild renal impairment, eGFR ≥30 and <60 (mL/min/1.73 m^2) as moderate renal impairment, and eGFR ≥15 and <30 (mL/min/1.73 m^2) as severe renal impairment.

[45] Of the patients with MCL who met the criteria below and who were among the first 90 patients enrolled, patients who met the definition for PPK analysis population (Footnote 42) were included in the analysis (N = 73).
(1) Patients with histologically confirmed B cell malignancy diagnosed as MCL, with no known active CNS involvement; (2) patients treated with a prior BTK inhibitor-containing regimen; and (3) patients with at least 1 site of radiographically assessable disease as determined by the investigator, defined as lymph node longest diameter ≥1.5 cm, or extra nodal site ≥1.0 cm in the longest diameter of a lymph node by computed tomography, and received 1 or more doses of pirtobrutinib monotherapy

[46] The exposure was estimated based on the PPK analysis [see Section 6.2.7].

6.2.8.2 Exposure-safety relationship

Based on the results of Study 18001,[47] the relationships between pirtobrutinib exposure[46] (mean and maximum concentrations up to the time of adverse event[48]) and anaemia (Grade ≥3), neutrophil count decreased (Grade ≥3), infection (Grade ≥3), and hypertension (any grade) were investigated. The results showed no clear relationship between pirtobrutinib exposure and the incidence of adverse events listed above.

6.2.9 Differences in pirtobrutinib PK between Japanese and non-Japanese populations

There were no clear differences in pirtobrutinib PK parameters following oral administration of pirtobrutinib 200 mg QD in Japanese patients and non-Japanese patients in the global phase I/II study (Study 18001) (Table 21). The applicant explained that the results and other data suggest no clear differences in pirtobrutinib PK between Japanese and non-Japanese populations.

Table 21. PK parameters of pirtobrutinib

Measurement timepoint (Day)	Population	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{last} (ng·h/mL)
1	Japanese patients	3	5,060 (30.6)	4.02 (2.00, 4.15)	26,500 (29.0)
	Non-Japanese patients	81	4,350 (32.9)	2.08 (0.817, 7.67)	22,700 (31.0)
8	Japanese patients	4	7,790 (30.8)	5.79 (2.05, 7.75)	127,000 (30.2)
	Non-Japanese patients	204	6,480 (33.6)	2.10 (0.783, 8.00)	92,900 (38.9)

Geometric mean (coefficient of variation, %); * median (Min, Max)

6.R Outline of the review conducted by PMDA

Based on the submitted data and discussions in the following sections, PMDA concluded that the applicant's explanation about the clinical pharmacology of pirtobrutinib is acceptable.

6.R.1 Effects of formulations on pirtobrutinib PK, etc.

The applicant's explanation about the effects of the difference between the formulations (T1 and T2) used in the global phase I/II study (Study 18001) on the PK and other aspects of pirtobrutinib:

Study 18001 used 2 types of formulations (T1 and T2), which differ from each other in terms of constituents[49] (Table 18). Given the points shown below, it is unlikely that the difference between the formulations will have a marked effect on pirtobrutinib PK. In the majority of patients in Study 18001 received the T2 formulation.[50]

- There were no clear differences in pirtobrutinib exposure in patients who received pirtobrutinib (T1 or T2) 200 mg QD [see Section 6.2.1.1].

[47] Of the patients who received at least 1 dose of pirtobrutinib monotherapy, patients whose safety data were all available and met the definitions for PPK analysis population (Footnote 42) were included in the analysis regardless of starting dose (N = 595).

[48] For patients who did not develop adverse events, the mean or maximum concentration during the overall study period was used.

[49] For the purpose of manufacturing scale-up and formulation optimization, T1 was changed to T2 containing different [redacted] and different types and proportions of excipients.

[50] The numbers of subjects who received the types of formulations are as follows: in the phase I part of Study J-PAS (see Table 26), (N = 33), 19 subjects (T1) 14 subjects (T1 and T2), and 0 subjects (T2); in the phase II part of Study J-PAS (N = 32), 0 subjects (T1), 3 subjects (T1 and T2), and 29 subjects (T2); in Study J-MEAS (see Table 26) (N = 8), 0 subjects (T1), 0 subjects (T1 and T2), and 8 subjects (T2).

- Based on the PPK analysis [see Section 6.2.7], estimated pirtobrutinib exposure at steady state following oral administration of pirtobrutinib 200 mg QD is presented in Table 22. The results showed no clear differences in pirtobrutinib exposure.

Table 22. PK parameters of pirtobrutinib (estimated)

Formulation used	N	$C_{max,ss}$ (ng/mL)	$AUC_{0\text{-}24h,ss}$ (ng·h/mL)
T1 only	30	6,370 (26)	88,000 (45)
T2 only	341	6,240 (66)	88,100 (68)

Geometric mean (coefficient of variation, %)

In Study 18001, patients who received only the T1 formulation at a starting dose of 200 mg in the phase I part of J-PAS (N = 10) had an overall response rate of 50%; patients who received only the T2 formulation at a starting dose of 200 mg in the phase II part of J-PAS (N = 29) had an overall response rate of 41.4%; and patients who received only the T2 formulation at a starting dose of 200 mg in the J-MEAS (N = 8) had an overall response rate of 50.0%.[51)] Although factors including the limited number of patients evaluated preclude precise evaluation, no clear difference in the efficacy of pirtobrutinib was detected between the formulations.

PMDA accepted the applicant's explanation.

6.R.2 Pharmacokinetic interactions with CYP3A inhibitors and inducers

The applicant's explanation about co-administration of pirtobrutinib with CYP3A inhibitors and inducers:
Given that pirtobrutinib is a CYP3A4 substrate [see Section 4.3.1] and that co-administration with itraconazole (a strong CYP3A inhibitor and a P-gp inhibitor) or rifampicin (strong CYP3A inducer) had impacts on pirtobrutinib exposure [see Section 6.2.3.1], the effects of CYP3A inhibitors and inducers on the PK of pirtobrutinib were evaluated using a physiologically based pharmacokinetic (PBPK) model.

For PBPK modeling analysis, Simcyp version 19 was used. For pirtobrutinib absorption, the first-order absorption model was used, and for pirtobrutinib distribution, the minimal PBPK model was selected. A contribution of 40% was selected for CYP3A contribution to the metabolism of pirtobrutinib based on data including the results of *in vitro* studies [see Section 4.3.1]. For physiological parameters and parameters related to CYP3A inhibitors/inducers, parameters such as the default setting values for Simcyp were used. Based on the findings including the following, the PBPK model used to predict the CYP3A-mediated pharmacokinetic interaction of pirtobrutinib is appropriate.

- The observed exposure values including those obtained in the foreign phase I study (Study 20010) were roughly consistent with the predicted values based on the PBPK model above, demonstrating that the observed time-course of plasma pirtobrutinib concentrations are similar to predicted values.

[51)] In the J-PAS of the phase I part, there were no patients who received only the T2 formulation at a starting dose of 200 mg. However, in the J-PAS of the phase I part, 1 patient who received both T1 and T2 formulations (T2 was used in ≥80% of the overall study) at a starting dose of 200 mg achieved response.

- For the pirtobrutinib exposure ratio (co-administered with itraconazole or rifampicin/pirtobrutinib monotherapy), the observed values including those from the foreign phase I study (Study 20006) were roughly consistent with values predicted by the PBPK model.
- For the CYP3A substrate (e.g., midazolam) exposure ratio (co-administered with CYP3A inhibitor or inducer/CYP3A substrate monotherapy), the observed values (e.g., *Clin Pharmacol Ther*. 2017;101:519-30) were roughly consistent with the values predicted by the PBPK model above.

Table 23 shows the simulated results of geometric mean ratios for C_{max} and AUC_{tau} (co-administered with CYP3A inhibitors or inducers/pirtobrutinib monotherapy) using the PBPK model above.

Table 23. Effects of CYP3A inhibitors and inducers on the PK of pirtobrutinib

Co-administered drug	Observed or predicted value	Geometric mean ratio*1	
		C_{max}	AUC_{tau}
Itraconazole (strong CYP3A inhibitor and P-gp inhibitor)	Observed*2	1.04	1.49
Ritonavir (strong CYP3A inhibitor)	Predicted	1.35	1.51
Ketoconazole (strong CYP3A inhibitor)		1.34	1.49
Clarithromycin (strong CYP3A inhibitor)		1.25	1.37
Diltiazem (moderate CYP3A inhibitor)		1.14	1.20
Fluconazole (moderate CYP3A inhibitor)		1.20	1.29
Verapamil (moderate CYP3A inhibitor)		1.21	1.30
Rifampicin multiple doses (strong CYP3A inducer)	Observed*2	0.576	0.293
Efavirenz (moderate CYP3A inducer)	Predicted	0.67	0.51
Bosentan (moderate CYP3A inducer)		0.80	0.73
Modafinil 400 mg QD (moderate CYP3A inducer)		0.86	0.80
Modafinil 200 mg QD (weak CYP3A inducer)		0.90	0.86

*1, ratio (co-administered with CYP3A inhibitor or inducer/pirtobrutinib monotherapy); *2, data from the foreign phase I study (Study 20006) [see Section 6.2.3.1]

Based on the above results, the applicant's discussion regarding co-administration of pirtobrutinib with CYP3A inhibitors or inducers is outlined as follows:

- While it remains possible that co-administration with a strong CYP3A inhibitor may increase pirtobrutinib exposure, in view of the following observations, no cautionary advice is necessary on the co-administration with CYP3A inhibitors in the package insert.
  - Given the pirtobrutinib exposure-safety relationship [see Section 6.2.8.2], it is not likely that an increase in pirtobrutinib exposure resulting from co-administration with CYP3A inhibitors will have a clinically meaningful impact and cause significant concerns over pirtobrutinib safety.
  - Table 24 shows the incidence of adverse events organized by category of the ratio of variation to geometric mean for the $AUC_{0\text{-}24,ss}$ estimated by the PPK analysis following administration of oral doses of pirtobrutinib 200 mg QD [see Section 6.2.7]. The results showed no clear correlation between pirtobrutinib exposure and the incidence of adverse events.

Table 24. Summary of safety by exposure

	Ratio vs geometric mean ratio for $AUC_{0\text{-}24,ss}$ following administration of pirtobrutinib 200 mg QD				
	≥0.8 and <1.25 (N = 222)	≥1.25 and <1.4 (N = 51)	≥1.4 and <1.6 (N = 46)	≥1.6 and <2 (N = 37)	≥2 (N = 18)
Serious adverse events (%)	32.9	37.3	41.3	24.3	44.4
Adverse events leading to treatment discontinuation of pirtobrutinib (%)	5.0	3.9	8.7	2.7	0
Adverse events leading to dose interruption of pirtobrutinib (%)	33.8	37.3	37.0	37.8	33.3
Adverse events leading to dose reduction of pirtobrutinib (%)	6.8	2.0	2.2	10.8	0

- Since the exposure of pirtobrutinib may decrease when pirtobrutinib is co-administered with a moderate or stronger CYP3A inducer, a cautionary statement to this effect will be included in the package insert.
- It is unlikely that co-administration with a weak CYP3A inducer has a clinically significant impact on pirtobrutinib exposure; therefore, no cautionary advice is necessary on the co-administration with weak CYP3A inducers in the package insert.

PMDA's view:

The applicant's explanation about co-administration with CYP3A inhibitors and inducers is acceptable. However, information on the CYP3A-mediated pharmacokinetic interactions of pirtobrutinib is important in order to verify the appropriateness of cautionary statements regarding co-administration with CYP3A inhibitors and inducers based on the estimated results of the PBPK model. Therefore, the applicant should continue to gather information on pharmacokinetic interactions, and if new information becomes available, the applicant should provide such information to health professionals in an appropriate manner.

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

The applicant submitted efficacy and safety evaluation data, as well as reference data as summarized in Table 25.

Of the results from the global phase I/II study (Study 18001), the following results were not submitted: efficacy results for Cohorts 2 to 6 in the phase II part, which do not include patients with MCL, and results for the phase Ib part,[52)] in which pirtobrutinib was co-administered with venetoclax or other drugs.

[52)] This was a safety assessment of pirtobrutinib plus venetoclax with or without rituximab (in patients with relapsed or refractory CLL/SLL).

Table 25. List of clinical studies on efficacy and safety

Data category	Geographical location	Study ID	Phase	Study population	No. of subjects enrolled	Summary of dosage regimen	Main endpoint
Evaluation	Global	18001	I/II	Phase I part Patients with relapsed or refractory B-cell malignancy Phase II part (1) Cohort 1: patients with non-blastoid MCL who received a prior BTK inhibitor-containing regimen (2) Cohort 2: patients with CLL/SLL who received ≥2 prior BTK inhibitor-containing regimens (3) Cohort 3: patients with treatment naïve CLL/SLL (4) Cohort 4: patients with CLL/SLL who received prior non-BTK inhibitor treatment (5) Cohort 5: patients with WM who received a prior BTK inhibitor-containing regimen (6) Cohort 6: patients with MZL who received a prior BTK inhibitor-containing regimen (7) Cohort 7: non-classifiable patients (e.g., patients with CLL/SLL or NHL not otherwise specified in Cohorts 1 through 6 [including patients with Richter's transformation, low-grade NHL with transformation, blastoid MCL, or patients with history of CNS involvement or PCNSL])	Phase I part and phase II part N = 725 (1) 122 (2) 257 (3) 0 (4) 35 (5) 37 (6) 11 (7) 263	Phase I part Pirtobrutinib 25, 50, 100, 150, 200, 250, or 300 mg orally QD Phase II part Pirtobrutinib 200 mg QD orally	Efficacy Safety PK
Reference	Foreign	20006	I	Healthy adults	Part 1: 15 Part 2: 12	Part 1: in combination with itraconazole, pirtobrutinib 200 mg was orally administered on Days 1 and 12 Part 2: in combination with rifampicin, pirtobrutinib 200 mg was orally administered on Days 1, 8, and 17	PK
		20007	I	Healthy adults	Part 1: 4 Part 2: 5	Part 1: a single oral dose of ^{14}C-labeled pirtobrutinib 200 mg was administered Part 2: after administration of a single oral dose of pirtobrutinib 200 mg, ^{14}C-labeled IV pirtobrutinib <100 μg was administered	PK
		20008	I	Healthy adults	15	Period 1: a single IV dose of midazolam was administered on Day 1, and a single oral dose of midazolam on Day 3 Period 2: in combination with midazolam, pirtobrutinib 200 mg was administered QD orally on Days 5-17	PK
		20009	I	Healthy adults	20	A single oral dose of pirtobrutinib 200 mg was administered on Day 1 or 8 under fasting conditions or after a high-fat meal	PK

Data category	Geographical location	Study ID	Phase	Study population	No. of subjects enrolled	Summary of dosage regimen	Main endpoint
		20010	I	Healthy adults	16	Period 1: a single dose of probe substrates (caffein, omeprazole, and warfarin) was administered orally on Day 1 Period 2: in combination with cocktail substrates, pirtobrutinib 200 mg was orally administered QD on Days 6-19	PK
		20011	I	Healthy adults	31	Treatment A: a single oral dose of pirtobrutinib 900 mg was administered Treatment B: a single oral dose of placebo was administered Treatment C: a single oral dose of moxifloxacin 400 mg was administered	Safety PK
		20012	I	Healthy adults or patients with hepatic impairment	36	A single oral dose of pirtobrutinib 200 mg was administered	Safety PK
		20013	I	Healthy adults or patients with renal impairment	16	A single oral dose of pirtobrutinib 200 mg was administered	Safety PK
		20014	I	Healthy adults	10	In combination with omeprazole, pirtobrutinib 200 mg was orally administered on Days 1 and 8 under fasting conditions or after a standard meal	PK
		20016	I	Healthy adults	16	In combination with repaglinide, pirtobrutinib 200 mg was administered orally QD on Days 2-12	PK
		20017	I	Healthy adults	Cohort 1: 6 Cohort 2: 6 Cohort 3: 6 Cohort 4: 6	Cohort 1: a single oral dose of pirtobrutinib 300 mg was administered Cohort 2: a single oral dose of pirtobrutinib 600 mg was administered Cohort 3: a single oral dose of pirtobrutinib 800 mg was administered Cohort 4: a single oral dose of pirtobrutinib 900 mg was administered	Safety PK
		20021	I	Healthy adults	15	In combination with digoxin, pirtobrutinib 200 mg was administered orally QD on Days 8-16	PK
		21050	I	Healthy adults	28	A single oral dose of pirtobrutinib 200 mg (2 batch formulations) was administered on Days 1 and 8	PK
		JZNW	I	Healthy adults	32	In combination with rosuvastatin, pirtobrutinib 200 mg was administered orally QD on Days 6-17	PK

The following is the summary of the clinical studies. Main adverse events other than death reported in each clinical study in the submitted data for safety evaluation are reviewed in Section "7.3 Adverse events and other findings reported in clinical studies," PK-related results data are discussed in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Global clinical 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, Study 18001 [ongoing since [redacted] 20[redacted], data cut-off on [redacted] [redacted], 20[redacted], [redacted] [redacted], 20[redacted], and [redacted] [redacted], 20[redacted]])

An open-label, uncontrolled study was conducted to assess the efficacy and safety of pirtobrutinib in patients with relapsed or refractory B-cell malignancy (target sample size, approximately 25 subjects in the phase I dose escalation part; a maximum of 10 subjects in the part to assess the recommended phase 2 dose [RP2D] in Japan; a maximum of approximately 150 subjects in the dose expansion part; a total of approximately 600 subjects at maximum, each cohort comprising approximately 100 subjects at maximum in the phase II part) at 57 study centers in 10 countries including Japan.

Both the phase I and phase II parts of the study enrolled "patients with histologically confirmed B-cell malignancy who have failed or intolerant to ≥2 prior standard of care regimens given in combination or sequentially, or who became resistant or intolerant to 1 prior BTK inhibitor-containing regimen." The phase II part of study consisted of the following 7 cohorts:

- Cohort 1: patients with non-blastoid MCL who received a prior BTK inhibitor-containing regimen
- Cohort 2: patients with CLL/SLL who received ≥2 prior BTK inhibitor-containing regimens
- Cohort 3: patients with treatment naïve CLL/SLL
- Cohort 4: patients with CLL/SLL who received prior non-BTK inhibitor treatment
- Cohort 5: patients with Waldenström's macroglobulinaemia (WM) who received a prior BTK inhibitor-containing regimen
- Cohort 6: patients with marginal zone lymphoma (MZL) who received a prior BTK inhibitor-containing regimen
- Cohort 7: patients with B-cell malignancy[53)] not otherwise specified in Cohorts 1 through 6

Table 26 shows the analysis sets for this study.

[53)] Blastoid MCL is included in the cohort.

Table 26. List of analysis sets for Study 18001[*1]

Analysis set		N	Data cut-off date[*2]	Definition
J-PAS (Japan-Primary Analysis Set)	Efficacy analysis set	65	(1)	The first 65 enrolled patients with non-blastoid MCL treated with a prior BTK inhibitor-containing regimen
J-MEAS (Japan-MCL Efficacy Analysis Set)		8	(3)	The first 8 enrolled Japanese patients with non-blastoid MCL treated with a prior BTK inhibitor-containing regimen (efficacy analysis set for Japanese patients)
OMTSAS (Overall Monotherapy Safety Analysis Set)	Safety analysis set	725	(2)	Patients with MCL, CLL/SLL, or other B-cell malignancy who were enrolled in the study and received ≥1 dose of pirtobrutinib monotherapy
MSAS (MCL Safety Analysis Set)		164	(2)	All patients with MCL who were enrolled in the study and received ≥1 dose of pirtobrutinib monotherapy
J-OMTSAS (Japan-Overall Monotherapy Safety Analysis Set)		29	(3)	Japanese patients who meet the OMTSAS eligibility criteria
J-MSAS (Japan-MCL Safety Analysis Set)		12	(3)	Japanese patients who meet the MSAS eligibility criteria

*1, In addition to data from patients enrolled in the phase I part who met the definition for the analysis set, each analysis set includes the following data: data from patients in Cohort 1 of the phase II part who meet the definition for the corresponding analysis set (J-PAS and J-MEAS); data from patients in Cohort 1 and 7 of the phase II part who meet the definition for the corresponding analysis set (MSAS and J-MSAS); and data from patients in all the cohorts of the phase II part who meet the definition for the corresponding analysis set (OMTSAS and J-OMTSAS); *2, (1) [redacted], (2) [redacted], and (3) [redacted]

In the phase I part, subjects were to receive oral doses of pirtobrutinib 25, 50, 100, 150, 200, 250, or 300 mg QD, and in the phase II part, subjects were to receive oral doses of pirtobrutinib 200 mg QD, which was determined to be RP2D in the phase I part. Treatment was to be continued until disease progression or criteria for treatment discontinuation were met. In Japan, subjects were to receive pirtobrutinib 200 mg[54] QD in the phase I part.

Of the patients enrolled in the study, the first 65 patients[55] (in the order of the start of treatment) with non-blastoid MCL[56] treated with a prior BTK inhibitor-containing regimen (33 subjects from the phase I part and 32 subjects from the phase II part) were included in the primary efficacy analysis set (J-PAS).[57] Of the patients with B-cell malignancy enrolled in the study, 725 subjects[58] who received ≥1 dose of pirtobrutinib monotherapy were included in the safety analysis set (OMTSAS[59]). The assessment of dose limiting toxicity (DLT) was based on 21 subjects enrolled in the dose escalation cohort of the phase I part.

[54] After the RP2D had been determined to be 200 mg QD in the phase I dose escalation part in other countries (non-Japanese subjects), pirtobrutinib was administered to Japanese patients at this dose level.

[55] It has been reported that monotherapy drugs (e.g., lenalidomide) approved in the treatment of patients with MCL without prior BTK inhibitor treatment have an overall response rate of 20% to 30% (e.g., *Br J Haematol.* 2015;170:496-503). A threshold overall response rate of 20% and an expected response rate of 40% were selected. A sample size of 65 patients was estimated to provide 92% statistical power to achieve a lower bound of the 95% confidence interval that exceeds 20%. A retrospective observational study, in which patients received lenalidomide monotherapy after administration of a BTK inhibitor (ibrutinib), reported an overall response rate of 15% (*J Hematol Oncol.* 2017;10:171).

[56] Of the patients enrolled in the phase I part or phase II part of the study, those who met the eligibility criteria (1), (2), (3) for Cohort 1 of the phase II part:
(1) patients with histologically confirmed non-blastoid MCL who have received a prior BTK inhibitor-containing regimen
(2) patients with measurable lesion that was evaluated at baseline according to the Lugano criteria
(3) patients who received ≥1 dose of pirtobrutinib as a monotherapy

[57] Data cut-off on [redacted].

[58] Data cut-off on [redacted].

[59] All patients with B cell malignancy who were enrolled in Study 18001 and received ≥1 dose of pirtobrutinib as a monotherapy (MCL, 164 subjects; CLL/SLL, 311 subjects; other NHL, 250 subjects [WM, 78 subjects; Richter's transformation, 57 subjects; follicular lymphoma (FL), 37 subjects; diffuse large B-cell lymphoma (DLBCL), 32 subjects; MZL, 26 subjects; low-grade NHL with transformation, 6 subjects; B-cell prolymphocytic leukemia (B-PLL), 5 subjects; hairy cell leukemia (HCL) and primary central nervous system lymphoma (PCNSL), 4 subjects each; lymphoplasmacytic lymphoma (LPL), 1 subject]). These numbers include Japanese patients (MCL, 10 subjects; CLL/SLL, 2 subjects; and other 10 subjects).

In Cycle 1 (28 days) of the phase I dose escalation part, defined as the period for DLT assessment, no DLTs were reported up to a dose level of 300 mg QD, and no maximum tolerated dose (MTD) was established.

Table 27 shows the overall response rate by central review according to the Lugano criteria (*J Clin Oncol.* 2014;32:3059-68), the primary endpoint, in the efficacy analysis set (J-PAS).

Table 27. Best overall response and overall response rate
(Study 18001, J-PAS, central review, data cut-off on [redacted], 20[redacted])

Best overall response	N (%) N = 65
CR	13 (20.0)
PR	24 (36.9)
SD	9 (13.8)
PD	10 (15.4)
NE	9 (13.8)
Overall response (CR + PR) (Overall response rate, % [95% CI*])	37 (56.9 [44.0, 69.2])

* Clopper-Pearson method

During treatment and within 28 days after the end of pirtobrutinib treatment, 16 of 198 subjects (8.1%) in the phase I part died (1 of 20 subjects [150 mg QD], 13 of 113 subjects [200 mg QD], and 2 of 20 subjects [300 mg QD]) and 52 of 527 subjects (9.9%) in the phase II part died (11 of 89 subjects [Cohort 1], 20 of 174 subjects [Cohort 2], 2 of 19 subjects [Cohort 4], 1 of 33 subjects [Cohort 5], and 18 of 203 subjects [Cohort 7]). With the exception of disease progression (9 subjects in the phase I part and 21 subjects in the phase II part), the causes of death were as follows: in the phase I part, COVID-19 pneumonia, COVID-19, respiratory failure, dyspnoea, septic shock, escherichia sepsis, and malignant pleural effusion (1 subject each); in the phase II part, COVID-19 pneumonia (6 subjects), COVID-19 (3 subjects), respiratory failure (3 subjects), multiple organ dysfunction syndrome (2 subjects), sepsis (2 subjects); dyspnoea, septic shock, bacterial sepsis, failure to thrive, haemorrhage, infectious pleural effusion, Legionella infection, mucormycosis, pneumonia fungal, shock, splenic rupture, streptococcal infection, sudden death, [60] cardiac arrest, [61] and COVID-19 pneumonia/cerebrovascular accident (1 subject each). A causal relationship to pirtobrutinib could not be ruled out for COVID-19 pneumonia, respiratory failure, and septic shock (1 subject each) in the phase II part.

Of the events presented above, in the MSAS,[62] 3 of 40 subjects (7.5%) in the phase I part and 12 of 124 subjects (9.7%) in the phase II part died during treatment and within 28 days after the end of pirtobrutinib treatment. With the exception of disease progression (1 subject in the phase I part and 4 subjects in the phase II part), the causes of death were as follows: in the phase I part, COVID-19 pneumonia, and malignant pleural effusion (1

[60] A male patient aged 6[redacted] years with MCL, who had medical history of acute myocardial infarction. This patient had showed decreased cardiac function (ejection fraction of 40%) and reduced apical wall motion from before the start of pirtobrutinib treatment. On Day 22 (the last dose of pirtobrutinib was administered on Day 21), the patient suddenly became unconscious at home and went into cardiopulmonary arrest. The investigator reported no causal relationship between the event and pirtobrutinib.

[61] A male patient aged 7[redacted] years with MCL. The patient was admitted to hospital due to COVID-19 pneumonia on Day 241. When COVID-19 pneumonia was resolving, the patient was transferred to a long-term care facility where the patient was put on ventilator support due to increase in oxygen demand. On Day 266 (the last dose of pirtobrutinib was administered on Day 243), the patient suddenly went into cardiac arrest. The investigator reported no causal relationship between the event and pirtobrutinib.

[62] An analysis set for safety which includes only patients with MCL among those in the OMTSAS

subject each); and in the phase II part, respiratory failure (2 subjects); cardiac arrest, haemorrhage, mucormycosis, multiple organ dysfunction syndrome, streptococcal infection, and sudden death (1 subject each). A causal relationship to pirtobrutinib was ruled out for all the events.

In the J-OMTSAS (Japanese patients), 1 subject died due to disease progression during treatment and within 28 days after the end of pirtobrutinib treatment.

7.2 Reference data

7.2.1 Clinical pharmacology studies

Fourteen clinical pharmacology studies[63] were submitted (Table 25). In these studies, there were no reports of death during study drug treatment.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

Based on the following discussions, PMDA concluded that pirtobrutinib has a certain level of efficacy in the treatment of patients with relapsed or refractory MCL who were resistant or intolerant to BTK inhibitors.

7.R.1.1 Efficacy analysis sets

The applicant's explanation about the efficacy analysis population for Study 18001:

Main circumstances that led to the establishment of the J-PAS as the primary efficacy analysis population are as follows:

Initially, the phase II part of Study 18001 consisted of 6 cohorts according to specific disease, prior BTK inhibitor treatment, and presence of *BTK*C481 mutation. However, the study design was changed, and the phase II part has 7 cohorts to which subjects were to be assigned according to specific disease and prior BTK inhibitor treatment.[64] Compared to non-blastoid MCL, poor outcomes are predicted for blastoid MCL (e.g., *Leuk Lymphoma*. 2018;59:1814-28). Therefore, non-blastoid and blastoid MCL were separated into different cohorts (Cohort 1 [non-blastoid MCL] and Cohort 7 [blastoid MCL as part of "other" category]) to allow effective evaluation of efficacy by MCL histology [see Section 7.1.1.1]. The primary efficacy analysis population for efficacy evaluation of pirtobrutinib in patients with MCL was defined as patients with "non-blastoid MCL treated with a prior BTK inhibitor that meet the criteria for Cohort 1"[56] (Protocol, version [redacted], dated on [redacted], 20[redacted]).

An interim analysis, which had not been prespecified in the protocol or other documents, was performed (data cut-off on [redacted], 20[redacted])[65] and the primary efficacy analysis population [redacted] was modified[66] to "all patients with MCL including blastoid MCL treated with a prior BTK inhibitor (Cohort 1 and part of Cohort 7). The primary efficacy analysis population was defined as patients with "non-blastoid

[63] Studies 20006, 20007, 20008, 20009, 20010, 20011, 20012, 20013, 20014, 20016, 20017, 20021, 21050, and JZNW

[64] The change was made taking into consideration that tests for BTK mutation are not always performed in clinical settings, and that the BTK C481 mutation is not the only factor involved in the mechanism of resistance to BTK inhibitors.

[65] For the purpose of [redacted]

[66] Taking into consideration that the treatment plan for blastoid MCL is not clearly distinguished from that for non-blastoid MCL in clinical practice guidelines, etc., it was considered that evaluation on the integrated population would be possible.

MCL and blastoid MCL treated with a prior BTK inhibitor"[67] in the Statistical Analysis Plan regarding the efficacy on MCL, version [redacted] (dated on [redacted], 20[redacted]).

However, given that the new analysis set was established after the non-prespecified interim analysis (data cut-off on [redacted], 20[redacted]), it was considered more appropriate to follow the initial plan for the approval application in Japan. Accordingly, the primary efficacy analysis population was defined as patients with "non-blastoid MCL treated with a prior BTK inhibitor that meet the criteria for Cohort 1"[56] as defined in the Protocol, version [redacted] (dated on [redacted], 20[redacted]), and the first 65 patients[55] in the analysis set (in the order of the start of treatment) were defined as the subjects to be analyzed (i.e., J-PAS) in the Statistical Analysis Plan for Japan, version [redacted] (dated on [redacted], 20[redacted])[68] before conducting the primary analysis.

Because no Japanese patients were included in the J-PAS, an additional analysis was planned to evaluate efficacy in Japanese patients. In the Statistical Analysis Plan for Japan, version [redacted] (dated on [redacted], 20[redacted]), the analysis population was defined as "Japanese patients with non-blastoid MCL treated with a prior BTK inhibitor enrolled in Cohort 1"[69] and a target sample size of 8 subjects[70] was selected. Data with a cut-off date on [redacted], 20[redacted] were used (i.e., J-MEAS).

PMDA's view:
It is not appropriate to select the analysis set that was established after a non-protocol prespecified interim analysis as the population for the primary analysis. Therefore, as explained by the applicant, PMDA decided to evaluate the efficacy of pirtobrutinib in Study 18001 based primarily on the results of the J-PAS as the primary analysis set. The results of the J-MEAS will be evaluated to assess efficacy in Japanese patients.

7.R.1.2 Endpoints and evaluation results for efficacy

The applicant's explanation about the primary endpoint for Study 18001:
Patients with relapsed or refractory MCL who are resistant or intolerant to BTK inhibitors have poor clinical outcomes (e.g., *Blood*. 2016,127:1559-63) and no standard of care that demonstrated prolongation of overall survival (OS) has been established. Therefore, when such patients achieve response, tumor reduction (response) can lead to improvement in symptoms associated with tumors placing pressure on nearby organs (e.g., oedema, bowel obstruction, neurological symptoms) and disease associated symptoms (pyrexia, decrease in body weight, night sweats). It is considered that these improvements are clinically meaningful and therefore overall response rate was selected as the primary endpoint.

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[67] This was to be used for the application for approval in Europe and the US
[68] Before the data lock (implemented on [redacted], 20[redacted]) for data cut-off ([redacted], 20[redacted])
[69] Of the Japanese patients with non-blastoid MCL treated with a prior BTK inhibitor-containing regimen enrolled in Cohort 1 in the phase II part of Study 18001, patients who met one of the criteria (1) and (2) were excluded and the first 8 patients in the order of start of treatment were included (3 patients were excluded by the criteria below):
(1) As of the data cut-off date [redacted], 20[redacted], patients who underwent a post-baseline disease assessment at least once
(2) Patients who had a post-baseline disease assessment on or after [redacted], 20[redacted] whose data were confirmed by the sponsor before the finalization of the Statistical Analysis Plan for Japan, version [redacted] ([redacted], 20[redacted])
[70] Assuming an expected overall response rate of 40%, when the sample size is 8 patients, the probability that the point estimate for the overall response rate to exceed the threshold overall response rate 20% in the primary analysis is approximately 89%.

In addition, the applicant's explanation about the efficacy of pirtobrutinib in patients with relapsed or refractory MCL who are resistant or intolerant to BTK inhibitors in Study 18001:

In the J-PAS in Study 18001, the primary endpoint, the overall response rate (%) by central review according to the Lugano criteria [95% CI] was 56.9% [44.0%, 69.2%]. The lower bound of the 95% CI for overall response rate exceeded the threshold over response rate (20%)[55] [see Section 7.1.1.1]. A secondary endpoint, the median duration (months) of response by central review [95% CI], was unachieved (months) [8.31, NE].

Figure 2 shows the best change in tumor size by central review.

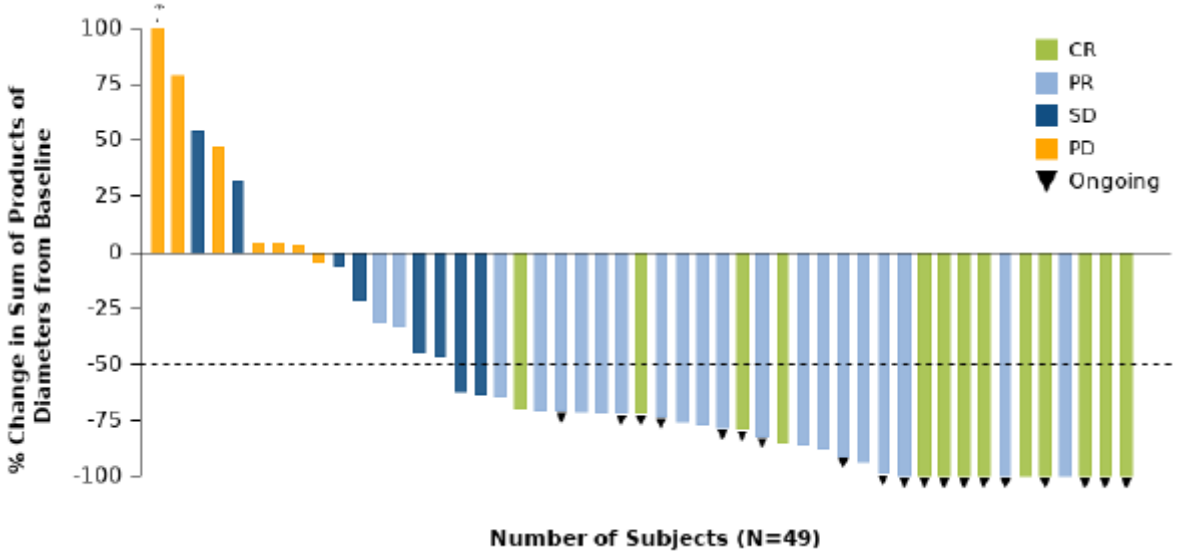

Figure 2. Best change in tumor size from baseline
(Study 18001, J-PAS, central review, data cut-off on [redacted])

Table 28 shows the results for overall response rate in the phase I part, phase II, and J-PAS total. There were differences in overall response rate between the phase I part and phase II part. More patients in the phase II part had a best overall response of NE,[71] which may be one of the factors contributing to the difference in overall response rate. The patient inclusion criteria were similar in both parts, and no marked differences were noted in terms of the baseline demographics and disease characteristics of patients between the parts. Although Study 18001 used 2 types of formulations, which differ from each other in terms of constituents, it is unlikely that the difference in the use of formulations had an effect on the efficacy of pirtobrutinib [see Section 6.R.1].

[71] The reason for being assessed as NE was that pirtobrutinib treatment was discontinued before the first scheduled tumor assessment in all of these subjects, resulting in the absence of an appropriate tumor assessment result. The applicant considers that subjects in the phase II part who were assessed as NE tended to have poorer disease characteristics, which may have been related to the NE results.

Table 28. Best overall response and overall response rate (by part)

(Study 18001, J-PAS, central review, data cut-off on [redacted], 20[redacted])

Best overall response	n (%)		
	J-PAS (Phase I part) N = 33	J-PAS (Phase II part) N = 32	J-PAS N = 65
CR	9 (27.3)	4 (12.5)	13 (20.0)
PR	13 (39.4)	11 (34.4)	24 (36.9)
SD	1 (3.0)	8 (25.0)	9 (13.8)
PD	9 (27.3)	1 (3.1)	10 (15.4)
NE	1 (3.0)	8 (25.0)	9 (13.8)
Overall response (CR + PR) (Overall response rate, % [95% CI*])	22 (66.7% [48.2%, 82.0%])	15 (46.9% [29.1%, 65.3%])	37 (56.9% [44.0%, 69.2%])

* Clopper-Pearson method

The overall response rate [95% CI] by pirtobrutinib starting dose (<200 mg QD [N = 6], 200 mg QD [N = 52], and >200 mg QD [N = 7]) in the J-PAS was 50.0% [11.8%, 88.2%] (3 of 6 subjects) for <200 mg QD, 57.7% [43.2%, 71.3%] (30 of 52 subjects) for 200 mg QD, and 57.1% [18.4%, 90.1%] (4 of 7 subjects) for >200 mg QD.

The applicant's explanation about the timing of efficacy analysis in the J-PAS:

The Statistical Analysis Plan for Japan, version [redacted] (dated on [redacted], 20[redacted]) specifies that the J-PAS should be analyzed based on data as of the cut-off of [redacted], 20[redacted]. This was established taking into account that, of the target sample size of 65 subjects who met the eligibility criteria for the J-PAS, [redacted], and [redacted]. The results show that the median follow-up was 8.6 months (Min, Max: 0.5, 27.9), [redacted], which met the prespecified efficacy hypothesis, and that the obtained results are clinically meaningful (Table 27). Thus, there is no significant problem with the timing of data cut-off.

The applicant's explanation about the efficacy of pirtobrutinib in Japanese patients:

Table 29 shows the results for overall response rate in the J-MEAS,[72)] the efficacy analysis set for Japanese patients. The median duration of response [95% CI] was 7.4 months [5.6, NE].

[72)] Of the Japanese patients with non-blastoid MCL treated with a prior BTK inhibitor-containing regimen enrolled in Cohort 1 in the phase II part of Study 18001, the first 8 patients, excluding patients whose efficacy results could be identified as of the data cut-off on [redacted], 20[redacted], were included in the order of start of treatment.

Table 29. Best overall response and overall response rate

(Study 18001, J-MEAS, central review, data cut-off on [redacted], 20[redacted])

Best overall response	n (%)
	J-MEAS N = 8
CR	2 (25.0)
PR	2 (25.0)
SD	3 (37.5)
PD	1 (12.5)
NE	0
Overall response (CR + PR) (Overall response rate, % [95% CI*])	4 (50.0% [15.7%, 84.3%])

* Clopper-Pearson method

Figure 3 shows the best change in tumor size by central review.

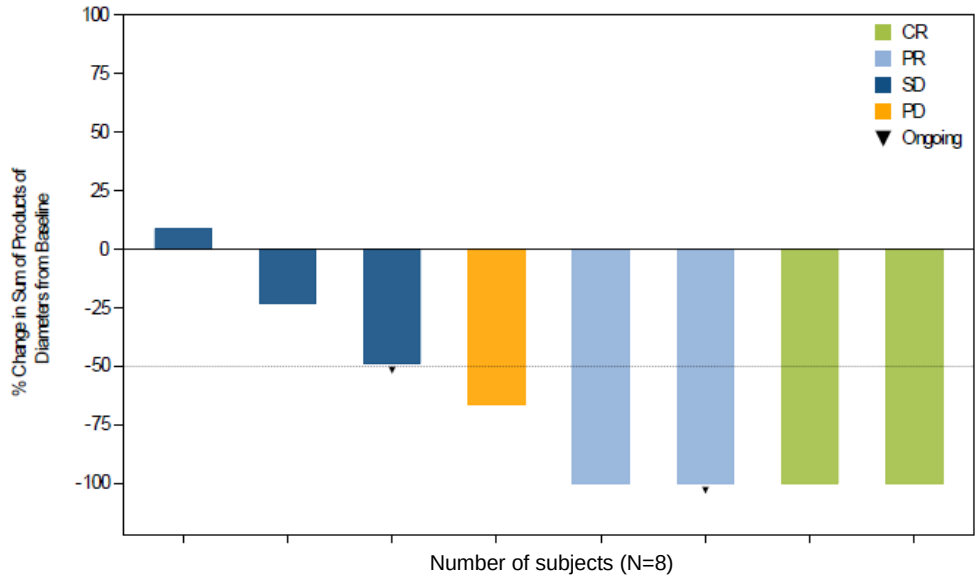

Figure 3.エラー! 参照元が見つかりません。 **Best change in tumor size from baseline**
(Study 18001, J-MEAS, central review, data cut-off on [redacted], 20[redacted])

PMDA's view:

The applicant's explanation about the efficacy endpoint is acceptable. As for the efficacy evaluation results, PMDA concluded that pirtobrutinib has a certain level of efficacy in the treatment of patients with relapsed or refractory MCL who are resistant or intolerant to BTK inhibitors based on the following points:

- In the J-PAS in Study 18001, the lower bound of the 95% CI for overall response rate by central review, the primary endpoint, exceeded the prespecified threshold over response rate. In addition, the results are considered to be clinically meaningful.
- The J-PAS, the primary efficacy analysis population, consists of subjects of the phase I part and II part, with data on different starting dose levels. The overall response rate of each phase subgroup does not differ markedly from that of the overall population of J-PAS. In addition, subjects who received 200 mg QD, the recommended (proposed) dosage regimen for pirtobrutinib, account for the majority of the population (80%, 52 of 65 subjects), and the results for the 200 mg QD group were similar to those for the overall population (J-PAS).

- The limited number of Japanese patients in Study 18001 precludes precise evaluation of efficacy in Japanese patients. However, given that a certain level of response has been achieved in the Japanese patient population (J-MEAS), and that there are no clear differences between Japanese and non-Japanese populations in terms of treatment plan for the disease of interest or the PK parameters following administration of pirtobrutinib [see Section 6.2.9], pirtobrutinib can be expected to be effective in Japanese patients.

7.R.2 Safety [for adverse events, see Section "7.3 Adverse events and other findings reported in clinical studies"]

Based on the discussions in the following sections, PMDA considered that adverse events of special interest when pirtobrutinib is used are infections, myelosuppression, and haemorrhage. When pirtobrutinib is used, patients should be closely monitored for development of these adverse events.

At the same time, while vigilance is required for the above-mentioned adverse events during treatment with pirtobrutinib, PMDA considers that pirtobrutinib is tolerable if appropriate measures such as monitoring and management of adverse events, dose interruption and reduction of pirtobrutinib are taken by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.

7.R.2.1 Safety profile

The applicant's explanation about the safety profile of pirtobrutinib based on the safety data reported in Study 18001:

Table 30 summarizes the safety data in the group of patients with MCL who received pirtobrutinib monotherapy (MSAS) in Study 18001.

Table 30. Summary of safety data (Study 18001)

	n (%)
	MSAS N = 164
All adverse events	146 (89.0)
Grade ≥3 adverse events	76 (46.3)
Adverse events leading to death	11 (6.7)
Serious adverse events	55 (33.5)
Adverse events leading to treatment discontinuation of pirtobrutinib	15 (9.1)
Adverse events leading to dose interruption of pirtobrutinib	47 (28.7)
Adverse events leading to dose reduction of pirtobrutinib	8 (4.9)

Table 31 shows adverse events occurring in ≥10% of subjects in the MSAS in Study 18001.

Table 31. Adverse events occurring in ≥10% of subjects

(Study 18001, MSAS, data cut-off on [redacted], 20[redacted])

PT (MedDRA/J ver.24.0)	n (%) N = 164	
	All Grades	Grade ≥3
All adverse events	146 (89.0)	76 (46.3)
Fatigue	49 (29.9)	4 (2.4)
Diarrhoea	35 (21.3)	0
Dyspnoea	27 (16.5)	3 (1.8)
Contusion	24 (14.6)	0
Back pain	21 (12.8)	2 (1.2)
Anaemia	21 (12.8)	8 (4.9)
Cough	20 (12.2)	0
Pyrexia	19 (11.6)	0
Platelet count decreased	19 (11.6)	9 (5.5)
Constipation	18 (11.0)	0
Nausea	18 (11.0)	0
Pneumonia	17 (10.4)	14 (8.5)
Myalgia	17 (10.4)	0

In the MSAS in Study 18001, adverse events leading to death were respiratory failure (2 subjects, 1.2%), cardiac arrest, haemorrhage, mucormycosis, multiple organ dysfunction syndrome, streptococcal infection, sudden death, COVID-19 pneumonia, pneumonia, and malignant pleural effusion (1 subject each, 0.6%). Serious adverse events occurring in ≥2 subjects were pneumonia (13 subjects, 7.9%), COVID-19 pneumonia (5 subjects, 3.0%), leukocytosis, pleural effusion, non-cardiac chest pain, and sepsis (3 subjects each, 1.8%); acute kidney injury, COVID-19, and respiratory failure (2 subjects each, 1.2%). Adverse events leading to pirtobrutinib treatment discontinuation occurring in ≥2 subjects were pneumonia (2 subjects, 1.2%). Adverse events leading to pirtobrutinib dose interruption occurring in ≥2 subjects were pneumonia (8 subjects, 4.9%); neutrophil count decreased (6 subjects, 3.7%); platelet count decreased, and upper respiratory tract infection (4 subjects each, 2.4%); leukocytosis, and anaemia (3 subjects each, 1.8%); COVID-19, COVID-19 pneumonia, abdominal pain, dyspepsia, white blood cell count decreased, pleural effusion, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, non-cardiac chest pain, and upper gastrointestinal haemorrhage (2 subjects each, 1.2%). Adverse events leading to pirtobrutinib dose reduction occurring in ≥2 subjects were neutrophil count decreased (2 subjects, 1.2%).

The applicant's explanation about the difference between Japanese and non-Japanese populations in the safety of pirtobrutinib:

Table 32 shows the summary of safety data in non-Japanese patients (MSAS minus Japanese patients) and Japanese patients (J-MSAS[73)]) in Study 18001.

[73)] The group consisted of 10 Japanese patients included in the MSAS (data cut-off on [redacted], 20[redacted]) and 2 additional Japanese patients who were enrolled when the study was continued up to the data cut-off on [redacted], 20[redacted].

Table 32. Summary of difference in safety data between Japanese and non-Japanese populations (Study 18001)

	n (%)	
	Non-Japanese (MSAS*) N = 154	Japanese (J-MSAS) N = 12
All adverse events	136 (88.3)	12 (100)
Grade ≥3 adverse events	70 (45.5)	7 (58.3)
Adverse events leading to death	11 (7.1)	0
Serious adverse events	50 (32.5)	5 (41.7)
Adverse events leading to treatment discontinuation of pirtobrutinib	14 (9.1)	1 (8.3)
Adverse events leading to dose interruption of pirtobrutinib	42 (27.3)	7 (58.3)
Adverse events leading to dose reduction of pirtobrutinib	6 (3.9)	2 (16.7)

* Japanese patients' data are excluded

Table 33 shows adverse events of any grade and Grade ≥3 adverse events occurring with an incidence higher in Japanese patients (J-MSAS) than in non-Japanese patients (MSAS minus Japanese patients) by ≥10%.

Table 33. Adverse events occurring with an incidence higher in Japanese patients than in non-Japanese patients by ≥10%

PT (MedDRA/J ver.24.0)	n (%)			
	Non-Japanese (MSAS*) N = 154		Japanese (J-MSAS) N = 12	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	136 (88.3)	70 (45.5)	12 (100)	7 (58.3)
Anaemia	18 (11.7)	7 (4.5)	3 (25.0)	1 (8.3)
Platelet count decreased	17 (11.0)	9 (5.8)	6 (50.0)	1 (8.3)
Pyrexia	15 (9.7)	0	4 (33.3)	1 (8.3)
COVID-19	8 (5.2)	4 (2.6)	2 (16.7)	0
AST increased	8 (5.2)	1 (0.6)	2 (16.7)	0
Pruritus	4 (2.6)	0	2 (16.7)	0
Hypokalaemia	4 (2.6)	0	2 (16.7)	1 (8.3)
Blood creatinine increased	3 (1.9)	0	2 (16.7)	0
White blood cell count decreased	2 (1.3)	0	2 (16.7)	1 (8.3)
Rash	1 (0.6)	0	3 (25.0)	0
Hypoalbuminaemia	1 (0.6)	0	2 (16.7)	1 (8.3)

* Japanese patients' data are excluded

Serious adverse events occurring with an incidence higher in Japanese patients than in non-Japanese patients by ≥3% were pneumonia (2 subjects [16.7%] and 11 subjects [7.1%] in Japanese and non-Japanese patients, respectively; the same applies hereinafter), febrile neutropenia (1 subject [8.3%] and 0 subjects), anti-neutrophil cytoplasmic antibody positive vasculitis (1 subject [8.3%] and 0 subjects), aspiration (1 subject [8.3%] and 0 subjects), cholecystitis (1 subject [8.3%] and 0 subjects), pneumocystis jirovecii pneumonia (1 subject [8.3%] and 0 subjects). Adverse events leading to pirtobrutinib treatment discontinuation with an incidence higher in Japanese patients than in non-Japanese patients by ≥3% were cholecystitis (1 subject [8.3%] and 0 subjects). Adverse events leading to pirtobrutinib dose interruption with an incidence higher in Japanese patients than in non-Japanese patients by ≥3% were COVID-19 (2 subjects [16.7%] and 2 subjects [1.3%]), neutrophil count decreased (1 subject [8.3%] and 5 subjects [3.2%]), pneumonia (2 subjects [16.7%] and 6 subjects [3.9%]), febrile neutropenia (1 subject [8.3%] and 0 subjects), white blood cell count decreased (1 subject [8.3%] and 1 subject [0.6%]), aspiration (1 subject [8.3%] and 0 subjects), proctitis (1 subject [8.3%]

and 0 subjects). Adverse events leading to pirtobrutinib dose reduction with an incidence higher in Japanese patients than in non-Japanese patients by ≥3% were neutrophil count decreased (1 subject [8.3%] and 1 subject [0.6%]), and rash (1 subject [8.3%] and 0 subjects). There were no adverse events leading to death with an incidence higher in Japanese patients than in non-Japanese patients by ≥3%.

The applicant's explanation about the difference in safety profile of pirtobrutinib between patients with MCL and patients with non-MCL B-cell malignancy in Study 18001:
Table 34 shows the summary of safety data in patients with MCL and patients with non-MCL B-cell malignancy.

Table 34. Summary of safety data by disease

(Study 18001, data cut-off on [redacted])

	n (%)	
	Patients with MCL N = 164	Patients with non-MCL B-cell malignancy* N = 561
All adverse events	146 (89.0)	535 (95.4)
Grade ≥3 adverse events	76 (46.3)	309 (55.1)
Adverse events leading to death	11 (6.7)	34 (6.1)
Serious adverse events	55 (33.5)	200 (35.7)
Adverse events leading to treatment discontinuation of pirtobrutinib	15 (9.1)	30 (5.3)
Adverse events leading to dose interruption of pirtobrutinib	47 (28.7)	205 (36.5)
Adverse events leading to dose reduction of pirtobrutinib	8 (4.9)	29 (5.2)

* Patients with MCL are excluded from the OMTSAS (consisting of patients with any B-cell malignancies who were enrolled in the study and received ≥1 dose of pirtobrutinib)

The data on adverse events of any grade,[74)] Grade ≥3 adverse events,[75)] and serious adverse events[76)] show that although the incidence of some adverse events differed between patients with MCL and patients with non-MCL B-cell malignancy, the difference was small. The results suggest that there is no clear difference in the safety profile of pirtobrutinib between patients with MCL and patients with non-MCL B-cell malignancy.

PMDA's view:
Adverse events with a high incidence, Grade ≥3 adverse events, and serious adverse events reported in patients with MCL in Study 18001 require particular vigilance when pirtobrutinib is used. PMDA concluded that information on the incidence of such adverse events should be provided to healthcare professionals using the package insert in an appropriate manner.

74) Adverse events of any grade occurring with an incidence higher in patients with MCL than in patients with non-MCL B-cell malignancy by ≥5% were peripheral swelling (13 subjects [7.9%] and 14 subjects [2.5%] in patients with MCL and patients with non-MCL B-cell malignancy, respectively; the same applies hereinafter), myalgia (17 subjects [10.4%] and 29 subjects [5.2%]), joint swelling (9 subjects [5.5%] and 2 subjects [0.4%]), paraesthesia (16 subjects [9.8%] and 22 subjects [3.9%]), dry eye (11 subjects [6.7%] and 9 subjects [1.6%]).

75) Grade ≥3 adverse events occurring with an incidence higher in patients with MCL than in patients with non-MCL B-cell malignancy by ≥2% were pneumonia (14 subjects [8.5%] and 21 subjects [3.7%] in patients with MCL and patients with non-MCL B-cell malignancy, respectively), leukocytosis (6 subjects [3.7%] and 8 subjects [1.4%] in patients with MCL and patients with non-MCL B-cell malignancy, respectively).

76) Serious adverse events occurring with an incidence higher in patients with MCL than in patients with non-MCL B-cell malignancy by ≥2% were pneumonia (13 subjects [7.9%] and 21 subjects [3.7%] in patients with MCL and patients with non-MCL B-cell malignancy, respectively).

Although the limited number of Japanese patients evaluated precludes a firm conclusion on the difference in the safety of pirtobrutinib between Japanese and non-Japanese populations, caution needs to be exercised regarding adverse events that occurred with a higher incidence in Japanese patients than in non-Japanese patients. PMDA concluded that information on the incidence of such adverse events should be provided to healthcare professionals in an appropriate manner.

In the following sections, PMDA reviews adverse events based mainly on the safety results of pirtobrutinib (MSAS) in patients with MCL from Study 18001, primarily focusing on Grade ≥3 adverse events occurring at a high incidence, serious adverse events, and adverse events leading to death, as well as events that are specified in the "Clinically Significant Adverse Reactions" section of the package insert for approved BTK inhibitors such as ibrutinib.

7.R.2.2 Infections

The applicant's explanation about the incidence of infections associated with pirtobrutinib treatment:
Preferred terms (PTs) under Medical Dictionary for Regulatory Activities ICH (MedDRA) system organ class (SOC) "infections and infestations" were included in the analysis of infection-related adverse events.

Table 35 shows the incidence of infections in the MSAS in Study 18001.

Table 35. Infections occurring in ≥5% of subjects (Study 18001, MSAS)

PT (MedDRA/J ver.24.0)	n (%) N = 164	
	All Grades	Grade ≥3
Infections	59 (36.0)	28 (17.1)
Pneumonia	17 (10.4)	14 (8.5)
Upper respiratory tract infection	9 (5.5)	0
Urinary tract infection	9 (5.5)	0

In the MSAS in Study 18001, infections led to death in 4 subjects (2.4%; pneumonia, COVID-19 pneumonia, streptococcal infection, and mucormycosis [1 subject each]), and a causal relationship to pirtobrutinib was ruled out for all these events. Serious infections occurred in 27 subjects (16.5%; pneumonia [13 subjects[77)]]; COVID-19 pneumonia [5 subjects]; sepsis [3 subjects]; COVID-19 [2 subjects]; bacteraemia, rhinovirus infection, neutropenic sepsis, endocarditis, infective aneurysm, mucormycosis, pneumocystis jirovecii pneumonia, pneumonia haemophilus, pneumonia pseudomonal, pneumonia viral, post herpetic neuralgia, and streptococcal infection [1 subject each]; some subjects had more than 1 event). Among these events, a causal relationship to pirtobrutinib could not be ruled out for pneumonia (3 subjects77[)]), sepsis (1 subject), and pneumocystis jirovecii pneumonia (1 subject). Infections led to pirtobrutinib treatment discontinuation in 6 of 164 subjects (3.7%; pneumonia [2 subjects]; COVID-19 pneumonia, sepsis, infective aneurysm, mucormycosis, and streptococcal infection [1 subject each]; some subjects had more than 1 event). Infections led to pirtobrutinib dose interruption in 21 subjects (12.8%) and pirtobrutinib dose reduction in 1 subject (0.6%).

[77)] Including 1 subject with a starting dose of 300 mg QD

PMDA asked the applicant to explain (1) implementation status of screening, monitoring, and prophylaxis for hepatitis B virus (HBV) infection and opportunistic infection (including virus reactivation) in Study 18001; and (2) the incidence of HBV infections and opportunistic infections in the study.

The applicant's response:

The status of HBV infections and opportunistic infections in Study 18001 was investigated based on cytomegalovirus (CMV), *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, fungi, varicella zoster virus (VZV), and JC virus.

(1) Antigen tests, antibody tests, and DNA assays were performed to screen or monitor for HBV and CMV infections. Conversely, although no corresponding screening tests were specified for *Mycobacterium tuberculosis*, *Pneumocystis jirovecii*, fungi, VZV, and JC virus, patients were screened at physical examination by the investigator for any infection that would violate the exclusion criteria. No requirements for prophylaxis for each infection were specified in the protocol. Prophylactic administration was performed as necessary according to the guidelines or at the discretion of the investigator.

(2) The incidences of HBV infections and opportunistic infections in Study 18001 (MSAS) are as follows:

- Prophylaxis against HBV infections[78)] was administered to 2 of 164 subjects (1.2%). No HBV infections were reported regardless of prophylaxis.
- Prophylaxis against CMV infections[79)] was administered to 2 of 164 subjects (1.2%) No CMV infections were reported regardless of prophylaxis.
- No *Mycobacterium tuberculosis* infections[80)] were reported.
- Prophylaxis against *Pneumocystis jirovecii* infections[81)] was administered to 41 of 164 subjects (25.0%). *Pneumocystis jirovecii* infections were reported in 1 of 41 subjects (2.4%) who received prophylaxis but were not reported in subjects who did not receive prophylaxis.
- Prophylaxis against fungal infections[82)] were administered to 4 of 164 subjects (2.4%). Fungal infections were not reported in subjects who received prophylaxis, but were reported in 4 of 160 subjects (2.5%) who did not receive prophylaxis.

78) MedDRA PTs "chronic hepatitis B," "hepatitis B reactivation," "acute hepatitis B," "hepatitis B surface antigen positive," "hepatitis B DNA assay positive," "hepatitis B DNA increased," and "hepatitis B virus test positive" were included.

79) The following MedDRA PTs were included: "cytomegalovirus infection," "cytomegalovirus infection reactivation," "cytomegalovirus hepatitis," "cytomegalovirus viraemia," "cytomegalovirus test positive," "cytomegalovirus syndrome," "cytomegalovirus gastritis," "cytomegalovirus gastroenteritis," "cytomegalovirus gastrointestinal ulcer," "cytomegalovirus duodenitis," "cytomegalovirus enteritis," "cytomegalovirus gastrointestinal infection," "cytomegalovirus oesophagitis," "cytomegalovirus myocarditis," "cytomegalovirus pericarditis," "cytomegalovirus nephritis," "cytomegalovirus myelomeningoradiculitis," "cytomegalovirus colitis," "cytomegalovirus mononucleosis," "cytomegalovirus enterocolitis," "cytomegalovirus urinary tract infection," "encephalitis cytomegalovirus," "pneumonia cytomegaloviral," "cytomegalovirus mucocutaneous ulcer," "cytomegalovirus chorioretinitis," "cytomegalovirus pancreatitis," and "disseminated cytomegaloviral infection."

80) Preferred terms under MedDRA HLT "tuberculous infections" were included.

81) Preferred terms under MedDRA HLT "pneumocystis infections" were included.

82) Preferred terms under MedDRA HLGT "fungal infectious disorders" were included.

- Prophylaxis against VZV infections[83)] were administered to 61 of 164 subjects (37.2%). Varicella zoster virus infections were reported in 1 of 61 subjects (1.6%) who received prophylaxis, and 2 of 103 subjects (1.9%) who did not receive prophylaxis.
- No JC virus infections[84)] were reported.

PMDA's view:

While there may have been an effect of the primary disease, given that more than one subject in the MSAS of Study 18001 developed serious infections for which a causal relationship to pirtobrutinib could not be ruled out, vigilance for infections is necessary when pirtobrutinib is administered. Therefore, PMDA concluded that information on the incidence of infections in the clinical studies should be provided to healthcare professionals using the package insert in an appropriate manner.

7.R.2.3 Myelosuppression

The applicant's explanation about the incidence of myelosuppression-related events associated with pirtobrutinib treatment:

Preferred terms under MedDRA standardised MedDRA Queries (SMQs) "haematopoietic cytopenias affecting more than one type of blood cell," "haematopoietic erythropenia," "haematopoietic leukopenia," and "haematopoietic thrombocytopenia" (broad scope for all) were included in the analysis.

Table 36 shows the incidence of myelosuppression in the MSAS in Study 18001.

Table 36. Myelosuppression occurring in ≥5% of subjects (Study 18001, MSAS)

PT (MedDRA/J ver.24.0)	n (%) N = 164	
	All Grades	Grade ≥3
Myelosuppression	47 (28.7)	35 (21.3)
Anaemia	21 (12.8)	8 (4.9)
Platelet count decreased	19 (11.6)	9 (5.5)
Neutrophil count decreased	14 (8.5)	14 (8.5)

In the MSAS in Study 18001, serious myelosuppression occurred in 4 subjects (2.4%; febrile neutropenia, anaemia, platelet count decreased, and neutropenic sepsis [1 subject each]), and a causal relationship to pirtobrutinib could not be ruled out for febrile neutropenia in 1 subject. Myelosuppression leading to pirtobrutinib treatment discontinuation occurred in 3 subjects (1.8%; Myelodysplastic syndrome, neutropenia, and neutrophil count decreased [1 subject each]). Myelosuppression leading to pirtobrutinib dose interruption

83) The following MedDRA PTs were included: "herpes zoster," "ophthalmic herpes zoster," "herpes zoster infection neurological," "herpes zoster oticus," "herpes zoster disseminated," "genital herpes zoster," "varicella zoster gastritis," "varicella zoster oesophagitis," "herpes zoster pharyngitis," "herpes zoster meningoencephalitis," "herpes zoster meningomyelitis," "herpes zoster necrotising retinopathy," "varicella zoster pneumonia," "herpes zoster meningitis," "herpes zoster cutaneous disseminated," "varicella zoster sepsis," "varicella zoster virus infection," "disseminated varicella zoster vaccine virus infection," "herpes zoster meningoradiculitis," "herpes zoster reactivation," "herpes zoster immunisation," "disseminated varicella zoster virus infection," "oral herpes zoster," and "varicella zoster viraemia."

84) The following MedDRA PTs were included: MedDRA PTs "JC polyomavirus test positive," "JC virus CSF test positive," "JC virus granule cell neuronopathy," "JC virus infection," "polyomavirus-associated nephropathy," and "progressive multifocal leukoencephalopathy."

occurred in 15 subjects (9.1%). Myelosuppression leading to pirtobrutinib dose reduction occurred in 3 subjects (1.8%). There were no myelosuppression-related deaths.

PMDA's view:
In the MSAS in Study 18001, serious myelosuppression for which a causal relationship to pirtobrutinib could not be ruled out occurred, and Grade ≥3 myelosuppression events have been reported in more than one subject, suggesting that vigilance for myelosuppression is necessary when pirtobrutinib is administered. Therefore, PMDA concluded that information on the incidence of myelosuppression in the clinical studies should be provided to healthcare professionals; in addition, the package insert should include cautionary statements for healthcare professionals to the effect that when pirtobrutinib is administered, hematological parameters should be monitored on a regular basis and that appropriate measures should be taken if any abnormalities are detected.

7.R.2.4 Haemorrhage

The applicant's explanation about the incidence of haemorrhage associated with pirtobrutinib treatment:
From PTs included in the MedDRA SMQ "haemorrhage terms (excl laboratory terms)," superficial contusion PTs were excluded, and remaining PTs were included in the analysis of haemorrhage-related adverse events.

Table 37 shows the incidence of haemorrhage in the MSAS in Study 18001.

Table 37. Haemorrhage occurring in ≥1% of subjects (Study 18001)

PT (MedDRA/J ver.24.0)	n (%) MSAS N = 164	
	All Grades	Grade ≥3
Haemorrhage	25 (15.2)	6 (3.7)
Epistaxis	5 (3.0)	1 (0.6)
Haematuria	2 (1.2)	0
Haematoma	2 (1.2)	0
Conjunctival haemorrhage	2 (1.2)	0
Rectal haemorrhage	2 (1.2)	0
Upper gastrointestinal haemorrhage	2 (1.2)	2 (1.2)

In the MSAS in Study 18001, haemorrhage led to death in 1 subject[85)] (0.6%; haemorrhage), and a causal relationship to pirtobrutinib was ruled out. Serious haemorrhage occurred in 3 subjects (1.8%; upper gastrointestinal haemorrhage, epistaxis, and haemorrhage [1 subject each]), and a causal relationship to pirtobrutinib was ruled out for all these events. Haemorrhage led to pirtobrutinib dose interruption in 6 subjects (3.7%). No haemorrhage led to pirtobrutinib treatment discontinuation or dose reduction.

[85)] The patient with MCL, aged 7[redacted] years, had presented with platelet count decreased (baseline platelet count, 41,000/μL) before the treatment with pirtobrutinib and a medical history of chronic confusion and amnesia. Pirtobrutinib treatment was started at 200 mg QD. The patient fell at home and suffered heavy external bleeding. It is considered that the patient died on Day 56 (the last dose of pirtobrutinib was administered on Day 56). A causal relationship to pirtobrutinib was ruled out.

In the OMTSAS in Study 18001, haemorrhage led to death in 1 subject85) (0.1%; haemorrhage), and a causal relationship to pirtobrutinib was ruled out. Serious haemorrhage occurred in 15 subjects (2.1%; upper gastrointestinal haemorrhage [4 subjects]; haematoma, and post procedural haemorrhage [2 subjects each]; epistaxis, haemarthrosis, haematochezia, haemorrhage, mucosal haemorrhage, subarachnoid haemorrhage, and subdural haemorrhage [1 subject each]). A causal relationship to pirtobrutinib could not be ruled out for upper gastrointestinal haemorrhage, haematoma, and haemarthrosis (1 subject each).

There were no haemorrhage-related deaths and no serious haemorrhage occurred in the J-OMTSAS in Study 18001.

PMDA asked the applicant to explain the relationship between haemorrhage associated with pirtobrutinib treatment and decreased platelets. The applicant's response:
In the OMTSAS in Study 18001, of the 20 patients who suffered serious or Grade ≥3 haemorrhage events, 5 patients also had decreased platelets[86)] at the same time. Based on the results, a decreased platelet count was not always present in patients who suffered haemorrhage; in addition, it has been reported that patients with haematopoietic malignancy have a relatively increased haemorrhagic risk due to comorbid factors (*Haematologica.* 2015;100:1571-8). Therefore, it is difficult to conclusively determine the relationship between haemorrhage associated with pirtobrutinib treatment and decreased platelets.

PMDA's view:
In Study 18001, although haemorrhage was reported in a relatively limited number of subjects in the MSAS, vigilance for haemorrhage is necessary when pirtobrutinib is administered given the following points: haemorrhage occurred in more than one subject in the OMTSAS and MSAS; serious haemorrhage that was not reported in the MSAS was reported in the OMTSAS and a causal relationship to pirtobrutinib could not be ruled out; and haemorrhage is listed as a "Clinically Significant Adverse Reaction" for all other BTK inhibitors approved in Japan.

In addition, although it is difficult to conclusively determine the relationship between haemorrhage associated with pirtobrutinib treatment and decreased platelets based on the currently available data, haemorrhage without decreased platelets occurred in more than one subject in Study 18001, suggesting that there are possibilities that haemorrhage will occur when pirtobrutinib is administered regardless of platelet status. Therefore, PMDA concluded that information on the incidence of haemorrhage in the clinical studies should be provided in the package insert and other materials in an appropriate manner.

Furthermore, given that (1) surgical procedures carry an increased risk of haemorrhage and (2) heavy bleeding associated surgical procedures has been reported with ibrutinib, an approved BTK inhibitor, the applicant should include a cautionary statement in the package insert to the effect that interruption of pirtobrutinib treatment should be considered in patients who undergo surgery or invasive procedures during treatment.

[86)] Defined as all PTs included in the MedDRA SMQ "haematopoietic thrombocytopenia"

7.R.2.5 Arrhythmia

The applicant's explanation about the incidence of arrhythmia associated with pirtobrutinib treatment:
Preferred terms under MedDRA SMQs "arrhythmia related investigations, signs and symptoms (narrow)" and "cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (narrow)" were included in the analysis of arrhythmia-related adverse events.

Table 38 shows the incidence of arrhythmia in the MSAS in Study 18001.

Table 38. Arrhythmia occurring in ≥1% (Study 18001)

PT (MedDRA/J ver.24.0)	n (%) MSAS N = 164	
	All Grades	Grade ≥3
Arrhythmia	14 (8.5)	3 (1.8)
Atrial fibrillation	4 (2.4)	2 (1.2)
Sinus tachycardia	3 (1.8)	0
Sinus bradycardia	2 (1.2)	1 (0.6)
Atrial flutter	3 (1.8)	0

In the MSAS in Study 18001, serious arrhythmia occurred in 2 subjects (1.2%; atrial flutter and sinus bradycardia [1 subject each]), and a causal relationship to pirtobrutinib was ruled out for both events. Arrhythmia led to pirtobrutinib dose interruption in 1 subject (0.6%). There were no arrhythmia-related deaths, pirtobrutinib treatment discontinuation, or dose reduction.

In the OMTSAS in Study 18001, serious arrhythmia occurred in 10 subjects (1.4%; atrial fibrillation [4 subjects]; sinus tachycardia [3 subjects]; atrial flutter, sinus bradycardia, and supraventricular tachycardia [1 subject each]), and a causal relationship to pirtobrutinib could not be ruled out for atrial fibrillation in 2 subjects.[87)] There were no arrhythmia-related deaths.

In the J-OMTSAS in Study 18001, there were no arrhythmia-related deaths, and no serious arrhythmia occurred.

PMDA's view:
Because serious arrhythmia was reported in a relatively limited number of subjects in Study 18001, it is difficult to conclusively determine the relationship between pirtobrutinib treatment and arrhythmia based on the currently available data. However, serious atrial fibrillation for which a causal relationship to pirtobrutinib could not be ruled out occurred; in addition, arrhythmia such as atrial fibrillation and atrial flutter is listed as a "Clinically Significant Adverse Reaction" for other BTK inhibitors approved in Japan. Given the situation above, PMDA concluded that the applicant should provide information on the incidence of arrhythmia in the

[87)] Of the 2 patients, 1 patient was a female aged 7[redacted] years with CLL. On Day 361 (pirtobrutinib 200 mg), during an endoscopy exam, a decrease in heart rate occurred. Therefore, atropine was administered, and after that atrial fibrillation occurred. Diltiazem hydrochloride and apixaban were administered. The next day, atrial fibrillation resolved. The other patient was a female aged 7[redacted] years with CLL. On Day 456 (pirtobrutinib 200 mg), the patient noticed palpitations and was diagnosed as having atrial fibrillation. Metoprolol tartrate and amiodarone hydrochloride were administered. Sinus rhythm was restored in the evening of the same day.

clinical studies using the package insert and other materials; at the same time, the applicant should continue to gather post-marketing information on these events, and if new information becomes available, the applicant should provide such information to health professionals in an appropriate manner.

7.R.2.6 Second primary malignancies

The applicant's explanation about the incidence of second primary malignancies associated with pirtobrutinib treatment:

Preferred terms under MedDRA SMQ "malignant tumours"[88] were included in the analysis of second primary malignancy-related adverse events.

Table 39 shows the incidence of second primary malignancy in the MSAS in Study 18001.

Table 39. Incidence of second primary malignancy (Study 18001)

PT (MedDRA/J ver.24.0)	n (%) MSAS N = 164	
	All Grades	Grade ≥3
Second primary malignancies	6 (3.7)	1 (0.6)
Basal cell carcinoma	3 (1.8)	0
Bowen's disease	1 (0.6)	0
Malignant melanoma	1 (0.6)	0
Anal squamous cell carcinoma	1 (0.6)	0
Transitional cell carcinoma recurrent	1 (0.6)	0
Malignant melanoma in situ	1 (0.6)	0

In the MSAS in Study 18001, serious malignancy occurred in 1 subject (0.6%; transitional cell carcinoma recurrent), and a causal relationship to pirtobrutinib was ruled out. Malignancy led to pirtobrutinib treatment discontinuation in 1 subject (0.6%; anal squamous cell carcinoma). There were no malignancy-related deaths, pirtobrutinib dose interruption, or dose reduction.

In the OMTSAS in Study 18001, serious malignancy occurred in 9 subjects (1.2%; Bowen's disease, breast cancer, chronic lymphocytic leukaemia, malignant melanoma, malignant melanoma in situ, neoplasm malignant,[89] prostate cancer, second primary malignancy,[90] and transitional cell carcinoma recurrent [1 subject each]). Among these, a causal relationship to pirtobrutinib could not be ruled out for second primary malignancy in 1 subject. There were no malignancy-related deaths.

In the J-OMTSAS in Study 18001, serious malignancy occurred in 1 subject (3.4%; lung adenocarcinoma), and a causal relationship to pirtobrutinib was ruled out.

[88] This includes SMQ "haematological malignant tumours" and SMQ "non-haematological malignant tumours."
[89] Squamous cell carcinoma
[90] This was a female patient aged 6[redacted] years with DLBCL. The patient had been treated with multiple antineoplastic regimens and had received autologous peripheral blood stem cell transplantation against DLBCL, and had history of skin neoplasm excision. On Day 309, recurrent and new basal cell carcinoma lesions were noted. A causal relationship to pirtobrutinib could not be ruled out.

In Study 18001, the median time to first onset of malignancy was 35.6 weeks (range, 0.3-94.7) in the OMTSAS and 57.4 weeks (range, 6.4-83.9) in the MSAS.

Table 40 shows the details of patients with MCL who developed second primary malignancies associated with pirtobrutinib treatment in Study 18001.

Table 40. List of patients with MCL who developed second primary malignancies associated with pirtobrutinib treatment (Study 18001)

Age (years)	Sex	Starting dose	PT (MedDRA/J ver.24.0)	Time to event* (days)	Seriousness	Grade	Causal relationship to pirtobrutinib	Pirtobrutinib treatment	Outcome
8[redacted]	F	300 mg	Anal squamous cell carcinoma	587	Non-serious	2	No	Discontinued	Not resolved
8[redacted]	M	200 mg	Malignant melanoma	212	Non-serious	2	No	Continued	Resolving
6[redacted]	M	200 mg	Basal cell carcinoma	561	Non-serious	2	No	Continued	Resolved
5[redacted]	M	200 mg	Transitional cell carcinoma recurrent	45	Serious	3	No	Continued	Resolved
6[redacted]	M	200 mg	Malignant melanoma in situ	Unknown	Non-serious	2	No	Continued	Resolved
			Basal cell carcinoma	313	Non-serious	2	No	Continued	Resolved
			Bowen's disease	337	Non-serious	2	No	Continued	Resolved
7[redacted]	F	200 mg	Basal cell carcinoma	491	Non-serious	1	No	Continued	Resolved

* The start of treatment of pirtobrutinib was defined as Day 1.

PMDA's view:

In Study 18001, (1) there were a very limited number of patients who developed a second primary malignancy for which a causal relationship to pirtobrutinib could not be ruled out, or a serious second primary malignancy; (2) there were no consistent trends in the type and onset time of second primary malignancies; and (3) patients in the study population are in a chronically immunodeficient state due to primary diseases or past therapies, which increases the likelihood of developing second primary malignancies. Therefore, it is difficult to conclusively determine the relationship between pirtobrutinib treatment and second primary malignancies based on the currently available data. However, given that second primary malignancy for which a causal relationship to pirtobrutinib treatment could not be ruled out occurred in Study 18001, information on the incidence of second primary malignancy in the clinical studies should be provided using the package insert and other materials. At the same time, the applicant should continue to gather information on the incidence of such events in the post-marketing settings, and if new information becomes available, the applicant should provide such information to health professionals in an appropriate manner.

7.R.2.7 Other

Among events that are included in the "Clinically Significant Adverse Reaction" section of the package inserts of BTK inhibitors (e.g., ibrutinib), which have similar mechanism of action to that of pirtobrutinib, interstitial

lung disease (ILD), tumor lysis syndrome (TLS), and hepatic dysfunction are listed as "Clinically Significant Adverse Reactions" for more than one BTK inhibitor, while in Study 18001 (OMTSAS), serious adverse events for which a causal relationship to pirtobrutinib could not be ruled out (lymphocytosis and hypersensitivity) occurred. The following subsections outline the applicant's explanation about the incidence of the above-mentioned events.

(1) ILD

The applicant's explanation about the incidence of ILD associated with pirtobrutinib treatment:

Preferred terms under MedDRA SMQs "interstitial lung disease (narrow and broad)" were included in the analysis of ILD-related events.

Table 41 shows the incidence of ILD in the MSAS in Study 18001.

Table 41. Incidence of ILD (Study 18001)

PT (MedDRA/J ver.24.0)	n (%) MSAS N = 164	
	All Grades	Grade ≥3
ILD	3 (1.8)	0
Lung opacity	1 (0.6)	0
Pneumonitis	2 (1.2)	0

In the MSAS in Study 18001, ILD led to pirtobrutinib treatment discontinuation in 1 subject (0.6%; pneumonitis). There were no ILD-related deaths and no serious ILD occurred. No ILD led to pirtobrutinib dose interruption, or dose reduction.

In the OMTSAS in Study 18001, there were no ILD-related deaths and no serious ILD occurred.

(2) Lymphocytosis

The applicant's explanation about the incidence of lymphocytosis associated with pirtobrutinib treatment:

MedDRA PTs "lymphocyte count increased," "lymphocytosis," "leukocytosis," "lymphocyte percentage increased," and "white blood cell count increased" were included in the analysis of lymphocytosis-related adverse events.

Table 42 shows the incidence of lymphocytosis in the MSAS in Study 18001.

Table 42. Incidence of lymphocytosis (Study 18001)

PT (MedDRA/J ver.24.0)	n (%) MSAS N = 164	
	All Grades	Grade ≥3
Lymphocytosis*	10 (6.1)	7 (4.3)
Lymphocyte count increased	4 (2.4)	2 (1.2)
Leukocytosis	6 (3.7)	6 (3.7)
Lymphocytosis	2 (1.2)	1 (0.6)

* The sum of events included in the analysis of lymphocytosis-related adverse events

In the MSAS in Study 18001, serious lymphocytosis occurred in 3 subjects (1.8%; leukocytosis [3 subjects]), and a causal relationship to pirtobrutinib could not be ruled out for leukocytosis in 2 subjects. Lymphocytosis led to pirtobrutinib dose interruption in 3 of 164 subjects (1.8%; leukocytosis [3 subjects]). There were no lymphocytosis-related deaths, pirtobrutinib treatment discontinuation, or dose reduction.

In the OMTSAS in Study 18001, serious lymphocytosis occurred in 6 subjects (0.8%; leukocytosis [6 subjects]), and a causal relationship to pirtobrutinib could not be ruled out for leukocytosis in 3 subjects. There were no lymphocytosis-related deaths.

In the J-OMTSAS in Study 18001, there were no lymphocytosis-related deaths and no serious lymphocytosis occurred.

(3) TLS

The applicant's explanation about the incidence of TLS associated with pirtobrutinib treatment:
MedDRA PT "TLS" was included in the analysis of TLS-related adverse events.

In the MSAS in Study 18001, TLS occurred in 1 subject (0.6%; TLS [Grade 3]). Serious TLS occurred in 1 subject (0.6%; TLS), and a causal relationship to pirtobrutinib was ruled out. Tumor lysis syndrome led to pirtobrutinib dose interruption in 1 subject (0.6%; TLS). There were no TLS-related deaths, pirtobrutinib treatment discontinuation, or dose reduction.

In the OMTSAS in Study 18001, serious TLS occurred in 2 subjects (0.3%; TLS [2 subjects]), and a causal relationship to pirtobrutinib was ruled out for both events. There were no TLS-related deaths.

In the J-OMTSAS in Study 18001, there were no TLS-related deaths and no serious TLS occurred.

(4) Hypersensitivity

The applicant's explanation about the incidence of hypersensitivity associated with pirtobrutinib treatment:
Preferred terms under MedDRA SMQs "hypersensitivity (narrow)," "anaphylactic reaction (narrow)," and "angioedema (narrow)" were included in the analysis for hypersensitivity-related adverse events.

Table 43 shows the incidence of hypersensitivity in the MSAS in Study 18001.

Table 43. Incidence of hypersensitivity occurring in ≥2 subjects (Study 18001)

PT (MedDRA/J ver.24.0)	n (%) MSAS N = 164	
	All Grades	Grade ≥3
Hypersensitivity	23 (14.0)	1 (0.6)
Rash maculo-papular	10 (6.1)	1 (0.6)
Rash	3 (1.8)	0
Urticaria	2 (1.2)	0
Dermatitis acneiform	2 (1.2)	0
Rash pustular	2 (1.2)	0

In the MSAS in Study 18001, serious hypersensitivity occurred in 2 subjects (1.2%; anti-neutrophil cytoplasmic antibody positive vasculitis and contrast media allergy [1 subject each]), and a causal relationship to pirtobrutinib could not be ruled out for anti-neutrophil cytoplasmic antibody positive vasculitis in 1 subject. Hypersensitivity led to pirtobrutinib dose interruption in 3 subjects (1.8%; rash maculo-papular, rash, and urticaria [1 subject each]). Hypersensitivity led to pirtobrutinib dose reduction in 1 subject (0.6%; rash). There were no hypersensitivity-related deaths or pirtobrutinib treatment discontinuation.

In the OMTSAS in Study 18001, hypersensitivity led to death in 1 subject[91)] (0.1%; shock), and a causal relationship to pirtobrutinib was ruled out. Serious hypersensitivity occurred in 4 subjects (0.6%; anti-neutrophil cytoplasmic antibody positive vasculitis, contrast media allergy, dermatitis exfoliative, and shock [1 subject each]), and a causal relationship to pirtobrutinib could not be ruled out for anti-neutrophil cytoplasmic antibody positive vasculitis in 1 subject.

In the J-OMTSAS in Study 18001, serious hypersensitivity occurred in 1 subject (3.4%; anti-neutrophil cytoplasmic antibody positive vasculitis), and a causal relationship to pirtobrutinib was ruled out. There were no hypersensitivity-related deaths.

(5) Hepatic dysfunction

The applicant's explanation about the incidence of hepatic dysfunction associated with pirtobrutinib treatment: Preferred terms under MedDRA SMQs "liver related investigations, signs and symptoms (narrow and broad)," "cholestasis and jaundice of hepatic origin (narrow and broad)," "hepatitis, non-infectious (narrow and broad)," "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow and broad)," and "liver-related coagulation and bleeding disturbances (narrow)" were included in the analysis of hepatic dysfunction.

Table 44 shows the incidence of hepatic dysfunction in the MSAS in Study 18001.

91) The patient, aged 7[redacted] years with CLL, died of shock due to urinary tract infection or urosepsis, and multiple organ dysfunction syndrome. A causal relationship to pirtobrutinib was ruled out.

Table 44. Incidence of hepatic dysfunction occurring in ≥2 subjects (Study 18001)

PT (MedDRA/J ver.24.0)	n (%) MSAS N = 164	
	All Grades	Grade ≥3
Hepatic dysfunction	19 (11.6)	3 (1.8)
AST increased	9 (5.5)	1 (0.6)
ALT increased	8 (4.9)	2 (1.2)
Blood bilirubin increased	4 (2.4)	1 (0.6)
Blood ALP increased	4 (2.4)	0
Hypoalbuminaemia	3 (1.8)	1 (0.6)

In the MSAS in Study 18001, hepatic dysfunction led to pirtobrutinib dose interruption in 3 subjects (1.8%; ALT increased and AST increased [2 subjects each]; ascites [1 subject]). There were no hepatic dysfunction-related deaths and no serious hepatic dysfunction occurred. No hepatic dysfunction led to pirtobrutinib treatment discontinuation or dose reduction.

In the OMTSAS in Study 18001, serious hepatic dysfunction occurred in 2 subjects (0.3%; ascites [2 subjects]), and a causal relationship to pirtobrutinib was ruled out for both events. There were no hepatic dysfunction-related deaths.

PMDA's view:
It is difficult to conclusively determine the risk of developing ILD, TLS, and hepatic dysfunction, given that these events occurred in a limited number of patients in the clinical studies of pirtobrutinib; in addition, the majority of events reported were either non-serious or those for which a causal relationship to pirtobrutinib was ruled out. Therefore, PMDA concluded that the applicant should monitor the incidence of these events in the post-marketing setting, and if new information becomes available, the applicant should provide such information to health professionals in an appropriate manner.

As for lymphocytosis, although serious events for which a causal relationship to pirtobrutinib could not be ruled out occurred in the clinical studies of pirtobrutinib, lymphocytosis is not considered to become a critical problem at this stage given the following points: (1) it is known that lymphocytosis is an on-target effect of BTK inhibitors, and its emergence may indicate the patient's disease state or treatment efficacy; (2) many of the reported events were Grade <3 events; and (3) lymphocytosis cases requiring treatment are not common, and during pirtobrutinib treatment patients are to be monitored in an appropriate manner by conducting blood tests, which include lymphocyte count, on a regular basis. However, PMDA concluded that information on the incidence of such events should be provided to healthcare professionals in an appropriate manner using the package insert and other materials.

Serious hypersensitivity was reported in the clinical studies of pirtobrutinib; however, it is difficult to conclusively determine the risk of developing these events, given the following points: the number of subjects who developed the events was small; in addition, the majority of the events were Grade <3 and non-serious.

Therefore, PMDA concluded that the applicant should monitor the incidence of such events in the post-marketing setting, and if new information becomes available, the applicant should provide such information to health professionals in an appropriate manner.

7.R.3 Clinical positioning and indication

The proposed indication of pirtobrutinib was "relapsed or refractory mantle cell lymphoma in patients who are resistant or intolerant to BTK inhibitors." No "Precautions concerning indication" section was established.

Based on the discussions in the following sections as well as those in Sections "7.R.1 Efficacy" and "7.R.2 Safety," PMDA concluded that the indication of pirtobrutinib should be "relapsed or refractory mantle cell lymphoma in patients who are resistant or intolerant to BTK inhibitors."

7.R.3.1 Clinical positioning of pirtobrutinib

The following are the descriptions of pirtobrutinib treatment in patients with relapsed or refractory MCL in the representative clinical practice guidelines[92)] and standard textbooks[93)] of hematology and clinical oncology published in Japan and other countries.

Clinical practice guidelines

- National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, B-Cell Lymphomas (v.6.2023): pirtobrutinib is a non-covalent BTK inhibitor that inhibits both wild type and C481S mutant BTK, and has been shown to be effective in patients intolerant to or with disease that is refractory to prior covalent BTK inhibitors[94)] without recurrence of prior symptoms. Therefore, pirtobrutinib is recommended as a third-line or subsequent therapy option in the treatment of patients with MCL resistant or intolerant to covalent BTK inhibitors (Category 2A[95)]).

Textbooks

- Cancer: Principles and Practice of Oncology 12th edition (Wolters Kluwer, 2023, USA): non-covalent BTK inhibitors are developed as a treatment that can avoid resistance conferred by C481 mutations, reported with covalent BTK inhibitors. Pirtobrutinib is a representative non-covalent BTK inhibitor, which binds to BTK harboring C481 mutations to inhibit BTK.

The applicant's explanation about the clinical positioning of pirtobrutinib:

Although chemotherapy, anti-CD20 antibody-containing regimens, and autologous stem cell transplantation are selected as first-line therapies for MCL, the recurrence rate is high. After a series of therapies against recurrence, the duration of response and survival becomes shorter (*Blood Cancer J.* 2019;9:50). In the clinical

92) *JSH Guidelines for Tumors of Hematopoietic and Lymphoid Tissues* 2023 [in Japanese] (Japanese Society of Hematology), NCCN Guidelines (v.6.2023), and ESMO clinical practice guidelines for diagnosis, treatment and follow-up (ESMO Guidelines) (*Ann Oncol*. 2017;28 Suppl 4:iv62-71)

93) Textbook of Hematology, revised 4th edition [in Japanese] (2023 Japanese Society of Hematology), Cancer: Principles and Practice of Oncology 12th edition (Wolters Kluwer, 2023, USA)

94) Such as ibrutinib, acalabrutinib (the indication is not approved in Japan), zanubrutinib (not approved in Japan)

95) Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

practice guidelines published in Japan (*JSH Guidelines for Tumors of Hematopoietic and Lymphoid Tissues* 2023, Japanese Society of Hematology), in addition to ibrutinib, a covalent BTK inhibitor, the following therapies are also recommended for the treatment of relapsed or refractory MCL: bendamustine alone, bendamustine plus rituximab, bortezomib alone, bortezomib plus rituximab, and combination chemotherapy (e.g., gemcitabine hydrochloride, dexamethasone, and cisplatin). In Japan, although ibrutinib (BTK inhibitor) can be used as a first-line therapy, there have been reports of poor outcomes in patients who experienced ibrutinib failure (e.g., *Blood.* 2016;127:1559-63). No standard of care has been established for patients with relapsed or refractory MCL who were resistant or intolerant to prior covalent BTK inhibitors. Furthermore, there have been reports that the efficacy of the bendamustine plus rituximab (BR) regimen and bortezomib plus rituximab is limited in patients who experienced ibrutinib failure (e.g., *Ann Oncol.* 2015;26:1175-9, *Hematol Oncol.* 2017;35:528-35, *Adv Ther.* 2022;39:4792-807), indicating a highly limited treatment option for patients with MCL after BTK inhibitor treatment failure.

Nevertheless, Study 18001, although an exploratory one, demonstrated pirtobrutinib's clinical usefulness in patients with MCL treated with a prior covalent BTK inhibitor [see Sections 7.R.1 and 7.R.2]; therefore, pirtobrutinib can be positioned as a treatment option for patients with relapsed or refractory MCL who are resistant or intolerant to BTK inhibitors. although data are,

PMDA accepted the applicant's explanation.

7.R.3.2 Indication and patients eligible for pirtobrutinib treatment

The applicant's explanation about the indication and patients eligible for pirtobrutinib treatment:
In Study 18001, pirtobrutinib was demonstrated to be clinically useful for patients with relapsed or refractory MCL who were resistant or intolerant to BTK inhibitors [see Sections 7.R.1 and 7.R.2]. The details on patients with MCL eligible for pirtobrutinib treatment are discussed below in terms of (1) prior BTK inhibitors, and (2) patient's MCL histology.

(1) Prior BTK inhibitors

In the primary efficacy analysis set (J-PAS) in Study 18001, BTK inhibitors used as prior treatment were ibrutinib (43 subjects), acalabrutinib (23 subjects; the indication is not approved in Japan), zanubrutinib (4 subjects; not approved in Japan), and other BTK inhibitors[96)] (3 subjects) (some subjects received more than one BTK inhibitor). The overall response rate [95% CI] for each BTK inhibitor was 53.5% [47.7%, 74.6%] (ibrutinib), 60.9% [36.6%, 77.9%] (acalabrutinib), 75.0% [19.4%, 99.4%] (zanubrutinib), and 33.3% [0.8%, 90.6%] (other), which were similar to the overall response rate (56.9%) in the overall population. Based on the above, it is unlikely that differences in the BTK inhibitors used in the prior treatment will have an impact on the efficacy of pirtobrutinib.

[96)] Study drugs in development as covalent BTK inhibitors (code names: M7583, TG-1701, or TG-1701-101)

(2) Patient's MCL histology

The primary efficacy analysis set (J-PAS) in Study 18001 consisted of patients with non-blastoid MCL (Cohort 1) but not of patients with blastoid MCL (Cohort 7) [see Section 7.R.1.1]. However, it is considered that patients with blastoid MCL can also be included in eligible patients given the following points:

- Although the number of patients with blastoid MCL enrolled in Cohort 7 in Study 18001 was small, of the 90 subjects in the primary efficacy analysis set used for application for approval in the US and Europe including blastoid MCL treated with prior BTK inhibitors, the overall response rate was 75.0% (6 of 8 subjects) in patients with blastoid MCL.
- The treatment approach for blastoid MCL is not clearly distinguished from that for non-blastoid MCL in the clinical practice guidelines published in Japan and other countries, suggesting that both approaches are similar to each other.

Based on the above, "relapsed or refractory mantle cell lymphoma in patients who are resistant or intolerant to BTK inhibitors" was proposed as the indication of pirtobrutinib.

PMDA accepted the applicant's explanation.

7.R.4 Dosage and administration

The proposed dosage and administration of pirtobrutinib was "The usual adult dosage is 200 mg of pirtobrutinib administered orally once daily. The dose should be reduced according to the patient's condition." The following statements were specified in the "Precautions concerning indication" section.

Precautions Concerning Dosage and Administration

- The efficacy and safety of pirtobrutinib in combination with other antineoplastic agents have not been established.
- Dose modification criteria of pirtobrutinib for adverse reactions

Based on the discussions in the following sections as well as those in Sections "7.R.1 Efficacy" and "7.R.2 Safety," PMDA concluded that the "Precautions concerning dosage and administration" section should be modified as shown below, and the dosage and administration proposed by the applicant should be specified without modification.

Precautions Concerning Dosage and Administration

- The efficacy and safety of pirtobrutinib in combination with other antineoplastic agents have not been established.
- If a Grade* ≥3 adverse reaction occurs, pirtobrutinib should be withheld until recovery to baseline or Grade ≤1. The dose should be modified based on the guidance for dose modification shown below.

*According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

Guidance on dose modification

Occurrence of adverse reaction	Dosage at resumption after recovery
First occurrence	200 mg
Second occurrence	100 mg
Third occurrence	50 mg
Fourth occurrence	Discontinue treatment

7.R.4.1 Dosage and administration of pirtobrutinib

The applicant's explanation about the dosage regimen for pirtobrutinib:

Pirtobrutinib 200 mg orally QD was selected as the dosage regimen for the phase II part of Study 18001 based on the following:

- The results of the phase I part (dose escalation part) of Study 18001, which was conducted in patients with relapsed or refractory MCL and other conditions, showed that pirtobrutinib up to 300 mg QD was tolerable in patients with MCL.
- Within the range evaluated in the phase I part (dose escalation part) of Study 18001 (25-300 mg QD), the BTK inhibition rate was expected to be >90% in almost all patients at pirtobrutinib 200 mg QD. With its promising continuous inhibitory effect, 200 mg QD was selected as the RP2D.

Study 18001 was conducted with the above regimen, and the results demonstrated the clinical usefulness of pirtobrutinib [see Sections 7.R.1 and 7.R.2]; therefore, the proposed regimen was established based on the regimen in the study.

Because there are no clinical data from a clinical study that evaluated the efficacy and safety of pirtobrutinib in combination with other antineoplastic agents, it is considered that use of pirtobrutinib in combination with other antineoplastic agents is not recommended. Therefore, a cautionary statement to the effect that the efficacy and safety of pirtobrutinib in combination with other antineoplastic agents have not been established should be included in the "Precautions concerning dosage and administration" section.

PMDA accepted the applicant's explanation.

7.R.4.2 Dose modifications of pirtobrutinib

The applicant's explanation about the dose modification of pirtobrutinib for adverse reactions:

The Study 18001 protocol specified the criteria for dose interruption/reduction/treatment discontinuation with pirtobrutinib after adverse reactions. Pirtobrutinib was well tolerated when these criteria were followed. In this view, the "Precautions concerning dosage and administration" section provides the dose modification criteria defined based on that in Study 18001 with the following changes.

- The Study 18001 protocol provided conservative criteria that allowed dose interruption/reduction for intolerable Grade 2 adverse reactions when deemed necessary by the investigator. In actual clinical practice, however, the decision on the necessity of dose modification for Grade ≤2 adverse reactions should be made by physicians based on the condition of individual patients. To this end, the dose modification criteria will clearly note that dose interruption/reduction be applied to Grade ≥3 adverse

reactions. Furthermore, the dose interruption/reduction criteria for neutropenia and thrombocytopenia have been set using dose modification criteria for other approved BTK inhibitors as a reference, with the presence or absence of symptoms and duration taken into account.

- The Study 18001 protocol specified that (1) if the adverse event does not recover to baseline or Grade ≤1 in 28 days after onset, permanently discontinue treatment; and (2) patients who have been tolerating a reduced dose for ≥2 weeks after dose reduction are allowed to resume treatment at the dose before reduction. However, the package insert does not include these detailed criteria, as pirtobrutinib is assumed to be used by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.
- In Study 18001, there were no specific criteria for asymptomatic lymphocytosis. However, it is an adverse event common in patients treated with BTK inhibitors that requires no therapeutic intervention. Thus, dose modification is unnecessary for asymptomatic lymphocytosis, and that is clearly noted in the package insert.
- In Study 18001, asymptomatic lipase increased, when considered clinically insignificant, was able to be placed under monitoring without dose interruption. Thus, dose modification is unnecessary for the event, and that is clearly noted in the package insert.

Dose modification criteria

If an adverse reaction* occurs in association with pirtobrutinib treatment, the doses should be interrupted/reduced, or discontinued.

- Grade 3 or 4 non-hematologic toxicities
- Grade 3 neutropenia with fever and/or infection, or Grade 4 neutropenia lasting ≥7 days
- Grade 3 or 4 thrombocytopenia with bleeding

Occurrence of adverse reaction	Action
First occurrence	Withhold doses until recovery to baseline or Grade ≤1. After recovery, resume at the starting dose.
Second occurrence	Withhold doses until recovery to baseline or Grade ≤1. After recovery, resume at 100 mg.
Third occurrence	Withhold doses until recovery to baseline or Grade ≤1. After recovery, resume at 50 mg.
Fourth occurrence	Discontinue treatment.

* Asymptomatic lymphocytosis or asymptomatic lipase increased does not require dose modification.
Severity is graded according to NCI-CTCAE ver.5.0.

PMDA asked the applicant whether the dose was modified in patients who presented with asymptomatic lymphocytosis or asymptomatic lipase increased in Study 18001. The applicant's response:

In the OMTSAS in Study 18001, increased lymphocytes[97)] were reported in 23 subjects; the dose was not modified in 20 of these subjects.[98)] Nine of these 20 subjects with increased lymphocytes did not undergo dose modification and their condition remained unresolved. In the OMTSAS in Study 18001, lipase increased[99)]

97) MedDRA PTs "lymphocyte count increased" and "lymphocytosis" were included in the analysis.
98) Pirtobrutinib dose was increased in 1 subject, while the dose modification status for the other 2 subjects was not known.
99) MedDRA PTs "lipase increased" and "hyperlipasaemia" were included in the analysis.

occurred in 26 subjects; the dose was not modified in 17 of these subjects.[100)] Five of these 17 subjects with lipase increased did not undergo dose modification and their condition remained unresolved. Note that whether each event was symptomatic or asymptomatic could not be determined for lymphocytosis and lipase increased reported in Study 18001.

PMDA's view:

The applicant's explanation was largely acceptable. The following are the views on neutropenia, thrombocytopenia, asymptomatic lymphocytosis, and asymptomatic lipase increased.

- In Study 18001, the presence/absence of symptoms or duration was not clearly specified for neutropenia or thrombocytopenia. It is uncertain whether the proposed description about neutropenia and thrombocytopenia is suitable as dose modification criteria of pirtobrutinib. Thus, the dose modification criteria should be applied to Grade ≥3 neutropenia or thrombocytopenia regardless of the presence or absence of symptoms and duration, as in Study 18001.
- The proposed descriptions about asymptomatic lymphocytosis and asymptomatic lipase increased clearly denies the necessity of dose modification for the events. For the following reasons, however, there is little need for these notes: In the clinical study, whether events were symptomatic or asymptomatic was outside the scope of investigation; in the study, a certain number of patients underwent dose modification, while some others did not and their events remained unresolved. Therefore, it is rather appropriate that the decision on the necessity of dose modification be made by treating physicians according to patient's condition at the onset of these events.

Based on the above, PMDA concluded that the dose modification criteria of pirtobrutinib for adverse reactions should be as follows:

Precaution Concerning Dosage and Administration

- If a Grade* ≥3 adverse reaction occurs, pirtobrutinib doses should be withheld until recovery to baseline or Grade ≤1. The dose should be modified based on the guidance for dose modification shown below.

  *According to NCI-CTCAE v5.0.

Guidance on dose modification

Occurrence of adverse reaction	Dosage at resumption after recovery
First occurrence	200 mg
Second occurrence	100 mg
Third occurrence	50 mg
Fourth occurrence	Discontinue treatment

7.R.5 Post-marketing investigations

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

The applicant plans to conduct post-marketing surveillance plan to investigate the safety and other aspects of pirtobrutinib in clinical use after the market launch, covering all patients treated with pirtobrutinib.

[100)] Pirtobrutinib doses were reduced or interrupted in 8 subjects, while the dose modification status for the 1 remaining subject was not known.

Based on the incidence and other aspects of adverse events in Study 18001, adverse events of special interest when pirtobrutinib is administered, namely, serious infections, serious haemorrhage, atrial fibrillation, atrial flutter, and second primary malignancies were included in the safety specification for the surveillance.

A planned sample size of 85 patients and an observation period of 52 weeks were selected taking into account the incidence in Study 18001 of the above events included in the safety specification for the surveillance.

PMDA's view:
Because only limited safety data on Japanese patients treated with pirtobrutinib are available, PMDA concluded that post-marketing surveillance should be conducted to collect safety data for pirtobrutinib in clinical use. However, there is no marked difference between the safety data of pirtobrutinib and those of other BTK inhibitors ever used in Japan, or no new safety-related concerns have been identified. Therefore, there is little need for all-case post-marketing surveillance.

Based on the discussion in Section "7.R.2 Safety," the safety specification for the post-marketing surveillance should include arrhythmia and second primary malignancies.

PMDA also concluded that the planned sample size and observation period should be reconsidered after examining the incidence of the above-mentioned adverse events that are to be included in the surveillance.

7.3 Adverse events and other findings reported in clinical studies

Cases of death reported in clinical studies submitted as the safety evaluation data are presented in Sections "7.1 Evaluation data" and "7.2 Reference data." Other main adverse events are summarized below. Descriptions of adverse events that did not occur are omitted.

7.3.1 Global phase I/II study (Study 18001)

7.3.1.1 Phase I part

Adverse events occurred in 194 of 198 subjects (98.0%), and adverse events for which a causal relationship to pirtobrutinib could not be ruled out occurred in 140 of 198 subjects (70.7%). Adverse events occurring in ≥20% of subjects were fatigue (83 subjects, 41.9%), diarrhoea (53 subjects, 26.8%), contusion (47 subjects, 23.7%), and cough (44 subjects, 22.2%).

Serious adverse events occurred in 79 of 198 subjects (39.9%). Serious adverse events occurring in ≥2% of subjects were pneumonia (13 subjects, 6.6%), COVID-19 pneumonia (8 subjects, 4.0%), leukocytosis (5 subjects, 2.5%), urinary tract infection (5 subjects, 2.5%), febrile neutropenia (4 subjects, 2.0%), sepsis (4 subjects, 2.0%), and COVID-19 (4 subjects, 2.0%). A causal relationship to pirtobrutinib could not be ruled out for pneumonia (4 subjects), febrile neutropenia (3 subjects), and leukocytosis (3 subjects).

Adverse events led to pirtobrutinib treatment discontinuation in 13 of 198 subjects (6.6%). Adverse events leading to pirtobrutinib treatment discontinuation that occurred in ≥2 subjects were COVID-19 (2 subjects, 1.0%), and a causal relationship to pirtobrutinib was ruled out.

7.3.1.2 Phase II part

Adverse events occurred in 487 of 527 subjects (92.4%), and adverse events for which a causal relationship to pirtobrutinib could not be ruled out occurred in 283 of 527 subjects (53.7%). Adverse events occurring in ≥15% of subjects were diarrhoea (107 subjects, 20.3%), fatigue (108 subjects, 20.5%), and contusion (91 subjects, 17.3%).

Serious adverse events occurred in 176 of 527 subjects (33.4%). Serious adverse events occurring in ≥2% of subjects were pneumonia (21 subjects, 4.0%), COVID-19 pneumonia (20 subjects, 3.8%), and COVID-19 (13 subjects, 2.5%). Among these events, a causal relationship to pirtobrutinib could not be ruled out for pneumonia (4 subjects) and COVID-19 pneumonia (2 subjects).

Adverse events led to pirtobrutinib treatment discontinuation in 32 of 527 subjects (6.1%). Adverse events leading to pirtobrutinib treatment discontinuation that occurred in ≥2 subjects were myelodysplastic syndrome and sepsis (2 subjects each, 0.4%), and a causal relationship to pirtobrutinib was ruled out for these 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 investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

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

The investigation is currently underway. The results and conclusion by PMDA will be reported in Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that pirtobrutinib has a certain level of efficacy in the treatment of relapsed or refractory MCL in patients who are resistant or intolerant to BTK inhibitors, and that pirtobrutinib has acceptable safety in view of its benefits. Pirtobrutinib is a drug with a new active ingredient that binds to an active site of BTK non-covalently and inhibits BTK harboring resistance mutations that are known to confer resistance to existing BTK inhibitors. Pirtobrutinib is clinically meaningful as a new treatment option for relapsed or refractory MCL in patients resistant or intolerant to BTK inhibitors. Details of efficacy and post-marketing investigations are subject to further discussion.

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

Review Report (2)

April 12, 2024

Product Submitted for Approval

Brand Name	Jaypirca Tablets 50 mg Jaypirca Tablets 100 mg
Non-proprietary Name	Pirtobrutinib
Applicant	Eli Lilly Japan K.K.
Date of Application	June 30, 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 global phase I/II study in patients with relapsed or refractory B cell malignancy (Study 18001), the primary endpoint, the centrally-assessed overall response rate according to the Lugano criteria [95% CI] was 56.9% [44.0%, 69.2%] (37 of 65 subjects) in patients with relapsed or refractory MCL who were resistant or intolerant to BTK inhibitors, the primary efficacy analysis set (J-PAS). In view of the discussion in Section "7.R.1 Efficacy" in Review Report (1), these results have demonstrated pirtobrutinib's certain level of efficacy in patients with relapsed or refractory MCL who are resistant or intolerant to BTK inhibitors.

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

1.2 Safety

In view of the discussions in Section "7.R.2 Safety" in Review Report (1), PMDA concluded that adverse events of special interest in patients treated with pirtobrutinib are infection, myelosuppression, and hemorrhage.

Although the treatment with pirtobrutinib warrants vigilance for the above-mentioned adverse events, PMDA considers that pirtobrutinib is tolerable when appropriate measures including adverse event monitoring and management, dose interruption and reduction, etc. are taken by physicians with adequate knowledge and experience in the treatment of hematopoietic malignancies.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion.

1.3 Clinical positioning and indication

Based on the discussion in Section "7.R.3 Clinical positioning and indication" of Review Report (1), PMDA concluded that the indication of pirtobrutinib should be "relapsed or refractory mantle cell lymphoma in patients who are resistant or intolerant to BTK inhibitors."

At the Expert Discussion, the expert advisors supported the PMDA's conclusion above. The expert advisors also made the following comments.

- Patients with blastoid MCL were not included in the primary efficacy analysis set (J-PAS) in Study 18001. Healthcare professionals should be informed of the results of not only the J-PAS but also of the efficacy in patients with blastoid MCL in the study.
- In the description of the indication, "other BTK inhibitors" is more appropriate instead of "BTK inhibitors" to make clear that it is referring to BTK inhibitors other than pirtobrutinib.

PMDA's view:

In view of the discussions at the Expert Discussion, PMDA concluded that the efficacy results of pirtobrutinib in patients with blastoid MCL in Study 18001[101)] should be made available for healthcare professionals via the package insert's "Clinical Studies" section. The indication of pirtobrutinib should be "relapsed or refractory mantle cell lymphoma in patients who are resistant or intolerant to other BTK inhibitors."

Accordingly, PMDA instructed the applicant to take appropriate actions for the issues above, and the applicant agreed with the instruction.

1.4 Dosage and administration

In view of the discussions in Section "7.R.4 Dosage and administration" in Review Report (1), PMDA concluded that the dosage and administration of pirtobrutinib should be the defined as per the proposal, i.e., "The usual adult dosage is 200 mg of pirtobrutinib administered orally once daily. The dose should be reduced according to the patient's condition." At the same time, the "Precautions concerning dosage and administration" section should provide the following advice.

Precautions Concerning Dosage and Administration

- The efficacy and safety of pirtobrutinib have not been established in combination with other antineoplastic agents.
- If a Grade* ≥3 adverse reaction occurs, pirtobrutinib should be withheld until recovery to baseline or Grade ≤1. The dose should be modified based on the guidance for dose modification shown below.

  *According to the NCI-CTCAE v5.0.

[101)] In the MSAS in Study 18001, the overall response rate in patients (N = 15) with blastoid MCL treated with prior BTK inhibitors [95% CI] was 46.7% [21.3%, 73.4%] (7 of 15 patients).

Guidance on dose modification

Occurrence of adverse reaction	Dosage at resumption after recovery
First occurrence	200 mg
Second occurrence	100 mg
Third occurrence	50 mg
Fourth occurrence	Discontinue treatment

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

Based on the above, PMDA instructed the applicant to describe the "Precautions concerning dosage and administration" section as above. The applicant agreed with the instruction, with minor modification.

1.5 Risk management plan (draft)

The applicant has planned post-marketing surveillance to investigate the safety, etc. of pirtobrutinib used in the clinical setting, covering all patients treated with pirtobrutinib, with a planned sample size of 85 patients and an observation period of 52 weeks.

Based on the discussions in Section "7.R.5 Post-marketing investigations" in Review Report (1), PMDA has concluded that post-marketing surveillance needs to be conducted to collect safety data of pirtobrutinib from the clinical setting, in view of limited safety data available from Japanese patients treated with pirtobrutinib. Nevertheless, pirtobrutinib has already yielded safety data with no marked difference from other BTK inhibitors ever used in Japan, indicating no obvious new safety-associated concerns. Therefore, there is little need for all-case post-marketing surveillance.

PMDA's conclusion on the surveillance plan:

- The safety specification should include arrhythmia and second primary malignancies.
- The planned sample size and observation period should be reconsidered in view of the occurrence of events included in the safety specification.

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

Based on the above discussion, PMDA instructed the applicant to refine the post-marketing surveillance plan. The applicant's response:

- Arrhythmia and second primary malignancies will be added in the safety specification for the surveillance.
- The sample size of 45 patients and an observation period of 52 weeks will be set, based on the occurrence of the adverse events in the clinical study that are included in the surveillance, etc.

PMDA accepted the applicant's response.

Based on the above discussions, PMDA concluded that the risk management plan (draft) for pirtobrutinib should include the safety specification presented in Table 45, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 46 and Table **47**.

Table 45. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infections • Myelosuppression • Hemorrhage	• Arrhythmia • Second primary malignancies	None
Efficacy specification		
None		

Table 46. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey	None	• Disseminate data gathered during early post-marketing phase vigilance

Table 47. Outline of use-results survey (draft)

Objective	To investigate the clinical safety of pirtobrutinib in post-marketing use
Survey method	Central registration system
Population	Patients with relapsed or refractory MCL who are resistant or intolerant to other BTK inhibitors
Observation period	52 weeks
Planned sample size	45 patients
Main survey items	Safety specification: arrhythmia, second primary malignancies Other main survey items: patient characteristics (e.g., age, sex, medical history, comorbidities), prior therapy, pirtobrutinib treatment status, concomitant drugs, adverse events

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

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

The new drug application data were subjected to a document-based 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.

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

The new drug application data (CTD 5.3.5.2.3) 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. The inspection confirmed that the study was generally conducted in compliance with GCP, and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following error at the clinical trial sponsor (In-Country Clinical Caretaker). Although it did not affect overall assessment of the study significantly, the sponsor (In-Country Clinical Caretaker) was notified of the matter and asked for a corrective actions.

Finding requiring corrective action

Clinical trial sponsor (In-Country Clinical Caretaker)

- Inadequacy in the contract on partial outsourcing of work related to sponsoring and management of the clinical trial

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the modified proposed indication and dosage and administration shown below with the following approval conditions, presuming that necessary cautions are given via the package insert, information about the product's proper use is disseminated appropriately in the post-marketing setting, and pirtobrutinib is properly used under the supervision of a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies and at medical institutions adequately capable of emergency care. Because the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as s a biological product or a specified biological product. Both the drug product and its drug substance are classified as powerful drugs.

Indication

Relapsed or refractory mantle cell lymphoma in patients who are resistant or intolerant to other BTK inhibitors

Dosage and Administration

The usual adult dosage is 200 mg of pirtobrutinib administered orally once daily. The dose should be reduced according to the patient's condition.

Approval Conditions

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

Warning

Pirtobrutinib should only be administered to patients who are deemed eligible for its use, under the supervision of a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies, and at medical institutions adequately capable of emergency care. Prior to the treatment, its benefits and risks should be thoroughly explained to the patient or his/her family and consent must be obtained.

Contraindication

Patients with a history of serious hypersensitivity to any ingredient of pirtobrutinib

Precautions Concerning Dosage and Administration

1. The efficacy and safety of pirtobrutinib in combination with other antineoplastic agents have not been established.
2. If a Grade* ≥3 adverse reaction occurs, pirtobrutinib doses should be withheld until recovery to baseline or Grade ≤1. The dose should be modified based on the guidance for dose modification shown below.

* According to the NCI-CTCAE ver.5.0.

Guidance on dose modification

Occurrence of adverse reaction	Dosage at resumption after recovery
First occurrence	200 mg
Second occurrence	100 mg
Third occurrence	50 mg
Fourth occurrence	Discontinue treatment

Appendix

List of Abbreviations

A/G ratio	albumin/globulin ratio
ABC-DLBCL	activated B cell subtype diffuse large B-cell lymphoma
ALP	alkaline phosphatase
ALT	alanine aminotransferase
application	application for marketing approval
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BA	bioavailability
BCR	B cell receptor
BCRP	breast cancer resistance protein
bendamustine	bendamustine hydrochloride
BID	bis in die
B-PLL	B-cell prolymphocytic leukemia
BR	bendamustine plus rituximab
BRET	bioluminescence resonance energy transfer
BRK	breast tumor kinase
BSEP	bile salt export pump
BTK	Bruton's tyrosine kinase
BTK C481 mutation	BTK in which cysteine is substituted by an amino acid at codon 481
CARD11	caspase recruitment domain family member 11
cDNA	complementary DNA
CI	confidence interval
CITCO	6-(4-chlorophenyl)imidazo[2,1-b][1,3]thiazole-5-carbaldehyde O-(3,4-dichlorobenzyl)oxim
CL/F	apparent oral clearance
CLL	chronic lymphocytic leukemia
CLL/SLL	chronic lymphocytic leukemia/small lymphocytic lymphoma
CMV	cytomegalovirus
CNS	central nervous system
COVID-19	corona virus infectious disease emerged in 2019
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CSF	cerebrospinal
CSK	C-terminal Src kinase
CYP	cytochrome P450
^{14}C-labeled pirtobrutinib	carbon-14 radiolabeled pirtobrutinib
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
ECL	electrochemiluminescence
efflux ratio	the ratio of permeability coefficient in the excretion direction to that in the absorption direction
eGFR	estimated glomerular filtration rate
ESMO Guidelines	ESMO clinical practice guidelines for diagnosis, treatment and follow-up
F	relative bioavailability
FISH	fluorescence *in situ* hybridization
FL	follicular lymphoma

FYN	tyrosine-protein kinase Fyn
GC	gas chromatography
HBV	hepatitis B virus
HCL	hairy cell leukemia
HER	human epidermal growth factor receptor
HPMC	hydroxypropyl methylcellulose
HTRF	homogeneous time-resolved fluorescence
ICH Q1E guidelines	“Guidelines on Evaluation of Stability Data” (PFSB/ELD Notification No. 0603004, dated June 3, 2003)
ICH Q3A guidelines	“Partial Revision of ‘Revision of Guidelines on Impurities in New Drug Substances’” (PFSB/ELD Notification No. 1204001, dated December 4, 2006)
ICH Q3B guidelines	“Revision of Guidelines on Impurities in New Drug Products” (PFSB/ELD Notification No. 0624001, dated June 24, 2003)
ILD	interstitial lung disease
IR	infrared absorption spectroscopy
ka	absorption rate constant
K_D	dissociation constant
LC	liquid chromatography
LC-MS/MS	liquid chromatography/tandem mass spectrometry
LPL	lymphoplasmacytic lymphoma
MATE	multidrug and toxin extrusion
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities ICH
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MEK	mitogen-activated protein kinase/extracellular signal-regulated kinase kinase
MPE	mean photo effect
mRNA	messenger ribonucleic acid
MS	mass spectrometry
MZL	marginal zone lymphoma
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN	National Comprehensive Cancer Network
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, B-Cell Lymphomas
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NE	not evaluated
NHL	non-Hodgkin lymphoma
NMR	nuclear magnetic resonance spectroscopy
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basal direction
PAR	proven acceptable range
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based pharmacokinetic
PCNSL	primary central nervous system lymphoma
PD	progressive disease
P-gp	P-glycoprotein
pirtobrutinib	pirtobrutinib
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency

PPK	population pharmacokinetics
PR	partial response
PT	preferred term
PTP	press through packaging
Q/F	apparent inter-compartmental clearance of pirtobrutinib
QD	quaque die
QT	QT interval
QTc	QT interval corrected
QTcF	QT interval corrected using Fridericia's formula
ΔΔQTcF	Difference versus placebo in change from baseline in QTcF
rituximab	rituximab (genetical recombination)
RP2D	recommended phase 2 dose
SCID mouse	severe combined immunodeficiency mouse
SD	stable disease
SLL	small lymphocytic lymphoma
SMQ	standardised MedDRA Queries
SOC	system organ class
Study 18001	Study LOXO-BTK-18001
Study 20006	Study LOXO-BTK-20006
Study 20007	Study LOXO-BTK-20007
Study 20008	Study LOXO-BTK-20008
Study 20009	Study LOXO-BTK-20009
Study 20010	Study LOXO-BTK-20010
Study 20011	Study LOXO-BTK-20011
Study 20012	Study LOXO-BTK-20012
Study 20013	Study LOXO-BTK-20013
Study 20014	Study LOXO-BTK-20014
Study 20016	Study LOXO-BTK-20016
Study 20017	Study LOXO-BTK-20017
Study 20021	Study LOXO-BTK-20021
Study 21050	Study LOXO-BTK-21050
Study JZNW	Study J2N-MC-JZNW
TDAR	T-cell dependent antibody response
TEC	tec protein tyrosine kinase
TLS	tumor lysis syndrome
TXK	tyrosine protein kinase
UDPGA	uridine diphosphate glucuronic acid
UGT	uridine diphosphate glucuronosyl transferase
UV-VIS	ultraviolet-visible spectroscopy
V_c/F	apparent volume of distribution of central compartment
V_p/F	apparent volume of distribution of peripheral compartment
VZV	varicella zoster virus
WM	Waldenström's macroglobulinaemia
YES	Yamaguchi sarcoma viral oncogene homolog