Report on the Deliberation Results

March 3, 2020
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Velexbru Tablets 80 mg
Non-proprietary Name	Tirabrutinib Hydrochloride (JAN*)
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	August 28, 2019

Results of Deliberation

In its meeting held on February 26, 2020, 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 10 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Conditions

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

2. Because of extremely limited number of cases in Japanese clinical studies, the applicant is required to conduct a drug use-results survey involving all patients treated with the product after its market launch until obtaining data from a certain number of patients, in order to identify the characteristics of patients using the product and to promptly collect safety and efficacy data so that necessary measures are taken for the proper use of the product.

**Japanese Accepted Name (modified INN)*

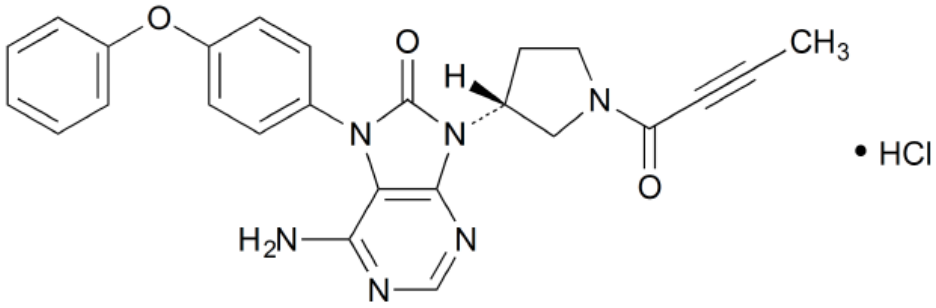
Review Report

February 6, 2020
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	Velexbru Tablets 80 mg
Non-proprietary Name	Tirabrutinib Hydrochloride
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	August 28, 2019
Dosage Form/Strength	Tablets, each containing 86.42 mg of Tirabrutinib Hydrochloride (80 mg of Tirabrutinib)
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{25}H_{22}N_6O_3$•HCl

Molecular weight: 490.94

Chemical name: 6-Amino-9-[(3*R*)-1-(but-2-ynoyl)pyrrolidin-3-yl]-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one monohydrochloride

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 441 of 2019 [*31 yaku*], PSEHB/PED Notification No. 0820-3 dated August 20, 2019, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with recurrent or refractory primary central nervous system lymphoma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Infection, severe skin disorder, bone marrow depression, hypersensitivity, interstitial lung disease, hepatic dysfunction, and hemorrhage are subject to further investigation through post-marketing surveillance.

Indication

Recurrent or refractory primary central nervous system lymphoma

Dosage and Administration

The usual adult dosage is 480 mg of tirabrutinib administered orally once daily under fasting conditions. The dose may be reduced according to the patient's condition.

Approval Conditions

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

2. Because of extremely limited number of cases in Japanese clinical studies, the applicant is required to conduct a drug use-results survey involving all patients treated with the product after its market launch until obtaining data from a certain number of patients, in order to identify the characteristics of patients using the product and to promptly collect safety and efficacy data so that necessary measures are taken for the proper use of the product.

Attachment

Review Report (1)

December 25, 2019

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

Product Submitted for Approval

Brand Name	Velexbru Tablets 80 mg
Non-proprietary Name	Tirabrutinib Hydrochloride
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	August 28, 2019
Dosage Form/Strength	Tablets, each containing 86.42 mg of Tirabrutinib Hydrochloride (80 mg of Tirabrutinib)
Proposed Indication	Recurrent or refractory primary central nervous system lymphoma

Proposed Dosage and Administration

The usual adult dosage is 480 mg of tirabrutinib administered orally once daily under fasting conditions. The dose may be reduced according to the patient's condition.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

Tirabrutinib hydrochloride (hereinafter referred to as tirabrutinib) is a low molecular weight compound discovered by the applicant, with an inhibitory effect on Bruton's tyrosine kinase (BTK). Tirabrutinib binds to BTK, a downstream signal transduction molecule of B cell receptor (BCR) expressed in B cells, and is thought to inhibit B-cell tumor growth.

1.2 Development history etc.

A foreign Phase I study (Study ONO-4059POE001 [Study POE001]) in patients with recurrent or refractory B-cell non-Hodgkin lymphoma (B-NHL) or chronic lymphocytic leukemia (CLL) was started by the applicant from August 2012.

As of November 2019, tirabrutinib has not been approved in any country or region.

In Japan, a Phase I study (Study ONO-4059-01 [Study 01]) in patients with recurrent or refractory B-NHL or CLL and a Phase I/II study (Study ONO-4059-02 [Study 02]) in patients with recurrent or refractory primary central nervous system lymphoma (PCNSL) were started from January 2015 and October 2017, respectively.

Recently, an approval application for tirabrutinib has been submitted with the results of Study 02 as the pivotal data.

Tirabrutinib was designated as an orphan drug with the intended indication of "primary central nervous system lymphoma" in August 2019 (Orphan Drug Designation No. 441 of 2019 [*31 yaku*]).

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white to slightly yellowish or slightly brownish powder. The general properties of the drug substance including description, dissociation constant, solubility, hygroscopicity, melting point, and optical rotation were determined.

The chemical structure of the drug substance was elucidated by elemental analysis, infrared absorption spectrum (IR), nuclear magnetic resonance spectrum (NMR) (^{1}H-NMR and ^{13}C-NMR), mass spectrometry, and ultraviolet and visible spectrophotometry. The drug substance contains an asymmetric carbon, but it is manufactured in a single conformation.

2.1.2 Manufacturing process

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

1) [redacted]
2) [redacted]

The quality control strategy was developed by the following investigations, etc., in a quality-by-design (QbD) approach (Table 1):

- Identification of critical quality attributes (CQAs)
- Identification of critical process parameters (CPPs) and investigation of the acceptable range of manufacturing process parameters, based on the results of quality risk assessment and design of experiments.

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

CQA	Controlling method
Content	Specifications
Description	Manufacturing process, specifications
Identification	Manufacturing process, specifications
Related substances	Manufacturing process, specifications
Enantiomer	Manufacturing process, specifications
Residual solvents	Manufacturing process, specifications
[redacted]	Manufacturing process, specifications
[redacted]	Manufacturing process

The process of [redacted] was defined as the critical step. In-process control parameters and control values are defined for the processes of [redacted][3], [redacted], [redacted][4], [redacted], [redacted][5], [redacted], and [redacted]. [redacted][5] and [redacted] are controlled as critical intermediates.

2.1.3 Control of drug substance

The proposed specification for the drug substance include content, description, identification (IR), purity (related substances [liquid chromatography (LC)], enantiomer [LC], residual solvents [gas chromatography]), [redacted], and assay (LC).

2.1.4 Stability of drug substance

Table 2 shows main stability studies conducted on the drug substance. Photostability testing showed that the drug substance is photostable.

Table 2. Stability studies of drug substance

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 commercial-scale batches	30°C	65% RH	Low-density polyethylene bag (double-layered) + fiber drum	24 months
Accelerated testing		40°C	75% RH		6 months

Based on the above, a retest period of 36 months was proposed for the drug substance when stored at room temperature in a double-layered low-density polyethylene bag and placed in a fiber drum, in accordance with ICH Q1E Guideline. The long-term testing will be continued up to [redacted] months.

3) [redacted]

4) [redacted]

5) [redacted]

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, each containing 86.42 mg of the drug substance (80 mg of tirabrutinib). The drug product contains, as excipients, crystalline cellulose, lactose hydrate, crospovidone, light anhydrous silicic acid, magnesium stearate, partially hydrolized polyvinyl alcohol, titanium oxide, macrogol 4000, talc, and yellow ferric oxide.

2.2.2 Manufacturing process

The drug product is manufactured through the process comprising [redacted], [redacted], [redacted], [redacted] mixing, tableting, [redacted], film-coating, and packaging/labeling steps.

The quality control strategy was developed by the following investigations, etc. in a QbD approach (Table 3):

- Identification of CQAs
- Identification of CPPs and material attributes that might affect the CQAs of the drug product and investigation of the acceptable range of manufacturing process parameters, based on the quality risk assessment

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

CQA	Controlling method
Content	Manufacturing process, specifications
Description	Manufacturing process, specifications
Related substances	Specifications
Uniformity of dosage unit	Specifications
Dissolution	Specifications
[redacted]	Manufacturing process
[redacted]	Manufacturing process

[redacted] is the critical step. In-process control parameters and control values are defined for the [redacted] and [redacted] steps.

2.2.3 Control of drug product

The proposed specification for the drug product include content, description, identification (ultraviolet spectrum and LC), purity (related substances [LC]), uniformity of dosage units (content uniformity [LC]), dissolution (LC), and assay (LC).

2.2.4 Stability of drug product

Table 4 shows main stability studies conducted on the drug product. Photostability testing showed that the drug product is photostable.

Table 4. Stability studies of drug product

Study	Primary batch	Temperature	Humidity	Storage form	Storage period
Long-term testing	3 commercial-scale batches	25°C	60% RH	Blister pack (and aluminum) + moisture-proof aluminum-laminated film	18 months
Accelerated testing		40°C	75% RH		6 months

Based on the above, a shelf-life of 30 months was proposed for the drug product when stored at room temperature packaged in the blister pack (and aluminum) and moisture-proof aluminum-laminated films, in accordance with the ICH Q1E Guideline. The long-term testing will be continued up to 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 the drug product is controlled in an appropriate manner.

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

In this section, the dose and concentration of tirabrutinib are expressed in terms of free base.

3.1 Primary pharmacodynamics

3.1.1 Inhibition of phosphorylation of kinases (CTD 4.2.1.1-1, 4.2.1.1-2, and 4.2.1.1-4)

The inhibitory effect of tirabrutinib against the phosphorylation of human BTK, FYN, lymphocyte-specific protein tyrosine kinase (LCK), and LYNa (recombinant proteins) was investigated by gel mobility shift assay. IC_{50} (n = 1) of tirabrutinib against phosphorylation of BTK, FYN, LCK, and LYNa was 2.10, 2,220, 788, and 3,490 nmol/L, respectively.

The inhibitory effect of tirabrutinib against phosphorylation of kinases (recombinant protein) was investigated by fluorescence resonance energy transfer (FRET) assay. Table 5 shows IC_{50} of tirabrutinib.

Table 5. Inhibitory effect of tirabrutinib against phosphorylation of kinases

Kinase	n	IC_{50} (nmol/L)
BTK	3	3.4 ± 0.8
BLK	2	127
BMX	3	3.2 ± 0.9
EGFR	3	2,150 ± 127
HER2	3	8,730 ± 3,493
HER4	3	318 ± 65
ITK	3	>20,000
JAK3	3	5,515 ± 2,425
TXK	3	46.9 ± 8.7
TEC	3	29.6 ± 4.7

Mean ± standard deviation (SD)

Using human peripheral blood mononuclear cells (PBMCs) and human diffuse large B cell lymphoma (DLBCL)-derived TMD8 cell line, the inhibitory effect of tirabrutinib against BTK phosphorylation was investigated by flow cytometry. Tirabrutinib inhibited the phosphorylation[6)] of BTK in B cells among

6) Phosphorylation inhibition rate = {[1 – "mean fluorescence intensity in each tirabrutinib concentration group" / "mean fluorescence intensity in vehicle (0.1% dimethyl sulfoxide [DMSO] group") × 100

PBMCs and in TMD8 cell line by 66.6% [64.2%, 69.0% (95% confidence interval [CI])] and 81.3% [77.2%, 85.4%], respectively.

3.1.2 Apoptosis induction (CTD 4.2.1.1-4)

TMD8 cell line was incubated with tirabrutinib (1-10,000 nmol/L) for 1, 6, 24, 48, and 72 hours, and the apoptosis-inducing effect of tirabrutinib was investigated by flow cytometry based on 7-amino actinomycin D (7-AAD) staining. Tirabrutinib concentration-dependent apoptosis was observed in cells treated for ≥48 hours.

3.1.3 Inhibitory effect against B and T cell activation (CTD 4.2.1.1-5)

Using human PBMCs, the inhibitory effect of tirabrutinib (0.3-10,000 nmol/L) against (a) B cells activated by anti-immunoglobulin (Ig)M antibody and (b) T cells activated by anti-CD3 and anti-CD28 antibodies was investigated by flow cytometry based on the expression of CD69, a surface antigen of activated B and T cells. Tirabrutinib inhibited B cell activation with IC_{50} [95% CI] of 13.8 [7.00, 27.0] nmol/L, but did not inhibit T cell activation.

3.1.4 Growth inhibitory effect against human DLBCL-derived cell line

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

The growth-inhibitory effect of tirabrutinib against TMD8 cell line was investigated based on adenosine triphosphate (ATP) content in viable cells. IC_{50} [95% CI] of tirabrutinib was 3.59 [2.24, 5.74] nmol/L.

The growth-inhibitory effect of tirabrutinib against TMD8 cell line and human DLBCL-derived OCI-LY10, Ri-1, and Pfeiffer cell lines was investigated based on ATP content in viable cells. Table 6 shows EC_{50} of tirabrutinib.

Table 6. Growth-inhibitory effect of tirabrutinib against human DLBCL-derived cell lines

Cell line	DLBCL type	n	EC_{50} (nmol/L)
TMD8	ABC-DLBCL	8	4.30 ± 2.80
OCI-LY10		6	13.0 ± 210
Ri-1		12	26 ± 110
Pfeiffer	GCB-DLBCL	10	9,100 ± 1,600

Mean ± SD

3.1.4.2 *In vivo* (CTD 4.2.1.1-9)

Using severe combined immunodeficient (SCID) mice (n = 10/group) subcutaneously transplanted with TMD8 cell line, the tumor growth inhibitory effect of tirabrutinib was investigated. Starting from the day when tumor volume reached 102.6 to 103.3 mm^3 (Day 0), tirabrutinib 1, 3, or 10 mg/kg was administered orally once on Day 0 and BID on Days 1 through 20, and tumor volume was calculated. On Day 21, a statistically significant tumor growth inhibitory effect was observed in the tirabrutinib 10 mg/kg group as compared with the control (0.5% methylcellulose 400 solution) group (Figure 1).

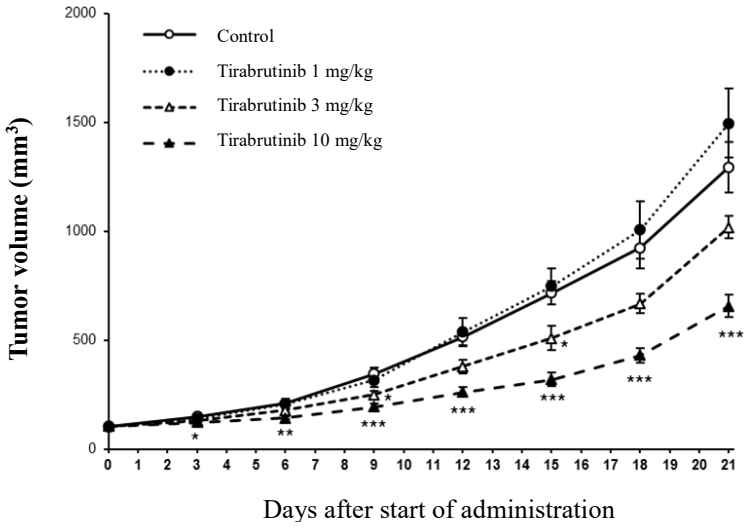


Figure 1. Tumor growth inhibitory effect of tirabrutinib in SCID mice subcutaneously transplanted with TMD8 cell line

n = 10, mean ± SD, * $P < 0.05$; ** $P < 0.01$; and *** $P < 0.001$ against the control group (Dunnett test)

3.2 Secondary pharmacodynamics

3.2.1 Effect on receptors, ion channels, transporters, etc. (CTD 4.2.1.2-1)

The inhibitory effect of tirabrutinib against 67 types of receptors, ion channels, transporters, etc. was investigated using respective ligands. Tirabrutinib (10 μmol/L) inhibited dopamine transporter and norepinephrine transporter by ≥50%, with IC_{50} of 3.91 and 10.2 μmol/L, respectively.

The IC_{50} of tirabrutinib against these transporters was ≥8.3-fold the C_{max} of unbound tirabrutinib in plasma (0.474 μmol/L)[7] following the administration of tirabrutinib by the proposed dosage regimen (480 mg QD under fasting conditions). Given this, the applicant explained that the clinical use of tirabrutinib is unlikely to cause adverse events.

3.2.2 Effect on immune system, etc. (CTD 4.2.1.2-2, 4.2.1.2-3, 4.2.1.2-4, 4.2.1.2-5, 4.2.1.2-6, and 4.2.1.2-7)

The effect of tirabrutinib on the immune system, etc. was as follows:

- Tirabrutinib inhibited anti-IgE-induced human basophil activation.
- Tirabrutinib inhibited immune complex-induced extracellular release of deoxyribonucleic acid (DNA) from human neutrophils.
- Tirabrutinib inhibited anti-Fcγ receptor (FcγR) - and Toll-like receptor (TLR) 9-induced production of tumor necrosis factor-α (TNF-α) and interleukin (IL) -6 by human monocytes.
- Tirabrutinib inhibited macrophage-colony stimulating factor (M-CSF) - and receptor activator of nuclear factor-κB ligand (RANKL) -induced differentiation of human osteoclast precursor cells.

7) Calculated based on C_{max} (2,690 ng/mL) on Day 28 following multiple oral administration of tirabrutinib (480 mg) QD to Japanese patients with recurrent or refractory PCNSL under fasted conditions [see Section 6.2.1.2] and on serum protein binding (92.0%) of ^{14}C-labeled tirabrutinib at 5 μg/mL [see Section 4.2.2].

3.3 Safety pharmacology

3.3.1 Effect on central nervous system (CTD 4.2.1.3-1 and 4.2.3.2-7)

A single dose of tirabrutinib 100, 300, or 1,000 mg/kg was administered orally to rats (n = 8/group), and the effect of tirabrutinib on clinical signs and on neurobehavioral function was investigated up to 48 hours post-dose by modified Irwin's method. Tirabrutinib 300 and 1,000 mg/kg reduced or eliminated pain reaction.

Tirabrutinib 3, 10, 30, or 100 mg/kg was administered orally QD for 4 weeks to cynomolgus monkeys (n = 8 or 12/group), and the effect of tirabrutinib on clinical signs and on neurobehavioral function was investigated by a functional observation battery. Tirabrutinib 100 mg/kg caused ataxic gait, ataxia, etc. [see Section 5.2].

3.3.2 Effect on cardiovascular system

3.3.2.1 Effect on hERG potassium current (CTD 4.2.1.3-3)

Using human fetal kidney-derived HEK293 cell line transfected with human ether-a-go-go related gene (hERG), the effect of tirabrutinib 0.1, 0.3, 1, 3, 10, and 30 μmol/L on hERG potassium current was investigated. Tirabrutinib inhibited hERG potassium current by 1.90 ± 2.46% (mean ± standard error, n = 5), 1.48 ± 1.30%, 14.28 ± 2.33%, 30.30 ± 1.55%, 67.02 ± 1.72%, and 88.88 ± 0.51%, respectively, with IC_{50} of 5.59 μmol/L. A statistically significant inhibition was observed in the tirabrutinib 1, 3, 10, and 30 μmol/L groups as compared with the control (0.1% dimethyl sulfoxide [DMSO]) group ($P < 0.01$ for all, Dunnett test).

3.3.2.2 Effect on blood pressure, heart rate, and electrocardiogram (CTD 4.2.1.3-2)

Following a sequential single-dose oral administration of tirabrutinib 10, 30, 100, and 300 mg/kg to cynomolgus monkeys (n = 5), the effect of tirabrutinib on blood pressure, heart rate, and electrocardiogram was investigated. No effect of tirabrutinib was observed.

3.3.3 Effect on the respiratory system (CTD 4.2.1.3-2)

Following a sequential single-dose oral administration of tirabrutinib 10, 30, 100, and 300 mg/kg to cynomolgus monkeys (n = 5), the effect of tirabrutinib on respiratory rate, arterial oxygen partial pressure, partial arterial pressure of carbon dioxide, etc. was investigated. No effect of tirabrutinib was observed.

3.3.4 Effect on human platelets (CTD 4.2.1.3-5)

Using platelet-rich plasma prepared from the blood of healthy adults, the effect of tirabrutinib 0.001, 0.01, 0.1, 1, 3, 6, 10, and 100 μmol/L on adenosine diphosphate (ADP) - and collagen-induced platelet aggregation was investigated. Tirabrutinib ≥10 μmol/L inhibited ADP- and collagen-induced platelet aggregation.

3.R Outline of the review conducted by PMDA

On the basis of the data submitted and the discussion in the following subsection, PMDA concluded that the applicant's explanation about the nonclinical pharmacology of tirabrutinib is acceptable.

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

The applicant's explanation about the mechanism of action of tirabrutinib and efficacy on PCNSL:
BTK is a signaling molecule mainly expressed in B cells and situated downstream of BCR. BTK is assumed to be activated upon BCR engagement and play a central role in the survival, growth, etc. of B cells (*Oncogene*. 2000;19:5651-61, *Nat Rev Cancer.* 2014;14:219-32, etc.).

Pathologically, ≥95% of PCNSL cases are B-NHL and are mostly classified as DLBCL (*Practical Guidelines for Neuro-Oncology 2019*. [The Japan Society for Neuro-Oncology.]). The BCR signal transduction pathway is constantly activated in B-cell tumor such as DLBCL including PCNSL (*Nature*. 2010;463:88-92, etc).

Tirabrutinib binds to BTK (*SLAS Discovery*. 2018;23:919-29) thereby inhibiting the kinase activity of BTK, and is expected to inhibit the growth of B-cell tumor [see Sections 3.1.1, 3.1.2, and 3.1.4].

In addition to the above-mentioned action mechanism of tirabrutinib, the following observations suggest promising efficacy of tirabrutinib against B-cell PCNSL:

- Tirabrutinib inhibited tumor growth in SCID mice subcutaneously transplanted with human DLBCL-derived cell line [see Section 3.1.4.2].
- Despite the difference between the growth inhibitory effect of tirabrutinib on germinal center B cell subtype diffuse large B cell lymphoma (GCB-DLBCL)-derived cell line and that on activated B cell subtype diffuse large B cell lymphoma (ABC-DLBCL)-derived cell line [see Section 3.1.4], there were patients with B-cell PCNSL responded to tirabrutinib regardless of PCNSL subtype in the Japanese Phase I/II study (Study 02) [see Section 7.1.2.2].

The applicant's explanation about the difference in pharmacological characteristics between tirabrutinib and ibrutinib, another BTK inhibitor approved in Japan:
Both tirabrutinib and ibrutinib inhibit BTK phosphorylation. However, tirabrutinib did not inhibit phosphorylation of inducible T cell kinase (ITK) and janus kinase (JAK) 3, which are molecules involved in T cell receptor (TCR) signal transduction [see Section 3.1.3], whereas ibrutinib had inhibitory effect on these molecules (*Proc Natl Acad Sci USA*. 2010;107:13075-80, *Blood*. 2013;122:2539-49). Thus, tirabrutinib differs from ibrutinib in not inhibiting T-cell activation.

PMDA accepted the explanation of the applicant.

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

In this section, the dose and concentration of tirabrutinib are expressed in terms of free base.

The pharmacokinetics (PK) of tirabrutinib was investigated in animals such as dogs, monkeys. Plasma protein binding of tirabrutinib, drug metabolizing enzymes, transporters, etc. were investigated using biomaterials of human and animal origins.

4.1 Absorption

4.1.1 Single-dose administration

A single dose of tirabrutinib 2 mg/kg was administered intravenously or orally to male dogs under fasting conditions, and plasma tirabrutinib concentration was investigated (Table 7). Bioavailability (BA) of tirabrutinib following the oral dose was 89.2%.

Table 7. PK parameters of tirabrutinib (male dogs, a single intravenous or oral dose)

Dose (Route of administration)	C_{max} (ng/mL)	t_{max} (h)	AUC_{last} (ng•h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
2 mg/kg (i.v.)	891 ± 100	0.66 ± 0.16	3,668 ± 614	3.56 ± 0.05	550 ± 100	2,030 ± 420
2 mg/kg (p.o.)	827 ± 186	1.00 ± 0	3,272 ± 327	3.28 ± 0.16	-	-

Mean ± SD; n = 3; -, Not calculated.

4.1.2 Repeated-dose administration

Tirabrutinib 1, 3, 10, or 30 mg/kg was administered orally QD for 13 weeks to male and female monkeys under fed conditions, and plasma tirabrutinib concentration was investigated (Table 8). No clear sex difference was observed in exposure to tirabrutinib. The exposure to tirabrutinib increased roughly in proportion to dose over the dose range studied.

Table 8. PK parameters of tirabrutinib (male and female monkeys, 13-week repeated oral administration)

Day of measurement	Dose (mg/kg)	C_{max} (ng/mL)		t_{max} (h)		AUC_{24h} (ng•h/mL)	
		Male	Female	Male	Female	Male	Female
1	1	61.1 ± 7.45	66.5 ± 15.3	3.0 ± 1.7	2.3 ± 1.5	371 ± 52.3	435 ± 121
	3	186 ± 4.51	226 ± 14.4	2.7 ± 1.2	1.3 ± 0.6	1,050 ± 150	1,020 ± 100
	10	505 ± 217	557 ± 298	1.3 ± 0.6	3.3 ± 1.2	3,180 ± 910	2,950 ± 1,120
	30	2,070 ± 570	1,790 ± 410	2.8 ± 1.1	2.2 ± 1.1	13,300 ± 3,500	11,400 ± 2,200
91	1	59.4 ± 21.4	64.9 ± 10.4	1.7 ± 0.6	1.3 ± 0.6	286 ± 39.8	323 ± 69.4
	3	163 ± 57.1	227 ± 55.7	1.7 ± 0.6	1.7 ± 0.6	918 ± 133	827 ± 204
	10	714 ± 274	484 ± 259	2.3 ± 1.5	2.7 ± 1.2	4,530 ± 2,130	2,540 ± 860
	30	1,940 ± 440	2,390 ± 710	1.8 ± 0.4	2.2 ± 1.1	12,400 ± 3,600	12,100 ± 6,200

Mean ± SD, n = 3

4.1.3 *In vitro* membrane permeability

Membrane permeability of tirabrutinib was investigated using human colon cancer-derived Caco-2 cell line. Apparent permeability in apical to basolateral direction ($P_{app\ A \rightarrow B}$) of tirabrutinib 10 μmol/L was 15.5×10^{-6} cm/second. The applicant explained that tirabrutinib has a high membrane permeability, based on the above results and the $P_{app\ A \rightarrow B}$ of propranolol 10 μmol/L that has high membrane permeability, 11.3×10^{-6} cm/second.

4.2 Distribution

4.2.1 Tissue distribution

A single dose of ^{14}C-labeled tirabrutinib hydrochloride (^{14}C-labeled tirabrutinib) 5 mg/kg was administered orally to male albino and pigmented rats under fasting conditions, and tissue distribution of the radioactivity was investigated. In albino rats, radioactivity was distributed to various tissues extensively, and the radioactivity concentration peaked within 0.5 hours post-dose in most tissues including blood. The ratio of radioactivity concentration in tissue to that in plasma at 0.5 hours post-dose was particularly high in the stomach, liver, small intestine, kidney, adrenal, aorta, and submandibular gland (26.3, 18.4, 12.8, 5.38, 2.86, 2.63, and 2.10, respectively). Because radioactivity

was detected even in the central nervous system (cerebrum, cerebellum, and spinal cord), the applicant explained that tirabrutinib or its metabolites are distributed in the central nervous system. The radioactivity concentration decreased to <10% of C_{max} within 168 hours post-dose in all tissues examined. In pigmented rats, no clear difference was observed in $t_{1/2}$ of the radioactivity between pigmented skin and non-pigmented skin (27 and 30 hours, respectively). The applicant explained that neither tirabrutinib nor its metabolites bind to melanin.

4.2.2 Plasma protein binding

Serum samples of rats, monkeys, and humans were incubated with ^{14}C-labeled tirabrutinib (0.5, 5, and 50 μg/mL) at 4°C for 24 hours, and binding of tirabrutinib to serum proteins was investigated by equilibrium dialysis. The serum protein binding of tirabrutinib (0.5, 5, and 50 μg/mL, respectively) was 98.2%, 97.6%, and 96.1% in rats, 90.7%, 89.6%, and 89.6% in monkeys, and 92.3%, 92.0%, and 90.8% in humans.

Human serum albumin (43 mg/mL) and human α1-acid glycoprotein (1 mg/mL) were incubated with ^{14}C-labeled tirabrutinib (0.5, 5, and 50 μg/mL) at 4°C for 24 hours, and binding of tirabrutinib to human serum albumin and human α1-acid glycoprotein was investigated by equilibrium dialysis. The binding of tirabrutinib (0.5, 5, and 50 μg/mL, respectively) was 87.5%, 84.7%, and 84.1% for human serum albumin and 29.9%, 17.2%, and 4.2% for human α1-acid glycoprotein. The applicant explained that these results suggest that tirabrutinib binds mainly to albumin in human serum.

4.2.3 Distribution in blood cells

Blood samples of rats, monkeys, and humans were incubated with ^{14}C-labeled tirabrutinib (0.5-50 μg/mL) at 37°C for 10 minutes, and distribution of tirabrutinib in blood cells was investigated. The blood/plasma ratio of tirabrutinib concentration was 0.79 to 0.89 in rats, 0.69 to 0.73 in monkeys, and 0.71 to 0.83 in humans. The applicant explained that the results show that tirabrutinib is distributed only minimally in blood cells.

4.2.4 Placental and fetal transfer

Placental and fetal transfer of tirabrutinib was not investigated. The applicant explained that tirabrutinib may possibly cross the placenta and be distributed in fetuses, judging from the physicochemical properties of tirabrutinib (molecular weight, 490.94; log P value, 2.69).

4.3 Metabolism

4.3.1 *In vitro*

Hepatocytes of rats, monkeys, and humans were incubated with ^{14}C-labeled tirabrutinib (1.5 μg/mL) at 37°C for 4 hours,[8)] and metabolites of tirabrutinib were investigated. Human-specific metabolites were not detected. Major metabolites detected were glutathione conjugate (percentage relative to total radioactivity in sample, 50.0%) in rats, glutathione conjugate and sulfate conjugate of the hydroxylated form (17.5% and 15.5%, respectively) in monkeys, and sulfate conjugate of the hydroxylated form (19.0%) in humans.

8) Incubated for 3 hours in the study using rat hepatocytes.

The following investigations were conducted on isoforms of cytochrome P450 (CYP) involved in the metabolism of tirabrutinib in humans. Based on the results, the applicant explained that mainly CYP3A4 contributes to the metabolism of tirabrutinib. CYP3A-mediated pharmacokinetic interactions of tirabrutinib are described in Section "6.R.3 Pharmacokinetic interactions mediated by CYP3A."

- Microsomes prepared from insect cells expressing human CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4) were incubated with ^{14}C-labeled tirabrutinib (1.5 μg/mL) at 37°C for 120 minutes in the presence of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH). The residual rate of tirabrutinib was 19.5% and 35.8%, respectively, in the presence of CYP3A4 and CYP2D6, and ≥97.3% in the presence of other CYP isoforms.

- Human liver microsomes were incubated with ^{14}C-labeled tirabrutinib (1.5 μg/mL) in the presence of inhibitors of CYP isoforms (furafylline for CYP1A2, tranylcypromine for CYP2A6, thiotepa for CYP2B6, quercetin for CYP2C8, sulfaphenazole for CYP2C9, nootkatone for CYP2C19, quinidine for CYP2D6, diethyldithiocarbamate for CYP2E1, and ketoconazole for CYP3A) and NADPH at 37°C for 60 minutes. Tirabrutinib metabolism was inhibited by 76.0% in the presence of ketoconazole but by ≤9.5% in the presence of inhibitors of other CYP isoforms.

4.3.2 *In vivo*

A single dose of ^{14}C-labeled tirabrutinib (5 mg/kg) was administered orally under fasting conditions to bile duct-cannulated or non-cannulated male rats, and metabolites in plasma, urine, feces, and bile were investigated. The following results were obtained:

- Mainly unchanged tirabrutinib and M35 (reduced form of water adduct) were detected in plasma collected within 24 hours post-dose from non-bile duct-cannulated male rats (accounting for 52.6% and 26.8%, respectively, of total radioactivity in plasma). Mainly M29 (oxidized form) and M27 (tetrahydrodioxy form) were detected in urine up to 24 hours post-dose (accounting for 1.72% and 1.67%, respectively, of the administered radioactivity). Unchanged tirabrutinib was barely detected (<0.1%). Mainly M29, M30 (dihydrodioxy form), and M27 were detected in feces up to 72 hours post-dose (8.41%[9)] and 5.03%, respectively), and unchanged tirabrutinib was barely detected (<1%).

- Mainly M28 (glutathione conjugate) and M21 (cysteine-glycine conjugate) were detected in the bile collected up to 72 hours post-dose from bile duct-cannulated male rats (31.5% and 12.4%, respectively), and no unchanged tirabrutinib was detected.

4.4 Excretion

4.4.1 Urinary, fecal, and biliary excretion

A single dose of ^{14}C-labeled tirabrutinib (5 mg/kg) was administered orally to bile duct-cannulated or non-cannulated male rats, and the urinary, fecal, and biliary excretion rate (percentage relative to the administered radioactivity) was investigated. In non-bile duct-cannulated male rats, the urinary and fecal excretion rate of radioactivity up to 168 hours post-dose was 13.1% and 74.4%, respectively. In bile duct-cannulated male rats, the urinary, fecal, and biliary excretion rate of radioactivity up to 168 hours post-dose was 3.64%, 7.20%, and 87.2%, respectively. Based on the results and the finding that mainly

9) Percentage of the sum of the radioactivity of M29 and M30, which were co-eluted.

metabolites were detected in urine, feces, and bile [see Section 4.3.2], the applicant explained that tirabrutinib is eliminated by metabolism and that metabolites of tirabrutinib are excreted in feces, mainly via bile.

4.4.2 Excretion in milk

Tirabrutinib excretion in milk was not investigated. The applicant explained that tirabrutinib may possibly be excreted in milk, judging from the physicochemical property of tirabrutinib (log P value, 2.69).

4.5 Pharmacokinetic interactions

4.5.1 Enzyme inhibition

The applicant's explanation:

On the basis of the following results and C_{max} (0.474 μmol/L[10)]) of the unbound tirabrutinib under steady state after the administration according to the proposed dosage regimen, tirabrutinib in clinical use may cause pharmacokinetic interactions via time-dependent CYP3A inhibition. The pharmacokinetic interactions of tirabrutinib are described in Section "6.2.3.1 Study on interaction with itraconazole or midazolam."

- Human liver microsomes were incubated with tirabrutinib (1-100 μmol/L) in the presence of the substrates of CYP isoforms (7-ethoxyresorufin for CYP1A2, bupropion for CYP2B6, paclitaxel for CYP2C8, diclofenac for CYP2C9, *S*-mephenytoin for CYP2C19, bufuralol for CYP2D6, and midazolam and testosterone for CYP3A) and NADPH, and the inhibitory effect of tirabrutinib against each CYP isoform was investigated. Tirabrutinib inhibited the metabolism of the substrates of CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A with IC_{50} of 24.6, 13.4, 29.1, 89.5, and 37.6 μmol/L, respectively,[11)] whereas tirabrutinib did not show any clear inhibitory effect against the metabolism of the substrates of other CYP isoforms.

- Human liver microsomes were incubated with tirabrutinib (10 or 100 μmol/L[12)]) in the presence of NADPH, followed by incubation with substrates of CYP isoforms (7-ethoxyresorufin for CYP1A2, bupropion for CYP2B6, paclitaxel for CYP2C8, diclofenac for CYP2C9, *S*-mephenytoin for CYP2C19, bufuralol for CYP2D6, and midazolam and testosterone for CYP3A), and the time-dependent inhibitory effect of tirabrutinib against each CYP isoform was investigated. Tirabrutinib inhibited the metabolism of the substrate of CYP3A in a time-dependent manner with an apparent inhibition constant ($K_{i,\ app}$) and maximum inactivation rate constant (k_{inact}) of 18.9 μmol/L and 0.0797 min^{-1}, respectively.[13)] Tirabrutinib showed a time-dependent inhibitory effect against the metabolism of the substrate of CYP2B6 as well (<10% inhibition at 10 μmol/L). On the other hand, tirabrutinib did not show a clear time-dependent inhibitory effect against the metabolism of the substrates of other CYP isoforms investigated.

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10) Calculated from C_{max} on Day 28 in multiple oral administration of tirabrutinib (480 mg QD) in Study 02 in Japanese patients with recurrent or refractory PCNSL and from the serum protein binding rate of ^{14}C-labeled tirabrutinib at 5 μg/mL.

11) Tirabrutinib inhibited CYP3A-mediated testosterone metabolism.

12) $K_{i,\ app}$ and k_{inact} were calculated from the data obtained at tirabrutinib concentration of 5 to 100 μmol/L.

13) Tirabrutinib inhibited the metabolism of midazolam and testosterone in a time-dependent manner. $K_{i,\ app}$ and k_{inact} were calculated from the results obtained with midazolam.

- Microsomes prepared from insect cells expressing human uridine diphosphate glucuronosyl transferase (UGT) 1A1 were incubated with tirabrutinib (0.2-50 μmol/L) in the presence of the substrate of UGT1A1 (estradiol) and uridine diphosphate glucuronic acid (UDPGA), and the inhibitory effect of tirabrutinib against UGT1A1 was investigated. Tirabrutinib inhibited the metabolism of the substrate of UGT1A1 with IC_{50} of 12.4 μmol/L.

4.5.2 Enzyme induction

Human hepatocytes were treated with tirabrutinib (1-30 μmol/L) for 3 days, and enzymatic activities of CYP1A2, CYP2B6, and CYP3A and expression level of CYP3A4 messenger ribonucleic acid (mRNA) were investigated. Tirabrutinib did not clearly induce enzymatic activities of the CYP isoforms studied or clearly increase the expression level of CYP3A4 mRNA. The applicant explained that the clinical use of tirabrutinib is unlikely to cause pharmacokinetic interactions mediated by the induction of CYP isoforms.

4.5.3 Transporters

The applicant's explanation:

The following study results demonstrated that tirabrutinib serves as a substrate for P-glycoprotein (P-gp), organic anion transporting polypeptide (OATP) 1B1, and OATP1B3. However, given that tirabrutinib is well absorbed from human gastrointestinal tract [see Section 6.2.2.1] and that P-gp contributes little to the gastrointestinal absorption of tirabrutinib, the concomitant use of a P-gp inhibitor with tirabrutinib is unlikely to pose a problems in the clinical setting. OATP1B1- or OATP1B3-mediated pharmacokinetic interactions of tirabrutinib are described in Section “6.2.3.2 Study on interaction with rifampicin.”

- Using porcine kidney-derived LLC-PK1 cell line expressing human P-gp, P-gp-mediated transport of ^{14}C-labeled tirabrutinib (2 μmol/L) was investigated. The ratio of the efflux ratio (the ratio of permeability coefficient in the secretary direction to that in the absorptive direction) of ^{14}C-labeled tirabrutinib in P-gp-expressing cell line to that in non-P-gp-expressing cell line was 1.1 in the presence of verapamil (30 μmol/L), a P-gp inhibitor, 0.9 in the presence of cyclosporin A (10 μmol/L), another P-gp inhibitor, and 2.5 in the absence of P-gp inhibitor.

- Using canine kidney-derived MDCKII cell line expressing human breast cancer resistance protein (BCRP), BCRP-mediated transport of tirabrutinib (1 μmol/L) was investigated. The ratio of the efflux ratio of tirabrutinib was 1.7 and 1.6, respectively, in the presence of a BCRP inhibitor (Ko143 1 and 10 μmol/L), and 2.1 in the absence of the inhibitor.

- Using Chinese hamster ovary cell line (CHO cell line) expressing human OATP1B1 or OATP1B3, OATP1B1- or OATP1B3-mediated transport of tirabrutinib (1 μmol/L) was investigated. The ratio of tirabrutinib uptake velocity in OATP1B1- or OATP1B3-expressing cell line to that in the non-expressing cell line was 2.4 and 1.5, respectively. In OATP1B1- or OATP1B3-expressing cell line, rifampicin (40 μmol/L), an inhibitor of OATP1B1 and OATP1B3, decreased the velocity of tirabrutinib uptake.

The following outcomes indicate that tirabrutinib may cause pharmacokinetic interactions mediated by the inhibition of P-gp, OATP1B1, and multidrug and toxin extrusion (MATE) 1, based on C_{max} (0.474 μmol/L[10)]) of unbound tirabrutinib under steady state following multiple oral doses of tirabrutinib according to the proposed dosage regimen and the solubility of tirabrutinib (630 μmol/L) in the fed-state simulated intestinal fluid.

- Using LLC-PK1 cell line expressing human P-gp, the inhibitory effect of tirabrutinib (2-50 μmol/L) on the transportation of ^{3}H-labeled digoxin (1 μmol/L) was investigated. Tirabrutinib inhibited the transportation of the substrate of P-gp with IC_{50} of 26.8 μmol/L.

- Using LLC-PK1 cell line expressing human BCRP, the inhibitory effect of tirabrutinib (150 μmol/L) on the transportation of ^{3}H-labeled prazosin (0.01 μmol/L) was investigated. Tirabrutinib inhibited the transportation of the substrate of BCRP by 42.0%.

- Using HEK293 cell line expressing human OATP1B1, OATP1B3, organic cation transporter (OCT) 1, OCT2, MATE1, or MATE2-K, the inhibitory effect of tirabrutinib (0.2-50 μmol/L) on the transportation of the substrate[14)] of each transporter was investigated. Tirabrutinib inhibited the transportation of the substrates of OATP1B1, OATP1B3, OCT1, OCT2, MATE1, and MATE2-K with IC_{50} of 13.4, 47.4, 2.06, 5.59, 0.829, and 37.6 μmol/L, respectively.

- Using Chinese hamster ovary-derived CHO-K1 cell line expressing human organic anion transporter (OAT) 1, the inhibitory effect of tirabrutinib (50 μmol/L) on the transportation of ^{3}H-labeled *p*-aminohippuric acid (1 μmol/L) was investigated. Tirabrutinib inhibited the transportation of the substrate of OAT1 by 58.8%.

- Using mouse proximal renal tubule-derived S_2 cell line expressing human OAT3, the inhibitory effect of tirabrutinib (0.2-50 μmol/L) on the transportation of ^{3}H-labeled estrone-3-sulfate (0.05 μmol/L) was investigated. Tirabrutinib inhibited the transportation of the substrate of OAT3 with IC_{50} of 5.95 μmol/L.

- Using MDCKII cell line expressing human multidrug resistance associated protein (MRP) 1, the inhibitory effect of tirabrutinib (0.412-100 μmol/L) on the transport of calcein-AM (10 μmol/L) was investigated. Tirabrutinib inhibited the transportation of the substrate of MRP1 with IC_{50} of 44 μmol/L.

4.R Outline of the review conducted by PMDA

On the basis of the data submitted and the results of the review in the following section, PMDA concluded that the applicant's explanation about the nonclinical pharmacokinetics of tirabrutinib is acceptable.

14) The following substrates were used: (a) ^{3}H-labeled estradiol 17β-D-glucuronide (0.05 μmol/L) for OATP1B1 and OATP1B3 and (b) ^{14}C-labeled metformin (10 μmol/L) for OCT1, OCT2, MATE1, and MATE2-K.

4.R.1 Pharmacokinetic interactions

The applicant's explanation about the pharmacokinetic interactions of tirabrutinib mediated by the inhibition of P-gp, OATP1B1, or MATE1:

Results of *in vitro* studies suggested the inhibitory effect of tirabrutinib on P-gp, OATP1B1, or MATE1 [see Section 4.5.3]. However, the clinical studies[15)] did not reveal any particular safety concern in the concomitant use of tirabrutinib with substrates of P-gp, OATP1B1, or MATE1, which suggests that the concomitant use of tirabrutinib with these substrates is unlikely to pose any clinical problem.

PMDA's view:

PMDA generally accepted the explanation of the applicant. At the same time, the observation on the pharmacokinetic interactions of tirabrutinib mediated by the inhibition of P-gp, OATP1B1, or MATE1 is important for the proper use of tirabrutinib. Relevant information should be collected continuously, and any useful findings should be provided appropriately to healthcare professionals.

5. Toxicity and Outline of the Review Conducted by PMDA

In this section, the dose and concentration of tirabrutinib are expressed in terms of free base.

The vehicles used in *in vivo* studies were 0.5% methylcellulose solution and those in *in vitro* studies were DMSO.

5.1 Single-dose toxicity

Acute toxicity of tirabrutinib was evaluated based on the results of the following toxicity studies in mice, rats, and monkeys. The approximate lethal dose was >1,500 mg/kg in mice and 1,000 mg/kg in rats and monkeys (Table 9).

15) The pooled analysis of Japanese Phase I study (Study 01), Japanese Phase I/II study (Study 02), and foreign Phase I study (Study POE001) conducted with the proposed dosage and administration for tirabrutinib application.

Table 9. Single-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female mice (CB6F1)	p.o.	300, 1,000, 1,500	No toxic changes	>1,500	4.2.3.1-1 Reference
Male rats (Sprague Dawley)	p.o.	1, 10, 100, 1,000, 2,000	Death: 2,000 (1 of 3 animals), loss of righting reflex, mydriasis, lacrimation, salivation, dark-red coloration of the lung, gastric distention ≥1,000: Decreased locomotor activity, bradypnea 2,000: Sedation, prone position, hypothermia, gastric distention	2,000	4.2.3.1-2 Reference
Male rats (Sprague Dawley)	p.o.	0, 100, 300, 1,000	Acute toxicity was evaluated by a micronucleus test (3-day repeated administration). Death: 1,000 (2 of 14[a)] animals) Moribund euthanasia: 1,000 (1 of 14[a)] animals), lacrimation, prone position, bradypnea, mydriasis, hypothermia 1,000: Decreased locomotor activity, decreased body weight	1,000	4.2.3.3.2-1
Male monkeys (cynomolgus)	p.o.	Group A: 1→10→1,000 Group B: 3→100	Acute toxicity was evaluated by a single-dose ascending dose study.[b)] Moribund euthanasia: 1,000 (2 of 3 animals), stupor, shivering, vomitus, ananastasia, lateral position, decreased locomotor activity, red lymph nodes 1,000: Flaccidity, decreased food consumption	1,000	4.2.3.1-3 Reference 4.2.3.1-4 Reference

a) In the 1,000 mg/kg group, 2 of 6 animals died, preventing the evaluation of bone marrow smear preparation in ≥5 animals. Therefore, an additional study involving the control group (6 animals) and the 1,000 mg/kg group (8 animals) was conducted. The total number of animals in the 2 studies is given.
b) Three each of animals were assigned to Groups A and B. Group A received 1, 10, and 1,000 mg/kg on Days 1, 2, and 4, respectively. Group B received 3 and 100 mg/kg on Days 1 and 3, respectively.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies were conducted in mice (1 and 4 weeks), rats (4, 13, and 26 weeks), and monkeys (1, 4, 13, and 39 weeks) (Table 10). Tirabrutinib affected the central nervous system (rats [see Section 5.6.3.1] and monkeys), immune system (mice, rats, and monkeys), liver (mice, rats, and monkeys) and other organs. In the repeated-dose toxicity studies in mice (4 weeks), rats (26 weeks), and monkeys (39 weeks), C_{max} and $AUC_{0\text{-}24h}$ of tirabrutinib at the no observed adverse effect level (NOAEL) (500 mg/kg/day in mice, 60 mg/kg/day in rats, and 30 mg/kg/day in monkeys) were 33.0 μg/mL and 163 μg·h/mL, respectively, in mice, 4.58 μg/mL and 30.8 μg·h/mL, respectively, in rats, and 2.33 μg/mL and 14.8 μg·h/mL, respectively, in monkeys, which were 12- and 12-fold (mice), 1.7- and 2.3-fold (rats), and 0.87- and 1.1-fold, respectively, the clinical exposure.[16)]

16) C_{max} (2.69 μg/mL) and $AUC_{0\text{-}24h}$ (13.4 μg·h/mL) of tirabrutinib during multiple oral administration of tirabrutinib (480 mg QD) in Study 02 in Japanese patients with recurrent or refractory PCNSL.

The PMDA's conclusion on the characteristic effects of tirabrutinib, i.e., those on the central nervous system and on the immune system and liver, are described in Section "5.R.1 Effect on central nervous system" and in Section "7.R.3 Safety," respectively.

Table 10. Repeated-dose toxicity studies

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Male and female mice (CB6F1)	p.o.	1 week (QD)	300, 1,000, 1,500	No toxic changes	NOAEL not evaluated	4.2.3.2-1 Reference
Male and female mice (CB6F1)	p.o.	4 weeks (QD)	0, 150, 500, 1,500	≥150: Increased platelet count, decreased MCV, increased blood ALT/ALP/total cholesterol/total protein/albumin, decreased blood triglyceride, decreased spleen weight, increased liver weight, hepatocyte hypertrophy, enlargement of renomedullary inner stripe. ≥500: Increased reticulocyte/white blood cell/lymphocyte count, decreased MCH, endosinusial erythrocytes in submandibular lymph node (female), splenic extramedullary hematopoiesis (female). 1,500: Increased eosinophil count (male), decreases in hemoglobin/MCHC (male), increased blood AST/albumin-globulin ratio (male), white foci in liver (female), adrenocortical hypertrophy (male), inflammatory cell infiltration in renomedullary inner stripe (female), localized necrosis of hepatocytes (female)	500[i)]	4.2.3.2-2 Reference
Male and female rats (Sprague-Dawley)	p.o.	4 weeks (QD) + 1 or 4 weeks withdrawal	0, 3, 10, 100, 1,000 (male), 1,000/300 (female)[a)]	Death: 1,000 (1 of 22 males), 1,000/300 (7 of 22 females) ≥10: Fibrosis of pancreatic islets/localized bleeding of islets and interstitium/atrophy of acinar cells/inflammatory cell infiltration in interstitium ≥100: Increased blood albumin/albumin-globulin ratio, decreased blood globulin, increased liver weight, diffuse eosinophilic change of hepatocytes 1,000 (male), 1,000/300 (female): Decreased locomotor activity, lacrimation, lateral position, bradypnea, decreased feces, emaciation (male), decreased body weight, fluctuation in food consumption, increased urinary volume (male), low urinary pH (male), decreased urinary protein/ketone body (male), decreases in red blood cells/hematocrit/hemoglobin, decreased MCH/MCHC (male), increased reticulocyte count (male), decreased creatinine, increased blood ALP (male), decreases in blood total protein/total cholesterol/total bilirubin (male), increased pancreatic weight (male), white adrenals (male), hepatocyte hypertrophy (male), focal hepatocyte necrosis (male), thyroid follicular cell hypertrophy, splenic extramedullary hematopoiesis/ splenic white pulp shrinkage, diffuse hypertrophy of adrenal fasciculata cells and glomerulosa cells (male), increased corticosterone/aldosterone Reversibility: reversible	100[i)]	4.2.3.2-3 4.2.3.2-4 Reference
Male and female rats (Sprague-Dawley)	p.o.	13 weeks (QD) + 4 weeks withdrawal	0, 3, 30, 100, 300	≥3: Bleeding and fibrosis of pancreatic islets/bleeding and mononuclear cell infiltration in interstitium, mononuclear cell infiltration in prostatic interstitium ≥30: Increased blood albumin-globulin ratio, decreased blood globulin, brown pancreas, hypertrophy and atrophy of pancreatic acinar cells ≥100: Decreased red cell count, increased white blood cell/monocyte count, increased blood ALP/albumin, increased liver weight, increased kidney weight (male), hepatocyte hypertrophy, cytoplasmic dilution	100[i)]	4.2.3.2-5

				suggesting glycogen accumulation in hepatocytes, endosinusial erythrocytes/hemosiderin deposition in mesenteric lymph nodes, thyroid follicular cell hypertrophy 300: Increased urinary chloride (male), decreased urinary sodium/potassium ratio (female), decreased hemoglobin, increased MCV/reticulocyte count (female), decreased hematocrit (female), decreased MCHC (male), increased neutrophil count (female), increased blood AST/ALT/potassium (male), decreased blood total cholesterol (male), increased thyroid weight (female), liver enlargement, white adrenals, kidney enlargement (male), white spots in lung (male), white spots in liver, prominent lobule structure (male), red spots in stomach (male), focal hepatocyte necrosis/eosinophilic mutated hepatocyte foci (male), increased adrenal glomerular vacuoles, glandular stomach erosion/ulcer/congestion (male), endosinusial erythrocytes/hemosiderin deposition in submandibular lymph node (female), increased centrilobular smooth endoplasmic reticulum in liver,[c] increased diffuse peroxisome in liver[c] Reversibility: reversible		
Male and female rats (Sprague-Dawley)	p.o.	26 weeks (QD) + 12 weeks withdrawal	0, 10, 60, 300	Death: 300 (1 of 20 females[d]) Moribund euthanasia: 60 (1 of 15 females[d]), 300 (2 of 20 males[e]) ≥10: Decreased red blood cell count, increased blood albumin-globulin ratio, decreased blood globulin/triiodothyronine/thyroxine, increased blood thyrotropin, decreased blood potassium (female), bleeding from pancreatic islets and interstitium/fibrosis/interstitial edema (male), degeneration of pancreatic acinar cells, hyperplasia of thyroid follicular cells, endosinusial erythrocytes/hemosiderin deposition in mesenteric and submandibular lymph nodes ≥60: Decreased body weight/body weight gain (male), decreased fibrinogen (male), increased blood ALP, decreased blood calcium, increased blood albumin (male), decreased blood total cholesterol (male), increased liver weight, decreased lymphocyte count in germinal center of lymph node, adrenocortical hypertrophy 300: Increased urine volume, increased urinary sodium/potassium/chloride/calcium, decreased urine specific gravity, decreased hemoglobin, increased reticulocyte/white blood cell/neutrophil/lymphocyte/monocyte count, decreased hematocrit (male), increased platelet count (male), increased blood triglyceride, decreased blood sodium (male), increased blood ALT (female), increased renal/adrenal weight, decreased splenic weight (male), increased thyroid/lung/uterine weight (female), hepatocyte hypertrophy, hepatocyte necrosis (male), decreased lymphocyte count in splenic white pulp (male) Reversibility: reversible	60[i]	4.2.3.2-6
Male monkeys (cynomolgus)	p.o.	1 week (QD)	300	Moribund euthanasia: 300 (2 of 3 animals), decreased locomotor activity, ataxia, ananastasia, somnolence, lateral position, mydriasis, red lymph nodes 300: Vomitus, ataxia, decreased body weight/food consumption, decreased blood chloride	<300	4.2.3.1-3 Reference 4.2.3.1-4 Reference
Male and female monkeys (cynomolgus)	p.o.	4 weeks (QD) + 4 weeks withdrawal	0, 3, 10, 30, 100[b]	Moribund euthanasia: 100 (2 of 6 males), decreased locomotor activity, prone position ≥3: Red submandibular lymph node (male), hemosiderin-containing macrophages/endosinusial erythrocytes in submandibular lymph node 100: Ataxic gait, ataxia, abnormal behavior,	30[i]	4.2.3.2-7

				somnolence, decreased body temperature (female), vomiting, decreased body weight/food consumption, urinary occult blood (female), increased urinary bilirubin/protein (female), decreased red blood cell count/hemoglobin/hematocrit (female), increased reticulocyte count/fibrinogen (female), increased blood α1 globulin ratio, decreased blood calcium (male), decreased blood albumin/albumin-globulin ratio (female), increased blood urea nitrogen, increased liver weight, increased kidney weight (male), decreased thymus weight (female), red foci in submandibular lymph node (male), diffuse degeneration of seminiferous tubule, bleeding of ventricular septum cardiac muscle and subendocardial bleeding, lipid depletion in adrenal fasciculata cells Reversibility: reversible		
Male and female monkeys (cynomolgus)	p.o.	13 weeks (QD) + 4 weeks withdrawal	0, 1, 3, 10, 30	≥1: Hemosiderin-containing macrophages in lymph nodes/endosinusial erythrocytes ≥3: Red lymph nodes, extramedullary hematopoiesis in lymph nodes 30: Decreased blood total cholesterol/phospholipid (male) Reversibility: reversible	30[i)]	4.2.3.2-8
Male and female monkeys (cynomolgus)	p.o.	39 weeks (QD) + 8 weeks withdrawal	0, 3, 10, 30	Death: 10 (1 of 4 males[f)]) Euthanasia: 30 (1 of 6 males[g)]) Moribund euthanasia: 30 (1 of 6 females[h)]) ≥3: Decreased spleen weight, decreased lymphocyte count in germinal center of spleen, endosinusial erythrocytes in submandibular lymph node ≥10: Increased blood ALP (male), decreased lymphocyte count in germinal center of mesenteric lymph node 30: Decreased blood total cholesterol, decreased blood potassium (male) Reversibility: reversible	30[i)]	4.2.3.2-9

a) Death associated with tirabrutinib occurred in females in the 1,000 mg group before administration on Day 4, and the dose was changed to 300 mg/kg from Day 4.
b) Of 6 males in the 100 mg/kg group, 1 animal was moribund euthanized on Day 10 and another animal on Day 16 because of serious toxicity associated with tirabrutinib. Further, 2 animals were autopsied after 13-day withdrawal following treatment discontinuation on Day 16. The remaining 2 animals were autopsied after 4-week repeated administration.
c) Electron microscopic examination of liver was performed on animals in the control group and the 300 mg/kg group.
d) The condition worsened immediately after blood sampling. The death (or moribund) was considered associated with the blood sampling procedure.
e) Of the 2 cases, one was considered to have been moribund due to an accident because of the swelling observed in the right hind leg. The other case was considered to have been moribund due to spontaneous tumor because of the tumor observed at the inguinal region.
f) No clear cause of death was identified.
g) The animal was euthanized due to swelling, etc. on the left forelimb, which was considered to be caused by an accident, because of humeral fracture observed.
h) Considered to have been moribund due to typhlocolitis of spontaneous origin based on the general clinical signs (liquid stool and unformed stool) and histopathological findings (inflammatory cell infiltration in cecum and colon).
i) The changes observed at or below the NOAEL were also considered changes associated with tirabrutinib, and they were not considered toxicity for being pharmacological action-related changes, not extrapolatable to humans, and based on their seriousness and whether to have related changes.

5.3 Genotoxicity

Genotoxicity studies included *in vitro* studies (bacterial reverse mutation assay and chromosomal aberration assay in human peripheral lymphocytes) and an *in vivo* study (a rodent micronucleus assay) (Table 11). All study results were negative, from which tirabrutinib was determined to be non-genotoxic.

Table 11. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Result	Attached document CTD
In vitro	Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100, TA1535, TA1537 *Escherichia coli*: WP2*uvrA*	S9-	0, 20.5, 51.2, 128, 320, 800,[a] 2,000,[a] 5,000[a]	Negative	4.2.3.3.1-1
			S9+	0, 51.2, 128, 320, 800, 2,000, 5,000[a]		
	Chromosomal aberration assay in mammalian cultured cells	Human peripheral lymphocytes	S9- (3 hours)	0, 40, 80, 120, 160, 200	Negative	4.2.3.3.1-2
			S9+ (3 hours)	0, 80, 120, 160, 200		
			S9- (24 hours)	0, 5, 10, 20		
In vivo	Micronucleus assay in rodents	Male rats (Sprague Dawley)		0, 100, 300, 1,000 (p.o., 3 days)	Negative	4.2.3.3.2-1

a) Precipitates were observed.

5.4 Carcinogenicity

Because tirabrutinib is an antineoplastic agent intended for the treatment of advanced cancer, no carcinogenicity study was conducted.

5.5 Reproductive and developmental toxicity

Tirabrutinib is an antineoplastic agent intended for the treatment of advanced cancer. Studies on fertility and early embryonic development to implantation or on pre- and postnatal development, including maternal function, were thus not conducted.

The applicant's explanation about the effect of tirabrutinib on the fertility and early embryonic development to implantation:

Tirabrutinib is unlikely to affect male or female fertility for the following reasons.

- No effect on the male and female reproductive organs associated with tirabrutinib were observed in the 4-week repeated-dose toxicity study in mice, 4-, 13-, and 26-week repeated-dose toxicity studies in rats, or 13- and 39-week repeated-dose toxicity studies in monkeys.

- In the 4-week repeated-dose toxicity study in monkeys, diffuse degeneration of seminiferous tubule was observed in the 100 mg/kg/day group, but the change was considered reversible.

Embryo-fetal development studies were conducted in rats and rabbits (Table 12). Rats in the 600 mg/kg/day group showed embryofetal toxicity (e.g., increased embryofetal mortality), visceral anomalies (small accessory lobe of the liver), skeletal anomalies (costal cartilage anomaly and fusion of sternebrae), etc., and rabbits in the 100 mg/kg/day group showed embryo-fetal toxicity (e.g., increased embryo-fetal mortality). C_{max} and $AUC_{0\text{-}24h}$ of tirabrutinib at the NOAEL in embryo-fetal development of rats and rabbits (300 and 30 mg/kg, respectively) were 12.8 μg/mL and 123 μg·h/mL, respectively, in rats and 3.08 μg/mL and 18.4 μg·h/mL, respectively, in rabbits, which were 4.8- and 9.2-fold (rats) and 1.1- and 1.4-fold (rabbits) the clinical exposure.[16)]

Table 12. Reproductive and developmental toxicity studies

Study type	Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Attached document CTD
Embryo-fetal development study	Female rats (Sprague Dawley)	p.o.	Gestation Day 6-17 (QD)	0, 30, 100, 300, 600	Maternal animals: ≥100: Reduced body weight gain ≥300: Decreased food consumption 600: Pale feces, decreased body weight, dark red uterine contents Embryos/fetuses: No effect on embryos or fetuses	Not evaluated	4.2.3.5.2-1
	Female rats (Sprague Dawley)	p.o.	Gestation Day 6-17 (QD)	0, 30, 100, 300, 600	Maternal animals: ≥300: Decreased food consumption, pale feces 600: Decreased feces, decreased body weight Embryos/fetuses: ≥300[a)]: Skeletal variations (short extra ribs, complete extra ribs, incomplete ossification of vertebral arch) 600: Increased embryo-fetal mortality, decreased live fetuses/live fetus rate, visceral anomalies (small accessory lobe of the liver), skeletal anomalies (costal cartilage anomaly, fusion of sternebrae), skeletal variations (decreased frequency of the first cervical vertebra ossification, unossified/malaligned sternebrae)	Maternal animals (general toxicity and reproductive toxicity): 300 Embryo-fetal development: 300	4.2.3.5.2-2
	Female rabbits (NZW)	p.o.	Gestation Day 7-20 (QD)	0, 10, 30, 100	Maternal animals: Death: 100 (1 of 8 animals) 100: Decreased feces, decreased body weight/food consumption Embryos/fetuses: 100: Increased embryo-fetal mortality, decreased live fetus rate	NOAEL was not evaluated.	4.2.3.5.2-4
	Female rabbits (NZW)	p.o.	Gestation Day 7-20 (QD)	0, 10, 30, 100	Maternal animals: Death or moribund euthanasia: 30 (1 of 22 animals), 100 (2 of 22 animals) 100: Decreased feces, decreased body weight/food consumption, abortion, premature birth Embryos/fetuses: 100: Increased embryo-fetal mortality, decreased live fetuses/live fetus rate	Maternal animals (general toxicity and reproductive toxicity): 10 Embryo-fetal development: 30	4.2.3.5.2-5

a) They were considered to disappear during the developmental process and thus not toxicities.

5.6 Other toxicity studies

5.6.1 Immunotoxicity

A T-cell-dependent antibody production assay was conducted in rats (Table 13). A decrease in T-cell-dependent antibody production was observed, which was considered to be a change related to the pharmacological action of tirabrutinib.

Table 13. Immunotoxicity study

Study type	Test system	Treatment period	Dose (mg/kg/day)	Main findings	Attached document CTD
T-cell-dependent antibody production assay	Male and female rats (Sprague Dawley)	4 weeks (QD) + 4-week withdrawal	0, 10, 30, 100	≥10: Decreases in anti- KLH IgM antibody titer and anti-KLH IgG antibody titer Reversibility: reversible	4.2.3.7.2-1

5.6.2 Photosafety

An *in vitro* phototoxicity assay was conducted using a mouse fibroblast cell line (Table 14). Tirabrutinib was considered not to be phototoxic.

Table 14. Photosafety study

Study type	Test system	Method	Main findings	Attached document CTD
In vitro	Mouse fibroblast strain Balb/c 3T3	0.781-100 μg/mL (with UVA irradiation[a)]) 0.781-100 μg/mL (without UVA irradiation)	Nonphototoxic	4.2.3.7.7-1

a) Irradiated with UVA (5 J/cm^2) for 50 minutes.

5.6.3 Studies on the mechanism of toxicity

5.6.3.1 Study on the cause of death of rats after the administration of tirabrutinib

The cause of death of rats after the administration of tirabrutinib was investigated (Table 15). Death occurred after abnormal gait, self-biting, ataxic gait, etc., based on which the applicant explained that the death of rats in the 4-week repeated oral toxicity study [see Section 5.2] was possibly caused by the effect of tirabrutinib on the central nervous system.

Table 15. Study on the cause of death of rats after the administration of tirabrutinib

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings	Attached document CTD
Female rats (Sprague Dawley)	p.o.	4 days (QD)	0, 100, 300, 600, 1,000	Death: 1,000 (2 of 8 animals), eyelid ptosis ≥300: Abnormal gait, 1,000[a)]: Self-biting, ataxic gait, lateral position	4.2.3.7.3-1 Reference

a) Abnormal gait, self-biting, ataxic gait, and lateral position observed in 2 animals resolved after the withdrawal period after a single-dose and 2-day repeated-dose administration, respectively.

5.6.3.2 Study on pancreatic toxicity

Because of pancreatic toxicity observed in the repeated-dose toxicity study in rats [see Section 5.2], a study was conducted to investigate the cause of the toxicity (Table 16). Tirabrutinib caused abnormal glucose tolerance and other changes probably related to pancreatic toxicity. The applicant explained that the pancreatic toxicity observed in rats is unlikely to pose any problem in human in the clinical use of tirabrutinib, given the results of toxicity studies on other BTK inhibitors including ibrutinib, a drug approved in Japan, which suggest that pancreatic toxicity owing to BTK inhibition occurs in rats of the Sprague Dawley strain (*J Pharmacol Exp Ther.* 2017;360:226-38).

Table 16. Study on pancreatic toxicity

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings	Attached document CTD
Male rats (Sprague Dawley)	p.o.	12/26 weeks (QD) + 4 or 8-week withdrawal	0, 300	Death: 300 (1 of 20[a)] animals), sedation, bradypnea, hypothermia 300: Abnormal glucose tolerance,[b)] low body weight, brown spots in pancreas, enlarged/yellow/white-spotted liver, white adrenals, enlarged kidney, pancreatic islet fibrosis/mononuclear cell infiltration in interstitium, mutated hepatocyte foci in liver, eosinophilic change/necrosis/crystal deposition in liver cells, increased lipid content in adrenal fascicular and glomerular zones, extramedullary hematopoiesis in spleen, disarrangement/fissure/chondromyxoid degeneration of femoral epiphyseal cartilage plates Reversibility: Reversible except for the findings of femoral epiphyseal cartilage plates	4.2.3.7.3-2 Reference

a) The sum of the animals in 12- and 26-week repeated administration groups (5 each) and those in the groups of 26-week repeated oral administration followed by a 4- and 8-week washout period (5 animals each).
b) As compared with the control group, decreased blood insulin and increased glucose were observed after glucose loading (oral administration of 2 g/kg glucose).

5.6.3.3 Study on mutated liver cell foci

Proliferative activity of mutated hepatocyte foci was investigated in the liver of male and female rats (n = 10/sex/group) in the 300 mg/kg/day group of the 13-week repeated-dose toxicity study and male rats (n = 5/group) in the 300 mg/kg/day group of the 26-week repeated-dose study to investigate pancreatic toxicity (Table 17). Tirabrutinib did not cause any change suggestive of proliferative activity of hepatocytes, based on which the applicant explained that tirabrutinib is unlikely to have hepatocarcinogenic potential in rats.

Table 17. Study on proliferative activity of mutated hepatocyte foci

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings	Attached document CTD
Male and female rats (Sprague Dawley)	p.o.	13 weeks (QD)	0, 300	300: No effect on the area or number of GST-P-positive hepatocyte foci or on the percentage of Ki-67-positive cells. No mutated hepatocyte foci.	4.2.3.7.3-3
Male rats (Sprague Dawley)	p.o.	26 weeks (QD)	0, 300	300: No effect on the area or number of GST-P-positive hepatocyte foci or on the percentage of Ki-67-positive cells. Mutated hepatocyte foci present (GST-P and Ki-67 negative in the mutated foci)	4.2.3.7.3-4 Reference

5.6.4 Toxicity of impurities

In accordance with ICH Q3A and Q3B guidelines, the evaluation of general toxicity and genotoxicity was performed on the impurities in tirabrutinib (Impurities A, B, C, and D) and impurities in the drug product (Impurity A) that were subjected to safety assessment.

General toxicity was evaluated by a 4-week repeated-dose toxicity study using tirabrutinib and the Drug Substances A and B spiked with the impurities (Table 18). No safety concern associated with impurity spiking was observed.

Based on the results of the genotoxicity study using the drug substance containing these impurities[17] [see Section 5.3] and the results of the *in silico* (quantitative) structure-activity relationship ([Q]SAR), it was determined that these impurities are unlikely to be genotoxic.

Table 18. Repeated-dose toxicity study on impurities

Test system	Route of administration	Treatment period	Dose (mg/kg/day)	Main findings	Attached document CTD
Male and female rats (Sprague Dawley)	p.o.	4 weeks (QD)	0, 10 (tirabrutinib), 10 (Drug Substance A),[a] 10 (Drug Substance B),[b]	10: Regardless of impurities, pancreatic changes (bleeding/inflammatory cell infiltration/fibrosis around pancreatic islets, atrophy/degeneration of acinar cells) were observed (male).	4.2.3.7.6-1

a) Contains Impurities A (0.66%), B (2.0%), C (0.07%), and D (0.70%).
b) Contains Impurities A (1.7%), B (0.06%), C (0.91%), and D (<0.05%).

5.R Outline of the review conducted by PMDA

On the basis of the data submitted and the results of the review in the following sections, PMDA concluded that the applicant's explanation about the toxicity of tirabrutinib is acceptable.

5.R.1 Effect on central nervous system

The applicant's explanation:

(a) Tirabrutinib affected the central nervous system of rats and monkeys [see Sections 3.3.1, 5.2, and 5.6.3.1], possibly inducing serious toxicity including death [see Section 5.6.3.1]. (b) The safety margin between the clinical dose and the NOAEL for the central nervous system (60 and 30 mg/kg/day, respectively, in rats and monkeys) was approximately 1 in both animal species [see Section 5.2]. The package insert will caution against the impacts of tirabrutinib on the central nervous system such as dyskinesia revealed in the toxicity studies.

PMDA's view:

Taking account of the applicant's explanation as well as the following factors, the package insert should give caution against the impacts of tirabrutinib on the central nervous system identified in the toxicity studies: (a) There is only limited use experience of tirabrutinib in humans until now, precluding a definite conclusion on the effect of tirabrutinib on the central nervous system, and (b) patients with brain lesion have partially impaired blood-brain barrier function at the tumor site, possibly resulting in a higher exposure of the entire brain tissue to tirabrutinib.

5.R.2 Use of tirabrutinib to pregnant women or women who may possibly be pregnant

The applicant's explanation:

The reproductive and developmental toxicity studies on tirabrutinib revealed embryo-fetal toxicity (rats and rabbits) and teratogenicity (rats) [see Section 5.5], suggesting possible adverse effects of tirabrutinib on fetuses if administered to pregnant women or women who may possibly be pregnant. The administration of tirabrutinib to this patient population is therefore not highly recommended. However,

[17] Contains Impurity A (0.91%) and Impurity B (0.26%).

given the poor prognosis of PCNSL, the use of tirabrutinib to these patients should be allowed if the expected therapeutic benefits outweigh the possible risks associated with treatment, with the premise that the physician and the patient fully understand the potential risk of tirabrutinib in the fetus. This will be highlighted in the package insert in an appropriate manner.

PMDA accepted the explanation of the applicant.

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

In this section, the dose and concentration of tirabrutinib are expressed in terms of free base.

6.1 Summary of biopharmaceutic studies and associated analytical methods

Oral tirabrutinib are available in capsules and tablets. The PK, etc. of tirabrutinib were investigated using these formulations (Table 19).

Table 19. Formulations used in each clinical study

Formulation	Study
Capsules (10, 25, and 100 mg)	Japanese Phase I studies (Studies 01 and 04[*1]), foreign Phase I studies (Studies POE001 and 1767[*2])
Tablet A (100 mg)	Foreign Phase I study (Study 1767)
Table B (100 mg)	Foreign Phase I study (Study 1765) and foreign Phase I study (Study 1767)
Proposed commercial tablets (80 mg)	Japanese Phase I study (Study 04[*1]), Japanese Phase I/II study (Study 02)

*1 10 mg capsules were used only in the study on drug-drug interaction with itraconazole. Proposed commercial tablets were used in other studies including the study on food effect.
*2 25 and 100 mg capsules were used.

6.1.1 Assay

Tirabrutinib in human plasma, cerebrospinal fluid, and urine was determined by liquid chromatography/tandem mass spectrometry (LC-MS/MS). The lower limit of quantitation was 1.00, 0.100, and 20.0 ng/mL, respectively.

6.1.2 Japanese clinical study

6.1.2.1 Japanese Phase I study (CTD 5.3.3.4-3, Study ONO-4059-04 [Study 04], Part A [[redacted] to [redacted] 20[redacted]])

A 2-treatment, 2-period cross-over study was conducted in 12 healthy adults (12 subjects included in the PK analysis) to investigate the food effect on PK of tirabrutinib (proposed commercial tablets).

A single dose of tirabrutinib (320 mg) was administered orally under fasting conditions (fasted from 10 hours pre-dose until 4 hours post-dose) or after the standard meal (lipids accounting for ≤20% of total calorie [≤700 kcal]), with a ≥2-day washout period between treatment periods.

The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of tirabrutinib taken after the standard meal to that under fasting conditions were 1.74 [1.40, 2.17] and 1.29 [1.14, 1.45], respectively. The applicant explained that exposure to tirabrutinib increased with food consumption because the solubility of tirabrutinib was increased by bile acid secreted upon food intake.

6.1.3 Foreign clinical study

6.1.3.1 Foreign Phase I study (CTD 5.3.3.4-2, Study GS-US-401-1767 [Study 1767], Cohort 3 [[redacted] to [redacted] 20[redacted]])

An open-label, randomized study was conducted in 24 healthy adults (24 subjects included in the PK analysis) to investigate the effect of omeprazole (proton pump inhibitor) on the PK of tirabrutinib.

A single dose of tirabrutinib (Tablet A 100 mg or Capsule 75 mg) was administered on Days 1 and 8 under fasting conditions, with multiple oral QD administration of omeprazole (20 mg) under fasting conditions on Days 4 through 8.

The least squares geometric mean ratios [90% CI] of C_{max} and AUC_{inf}, respectively, of tirabrutinib in combination with omeprazole to that of tirabrutinib alone were 0.92 [0.75, 1.11] and 1.05 [0.99, 1.11] for Tablet A and 0.80 [0.69, 0.94] and 1.06 [1.02, 1.10] for Capsule 75 mg.

Based on the above, the applicant explained that the combination of tirabrutinib with a drug affecting intragastric pH, such as proton pump inhibitors, is unlikely to cause a pharmacokinetic interaction.

6.2 Clinical pharmacology

The PK of tirabrutinib in healthy adults and patients with cancer was investigated using tirabrutinib alone or in combination with itraconazole or rifampicin. Also, the effect of tirabrutinib on the PK of midazolam was investigated.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese Phase I study (CTD 5.3.3.2-2, Study 01 [ongoing since January 2015 (data cut-off January 4, 2018)])

An open-label, uncontrolled study was conducted in 17 patients with recurrent or refractory B-NHL or CLL (17 patients included in the PK analysis) to investigate the PK, etc. of tirabrutinib.

Tirabrutinib was administered orally QD (160, 320, or 480 mg) or BID (300 mg) under fasting conditions, and plasma tirabrutinib concentration was investigated.

Table 20 shows PK parameters of tirabrutinib. The accumulation index[18)] of tirabrutinib (480 mg) was 1.76.

[18)] Ratio of AUC_{12h} on Day 28 to that on Day 1.

Table 20. PK parameters of tirabrutinib

Dosage regimen	Day of administration	n	C_{max} (ng/mL)	t_{max}*1 (h)	AUC_{12h} (ng•h/mL)	AUC_{24h} (ng•h/mL)	$t_{1/2}$ (h)
160 mg QD	1	3	611 ± 62.7	2.85 (1.92, 3.03)	2,860 ± 480	3,290 ± 555	4.96 ± 1.13
	28	3	484 ± 64.1	3.00 (2.95, 3.92)	2,590 ± 179	-	4.52 ± 1.38
320 mg QD	1	3	1,220 ± 266	2.00 (1.83, 4.08)	4,960 ± 527	5,700 ± 578	4.92 ± 0.745
	28	3	971 ± 394	3.00 (1.92, 4.05)	5,370 ± 1,140	-	4.47 ± 3.02
480 mg QD	1	4	1,280 ± 440	2.93 (2.70, 3.08)	6,790 ± 1,930	8,500 ± 1,700	6.38 ± 2.80
	28	4	1,940 ± 780	3.61 (2.20, 4.07)	12,100 ± 4,400	-	3.07 ± 0.486
300 mg BID	1	7	886 ± 311	2.85 (1.83, 11.7)	4,750 ± 1,580	-	4.37 ± 1.08*2
	28	4	961 ± 462	2.06 (0.900, 4.00)	5,510 ± 2,790	-	5.79 ± 2.64

Mean ± SD; *1 Median (range); *2 n = 5; -, Not calculated.

6.2.1.2 Japanese Phase I/II study (CTD 5.3.5.2-1, Study 02 [ongoing since October 2017 (data cut-off [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted in 44 patients with recurrent or refractory PCNSL (23 patients included in the PK analysis) to investigate the PK, etc. of tirabrutinib.
Tirabrutinib (320 or 480 mg[19)]) was administered orally QD, and tirabrutinib concentration in plasma and cerebrospinal fluid was investigated.

Table 21 shows the PK parameters of tirabrutinib. Tirabrutinib concentration (mean ± standard deviation [SD]) in cerebrospinal fluid before the dose on Day 28 was 2.19 ± 0.476 ng/mL at 320 mg and 14.0 ± 8.92 ng/mL at 480 mg.

Table 21. PK parameters of tirabrutinib

Dosage regimen	Day of administration	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{24h} (ng•h/mL)	$t_{1/2}$ (h)
320 mg Either fasted or non-fasted	1	3	2,070 ± 310	1.92 (1.88, 3.00)	7,050 ± 1,740	3.78 ± 0.349
	28	3	1,360 ± 229	1.97 (1.92, 3.00)	6,870 ± 898	2.89 ± 0.928
480 mg Either fasted or non-fasted	1	3	2,140 ± 868	1.87 (1.08, 6.03)	13,400 ± 6,480	4.72 ± 1.57
	28	3	2,270 ± 556	3.92 (3.05, 3.97)	13,500 ± 3,260	3.31 ± 0.600
480 mg Fasted	1	6	1,760 ± 929	2.49 (1.93, 6.20)	9,830 ± 2,650	5.21 ± 1.49
	28	5	2,690 ± 1,120	2.87 (2.05, 3.98)	13,400 ± 3,910	3.55 ± 0.841

Mean ± SD; * Median (range)

6.2.2 Foreign clinical studies

6.2.2.1 Foreign Phase I study (CTD 5.3.3.1-1, Study GS-US-401-1768 (Study 1768) [[redacted] to [redacted] 20[redacted]])

An open-label, uncontrolled study was conducted in 8 healthy adults (8 subjects included in the PK analysis) to investigate mass balance.

A single dose of ^{14}C-labeled tirabrutinib (75 mg) was administered orally under fasting conditions, and radioactivity concentrations in blood, plasma, urine, and feces were investigated.

19) At the start of the study, there was no rule of meal timing (tirabrutinib could be administered in either fasted or non-fasted state), and the group receiving tirabrutinib 480 mg (fasted) was added during the study [see Section 7.1.2.2]. Tirabrutinib concentration in cerebrospinal fluid was not measured in the group receiving 480 mg (fasted).

The ratio of blood/plasma radioactivity concentration up to 48 hours post-dose was 0.650 to 1.10, based on which the applicant explained that tirabrutinib or its metabolites are distributed in blood cells to only a limited extent. Mainly M33 (sulfate conjugate of hydroxylated form), M12 (glucuronate conjugate of hydroxylated form), and unchanged tirabrutinib were detected in the plasma up to 24 hours post-dose (accounting for 33.1%, 28.6%, and 17.3%, respectively, of total radioactivity in plasma).

The radioactivity excretion rate in urine and feces (percentage relative to the administered radioactivity) up to 360 hours post-dose was 42.1% and 52.2%, respectively. Mainly M33, M26 (cysteine conjugate), and M12 were detected in urine up to 96 hours post-dose (16.3%, 8.33%, 4.94%, respectively). Unchanged tirabrutinib was not detected. Mainly M35 (reduced form of water adduct) and M29 (oxidized form) were detected in feces up to 96 hours post-dose (7.58% and 7.18%, respectively). The unchanged tirabrutinib also was detected (1.49%). The applicant explained that tirabrutinib is well absorbed from the digestive tract, in light of the percentages of radioactivity excreted in urine and that excreted in feces in the form of metabolites.

6.2.2.2 Foreign Phase I study (CTD 5.3.3.2-1, Study POE001 [August 2012 to December 2015])

An open-label, uncontrolled study was conducted in 90 patients with recurrent or refractory B-NHL or CLL (89 patients included in the PK analysis) to investigate the PK of tirabrutinib.

Tirabrutinib (20-600 mg) was administered orally QD or BID, and plasma tirabrutinib concentration was investigated.

Table 22 shows the PK parameters of tirabrutinib. AUC of tirabrutinib was roughly linear within the range of dose administered QD, whereas C_{max} of tirabrutinib was non-linear. The applicant explained that the dissolution rate of tirabrutinib decreased with increased dose and led to the non-linear response of C_{max}.

Table 22. PK Parameters of tirabrutinib

Dosage regimen	Day of administration	n	C_{max} (ng/mL)	t_{max}[*1] (h)	AUC_{12h} (ng•h/mL)	AUC_{24h} (ng•h/mL)	$t_{1/2}$ (h)
20 mg QD	1	6	63.7 ± 17.9	2.00 (1.00, 3.00)	252 ± 78.2	294 ± 96.3	5.9 ± 0.67
	28	6	73.4 ± 18.3	1.00 (1.00, 2.00)	285 ± 67.6	306 ± 74.9	3.2 ± 0.80
40 mg QD	1	6	163 ± 25.3	1.00 (1.00, 4.00)	583 ± 82.0	667 ± 97.6	5.4 ± 1.3
	28	6	165 ± 47.2	1.50 (1.00, 3.07)	582 ± 244	660 ± 311	3.5 ± 1.2
80 mg QD	1	9	260 ± 102	1.17 (1.00, 2.17)	769 ± 367	850 ± 414	5.3 ± 1.1
	28	5	241 ± 90.7	1.08 (1.00, 2.00)	729 ± 367	762 ± 375	2.8 ± 0.62
160 mg QD	1	11	521 ± 207	2.03 (1.02, 3.17)	2,030 ± 815	2,340 ± 887	6.0 ± 3.4
	28	10	540 ± 142	2.14 (0.93, 3.02)	2,380 ± 840	2,680 ± 1,060	3.5 ± 1.2
320 mg QD	1	24	870 ± 371	2.07 (1.00, 4.08)	3,670 ± 1,210	4,300 ± 1,530	5.6 ± 2.6
	28	17	1,180 ± 380	2.00 (1.00, 4.00)	5,060 ± 1,630	5,660 ± 1,830	3.9 ± 2.0
400 mg QD	1	3	1,260 ± 1,020	2.02 (2.00, 6.13)	5,540 ± 3,760	6,840 ± 3,740	14 ± 15
	28	2	473, 1,180	2.08, 3.02	2,690, 6,930	3,020, 7,500	2.7, 3.4
480 mg QD	1	10	1,100 ± 463	2.00 (0.92, 2.15)	5,280 ± 1,890	6,700 ± 2,290	8.5 ± 3.8
	28	7	1,240 ± 517	2.00 (1.97, 4.08)	6,800 ± 1,910	8,000 ± 2,010	4.4 ± 0.92
500 mg QD	1	3	1,660 ± 605	2.00 (2.00, 2.08)	5,630 ± 561	6,600 ± 428	5.9 ± 0.58
	28	3	1,230 ± 286	2.00 (1.95, 3.00)	5,940 ± 962	6,770 ± 1,030	4.0 ± 0.70
600 mg QD	1	11	1,510 ± 594	2.08 (1.00, 3.00)	7,120 ± 1,940	8,330 ± 1,970	6.3 ± 3.4
	28	6	1,270 ± 486	2.58 (2.00, 4.33)	7,320 ± 2,450[*2]	8,440 ± 2,500[*2]	4.3 ± 1.6[*2]
240 mg BID	1	3	594 ± 169	2.00 (2.00, 2.22)	2,900 ± 571	-	6.0 ± 2.4
	28	3	704 ± 255	1.92 (1.25, 2.00)	3,420 ± 1,300	-	3.9 ± 0.29
300 mg BID	1	3	796 ± 71.5	2.00 (2.00, 4.00)	3,720 ± 1,290	-	2.8 ± 0.57
	28	3	674 ± 93.8	3.00 (2.07, 4.00)	2,360, 4,240[*3]	-	2.4, 3.4[*3]

Mean ± SD (individual values for n = 2); *[1] Median (range); *[2] n = 5; *[3] n = 2; -, Not calculated.

6.2.3 Drug-drug interactions

6.2.3.1 Study on interaction with itraconazole or midazolam (CTD 5.3.3.4-3, Study 04, Part B and C [[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 24 healthy adults (24 subjects included in the PK analysis)[20] to investigate the effect of itraconazole (potent CYP3A inhibitor) on the PK of tirabrutinib and the effect of tirabrutinib on the PK of midazolam (substrate of CYP3A) [see Section 6.1.2.1 for Part A].

The dosage regimen is shown below. A washout period of ≥2 days was set between the treatment periods.

Part B: In the first period, a single dose of tirabrutinib 20 mg was administered orally after a meal on Day 1. In the second period, itraconazole 200 mg was administered orally QD after a meal on

[20] In Parts B and C, 12 each of subjects (12 subjects included in the PK analysis) were enrolled.

Days 1 through 4, and a single dose of tirabrutinib 20 mg was administered orally after a meal on Day 4.

Part C: In the first period, a single dose of midazolam 2 mg was administered orally under fasting conditions on Day 1. In the second period, tirabrutinib 320 mg was administered orally QD after a meal on Days 1 through 5, and a single dose of midazolam 2 mg was administered orally under fasting conditions.

The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of tirabrutinib co-administered with itraconazole to those of tirabrutinib alone were 1.24 [1.14, 1.35] and 1.49 [1.39, 1.59], respectively. The geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of midazolam co-administered with tirabrutinib to those of midazolam alone were 0.74 [0.65, 0.84] and 0.79 [0.69, 0.90], respectively. Accordingly, the applicant explained that the concomitant use of tirabrutinib with substrates of CYP3A is unlikely to cause pharmacokinetic interactions, and that caution against the use of tirabrutinib in combination with substrates of CYP3A is unnecessary.

6.2.3.2 Study on interaction with rifampicin (CTD 5.3.3.4-1, Study GS-US-401-1765 [Study 1765] [[redacted] to [redacted] 20[redacted]])

An open-label study was conducted in 15 healthy subjects (15 subjects included in the PK analysis) to investigate the effect of rifampicin (a single dose of which inhibits OATP1B1 and OATP1B3, while multiple doses of which potently induce CYP3A) on the PK of tirabrutinib.

On Day 1, a single dose of tirabrutinib 100 mg was administered orally under fasting conditions. On Day 8, tirabrutinib 100 mg and rifampicin 600 mg were administered orally under fasting conditions. On Days 10 through 16, rifampicin 600 mg was administered orally QD under fasting conditions. On Day 17, a single dose of tirabrutinib 100 mg was administered orally under fasting conditions.

The least squares geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of tirabrutinib (a) with a single dose of rifampicin (Day 8) to that of tirabrutinib alone and (b) with multiple-dose of rifampicin (Day 17) were (a) 1.30 [1.11, 1.51] and 1.11[1.01, 1.22], respectively, and (b) 0.30 [0.26, 0.36] and 0.29 [0.27, 0.32], respectively. Based on the results, the applicant explained that the concomitant use of tirabrutinib with an OATP1B1 or OATP1B3 inhibitor is unlikely to cause pharmacokinetic interactions and therefore caution against the use of tirabrutinib in combination with these inhibitors is unnecessary.

6.2.4 Administration of tirabrutinib in patients with renal impairment

No clinical study was conducted in patients with renal impairment to investigate the effect of renal impairment on the PK of tirabrutinib.

The applicant's explanation:
Dose adjustment of tirabrutinib is not necessary in patients with renal impairment, in light of the following observations.

- Results of the foreign Phase I study (Study 1768) suggest that renal excretion contributes only minimally to the elimination of tirabrutinib [see Section 6.2.2.1].

- A pooled analysis of the Japanese Phase I study (Study 01), Japanese Phase I/II study (Study 02), and foreign Phase I study (Study POE001) was conducted. In patients[21] with normal renal function (14 patients), mild renal impairment (10 patients), or moderate renal impairment (7 patients) receiving tirabrutinib according to the proposed dosage regimen, the incidence of all-Grade adverse events was 100%, 80.0%, and 85.7%, respectively, and the incidence of Grade ≥3 adverse events was 57.1%, 40.0%, and 71.4%, respectively, showing no clear relationship between the severity of renal impairment and the incidence of adverse events.

6.2.5 Relationship between exposure and change in QT/QTc interval

On the basis of the results of Japanese clinical studies (Studies 01 and 02), a relationship between plasma tirabrutinib concentration and change in QT interval corrected by Fridericia's method (QTcF) from baseline (ΔQTcF) was investigated using a linear mixed effect model. No clear relationship was observed between plasma tirabrutinib concentration and ΔQTcF. Also, the upper limit of 90% CI of ΔQTcF was estimated to be <10 milliseconds at C_{max} (mean 2,690 ng/mL) of multiple doses of oral tirabrutinib 480 mg administered QD under fasting conditions.

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

6.2.6 PPK analysis

On the basis of the PK data (2,386 measuring time points in 130 patients) on tirabrutinib obtained from the Japanese clinical studies (Studies 01 and 02) and the foreign clinical study (Study POE001), a population pharmacokinetic (PPK) analysis was conducted using a nonlinear mixed-effects model (software NONMEM Version 7.3). The PK of tirabrutinib was described by a 2-compartment model with first order absorption process.

Possible covariates for (a) CL/F, (b) volume of distribution of the central compartment (V2/F), and (c) absorption rate constant (ka), respectively, were (a) body weight, age, estimated glomerular filtration rate (eGFR), dose, sex, race, hepatic impairment,[22] Eastern Cooperative Oncology Group (ECOG) performance status (PS), carcinoma, and concomitant use with CYP3A or P-gp inhibitor, (b) body weight, eGFR, sex, and race, and (c) dose. As a result of assessment, body weight was identified as a significant covariate for CL/F and V2/F, and dose. The applicant explained that these covariates are unlikely to have a clinically significant effect on the PK of tirabrutinib, given their limited effect on the PK parameters of tirabrutinib.

6.2.7 Relationship between exposure and efficacy or safety

On the basis of the results of treatment according to the proposed dosage regimen in the Japanese Phase I/II study (Study 02), relationship between exposure[23] to tirabrutinib (C_{max} and AUC under steady state)

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[21] Renal function was classified according to the following criteria: normal, eGFR ≥90 mL/min/1.73 m^2; mild impairment ≥60 mL/min/1.73 m^2 and <90 mL/min/1.73 m^2; and moderate impairment ≥30 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2.

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

[23] Estimated by the PPK analysis [see Section 6.2.6].

and efficacy was investigated. No clear relationship was observed between exposure to tirabrutinib and efficacy.

On the basis of the results of treatment according to the proposed dosage regimen in the Japanese Phase I study (Study 01), Japanese Phase I/II study (Study 02), and foreign Phase I study (Study POE001), relationship between exposure[23)] to tirabrutinib (C_{max} and AUC under steady state) and adverse events (all-Grade adverse events and Grade ≥3 adverse events) for which a causal relationship to tirabrutinib could not be ruled out was investigated. No clear relationship was observed between exposure to tirabrutinib and the occurrences of the adverse events of concern.

6.2.8 Difference in PK between Japanese and non-Japanese patients

The applicant's explanation about the difference in PK of tirabrutinib between Japanese and non-Japanese patients:

Difference in the PK of tirabrutinib between Japanese and non-Japanese patients was investigated based on the PK data of tirabrutinib obtained from the Japanese Phase I study (Study 01) and the foreign Phase I study (Study POE001). C_{max} and AUC_{24h} of tirabrutinib on Day 1 tended to be higher in Japanese patients than in non-Japanese patients [see Sections 6.2.1.1 and 6.2.2.2].

Because (a) the mean body weight differed between patients in Study 01 and patients in Study POE001 (54.3 kg and 76.2 kg, respectively), and (b) body weight was identified as a significant covariant for CL/F in the PPK analysis [see Section 6.2.6], the PK of tirabrutinib in Japanese patients and non-Japanese patients was compared based on C_{max} and AUC_{24h} on Day 1 in Studies 01 and POE001 adjusted for body weight (Table 23). Results showed no clear difference in body weight-adjusted C_{max} and AUC_{24h} of tirabrutinib between Japanese and non-Japanese patients.

Thus, the difference in the body weight may possibly have caused the observed difference in the PK of tirabrutinib between Japanese and non-Japanese patients. Nevertheless, in light of no clear difference in body weight-adjusted C_{max} and AUC_{24h} of tirabrutinib between Japanese and non-Japanese patients, there is no clear difference in the PK of tirabrutinib between these patient populations.

Table 23. Body weight-adjusted PK parameters of tirabrutinib*

	Dose (mg)	n	C_{max} (ng/mL/mg/kg)	AUC_{24h} (ng•h/mL/mg/kg)
Japanese patients	160	3	209 ± 41.0	1,130 ± 304
	320	3	203 ± 5.09	995 ± 324
	480	4	144 ± 55.4	945 ± 200
Non-Japanese patients	160	11	238 ± 80.7	1,100 ± 416
	320	24	204 ± 92.9	998 ± 361
	480	10	180 ± 88.0	1,080 ± 414

Mean ± SD; * Adjusted for dose per kg of body weight.

6.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA concluded that the applicant's explanation about the clinical pharmacology, etc. of tirabrutinib is acceptable, except for the matters mentioned in the following subsections.

6.R.1 Timing of tirabrutinib treatment

The applicant's explanation about the dose timing of tirabrutinib:

In the Japanese Phase I study (Study 04), the geometric mean ratios [90% CI] of C_{max} and AUC_{inf} of tirabrutinib administered after the standard meal to that administered under fasting conditions were 1.74 [1.40, 2.17] and 1.29 [1.14, 1.45], respectively. This suggested increased exposure to tirabrutinib after fed administration as compared to that following fasted administration [see Section 6.1.2.1].

In response to these results, a new treatment group receiving tirabrutinib 480 mg QD under fasting conditions (administered 1 hour before or 2 hours after a meal) was added in the Japanese Phase I/II study (Study 02) in patients with recurrent or refractory PCNSL, and the results demonstrated clinical benefits of tirabrutinib.

Accordingly, the administration of tirabrutinib should be avoided from 1 hour before until 2 hours after a meal, and this caution is to be given in the "Precautions for Dosage and Administration" section of the package inert [see Section 7.R.5].

PMDA accepted the explanation of the applicant.

6.R.2 Administration of tirabrutinib in patients with hepatic impairment

No clinical study was conducted in patients with hepatic impairment to investigate the effect of hepatic impairment on PK of tirabrutinib.

The applicant's explanation about the administration of tirabrutinib to patients with hepatic impairment:

Because tirabrutinib is mainly eliminated by metabolism in the liver [see Section 6.2.2.1], hepatic impairment may affect the PK of tirabrutinib. However, the dose adjustment of tirabrutinib is not necessary for patients with mild hepatic impairment, given the observations below. For treatment in patients with moderate or severe hepatic impairment, it is difficult to draw a definite conclusion on the dose adjustment due to the lack of clinical study data on the administration of tirabrutinib in this patient population according to the proposed dosage regimen. The lack of clinical studies involving this patient population is to be informed via the package insert.

- In the foreign Phase I study (Study POE001), C_{max} and AUC_{24h} of tirabrutinib on Day 1 in 3 patients with mild hepatic impairment receiving tirabrutinib 480 mg (765 ± 456 ng/mL and 5,100 ± 2,440 ng•h/mL, respectively) did not tend to be higher than those in 7 patients with normal hepatic function (1,240 ± 417 ng/mL and 7,390 ± 2,000 ng•h/mL, respectively). In 2 patients with severe hepatic impairment receiving tirabrutinib 320 mg in the foreign Phase I study (Study POE001), C_{max} (394 and 497 ng/mL) and AUC_{24h} (3,910 and 4,120 ng•h/mL) of tirabrutinib were within the range shown in 21 patients with normal hepatic function (355-1,580 ng/mL and 1,920-8,060 ng•h/mL, respectively).

- Of 130 patients subjected to the PPK analysis, 16 had mild hepatic impairment and 3 had severe hepatic impairment.[24] Hepatic impairment was not identified as a significant covariate for the PK of tirabrutinib [see Section 6.2.6].

- In the pooled analysis of the Japanese Phase I study (Study 01), Japanese Phase I/II study (Study 02), and the foreign Phase I study (Study POE001), the incidence of (a) all-Grade and (b) Grade ≥3 adverse events in patients with normal hepatic function (27 patients) and patients with mild hepatic impairment[22] (4 patients) receiving tirabrutinib according to the proposed dosage regimen was (a) 92.6% and 75.0%, and (b) 59.3% and 25.0%, respectively, showing no clear difference between the groups.

PMDA's view:
PMDA generally accepted the explanation of the applicant. However, tirabrutinib is mainly eliminated by liver metabolism, and safety information of tirabrutinib in patients with hepatic impairment is extremely limited. Therefore, careful use of tirabrutinib is essential for patients with hepatic impairment of any severity, and this should be communicated via the package insert. Data on the PK of tirabrutinib in patients with hepatic impairment are critical for the proper use of tirabrutinib and should be further collected. New findings should be communicated appropriately to healthcare professionals once available.

6.R.3 Pharmacokinetic interactions mediated by CYP3A

The applicant's explanation about concomitant use of tirabrutinib with a CYP3A inhibitor or inducer:
In the Japanese Phase I study (Study 04) and the foreign Phase I study (Study 1765), multiple doses of itraconazole (potent CYP3A inhibitor) or rifampicin (potent CYP3A inducer) affected the exposure to tirabrutinib [see Section 6.2.3]. Therefore, the effect of a CYP3A inhibitor or inducer on the PK of tirabrutinib was investigated using a physiologically based pharmacokinetics (PBPK) model.

Simcyp version 18 was used for the PBPK model analysis. Advanced dissolution, absorption and metabolism (ADAM) model was used as the absorption model, and the Full PBPK model was selected as the distribution model. The contribution rate of CYP3A to metabolism was determined to be 40% based on the results of the study on drug-drug interaction with itraconazole [see Section 6.2.3.1]. Simcyp default values were used for physiological parameters and compound parameters related to the CYP3A inhibitor and inducer. The use of PBPK model for the estimation of CYP3A-mediated pharmacokinetic interaction of tirabrutinib is considered appropriate, in light of the following observations:

- The exposure to tirabrutinib following multiple oral doses of tirabrutinib 480 mg in the Japanese Phase I/II study (Study 02) was nearly identical with the value estimated from the PBPK model, and change in plasma tirabrutinib concentration over time was similar between the measured values and the estimation.

[24] There were 316 and 54 time points, respectively, for plasma tirabrutinib concentration measurement in patients with mild and severe hepatic impairment.

- The ratio of the exposure to tirabrutinib following a dose of tirabrutinib alone to that following multiple doses of tirabrutinib with rifampicin was nearly identical between the value observed in the foreign Phase I study (Study 1765) and the value estimated from the above PBPK model.

- In terms of the ratio of the exposure to CYP3A substrate, such as midazolam, following administration with a CYP3A inhibitor or inducer to that of the substrate alone, the observed value (*Eur J Pharm Sci*. 2011;43:160-73, etc.) was nearly identical to the value estimated from the PBPK model.

Using the above-mentioned PBPK model, exposure to tirabrutinib was estimated under the following conditions: A single dose of tirabrutinib 480 mg was administered orally before and after 14-day oral administration of (a) clarithromycin (potent CYP3A inhibitor) 250 mg BID, (b) erythromycin (moderate CYP3A inhibitor) 500 mg QID, (c) diltiazem (moderate CYP3A inhibitor) 60 mg TID, (d) carbamazepine (potent CYP3A inducer) 400 mg BID, or (e) efavirenz (moderate CYP3A inducer) 600 mg QD. The geometric mean ratios of C_{max} and AUC of tirabrutinib used in combination with each drug to that after the administration of tirabrutinib alone were (a) 1.37 and 1.58, (b) 1.34 and 1.51, (c) 1.32 and 1.48, (d) 0.52 and 0.48, and (e) 0.56 and 0.46, respectively. Given these results and the results of the drug-drug interaction studies [see Section 6.2.3], the concomitant use of tirabrutinib with a moderate or potent CYP3A inhibitor or inducer requires caution, and this is to be communicated to healthcare professionals. On the other hand, the concomitant use of tirabrutinib with a weak CYP3A inhibitor or inducer does not require cautionary advice because they are unlikely to significantly affect exposure to tirabrutinib, in light of the contribution rate of CYP3A in tirabrutinib metabolism estimated as 40%, and the contribution rate of CYP3A in the metabolism of midazolam, a CYP3A substrate[25)] prone to drug-drug interaction, reported to be 93% (*Drug Metab Dispos*. 2007;35:246-55).

PMDA's view:
PMDA generally accepted the explanation of the applicant. Information on CYP3A-mediated pharmacokinetic interaction of tirabrutinib is important for confirming the appropriateness of cautionary advice against concomitant use with a CYP3A inhibitor or inducer based on the estimation from the PBPK model, relevant data should be collected continuously, and new findings should be communicated appropriately to healthcare professionals once available.

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

The applicant submitted efficacy and safety evaluation data in the form of results data from 2 Japanese Phase I studies, 1 Japanese Phase I/II study, and 1 foreign Phase I study as shown in Table 24. The applicant also submitted the results of 3 foreign Phase I studies as shown in Table 24 as reference data. In this section, the dose of tirabrutinib is expressed in terms of free base.

25) AUC of CYP3A substrate prone to drug-drug interaction increases by 1.25- to <2-fold when concomitantly administered with a weak CYP3A inhibitor and (b) decreases by 50% to 80% when concomitantly administered with a weak CYP3A inducer ("Guidelines on drug interaction for drug development and appropriate provision of information" (PSEHB/PED Notification No. 0723-(4), dated July 23, 2018). AUC of midazolam increased by 26% when concomitantly administered with ranitidine, a weak CYP3A inhibitor (*Clin Pharmacol Ther*. 1987;41:80-4).

Table 24. List of clinical studies on efficacy and safety

Data category	Region	Study ID	Phase	Study population	Number of enrollments	Dosage regimen	Main endpoint
Evaluation	Japan	01	I	Patients with recurrent or refractory B-NHL or CLL	17	Tirabrutinib was administered orally QD 160, 320, 480 mg or BID 300 mg (fasted).	Safety PK
		04	I	Healthy adults	36 (a)12 (b) 12 (c) 12	(a) A single dose of tirabrutinib 320 mg was administered orally (fasted or fed). (b) A single dose of tirabrutinib 20 mg was administered orally (fed) in combination with itraconazole. (c) Tirabrutinib 320 mg was administered orally QD (fed) for 5 days in combination with midazolam.	PK
		02	I/II	Patients with recurrent or refractory PCNSL	44 (a) 20 (b) 7 (c) 17	(a) Tirabrutinib 320 mg was administered orally QD. (b) Tirabrutinib 480 mg was administered orally QD. (c) Tirabrutinib 480 mg was administered orally QD (fasted).	Efficacy Safety PK
	Foreign	POE 001	I	Patients with recurrent or refractory B-NHL or CLL	90 (a) 62 (b) 28	(a) B-NHL: Tirabrutinib 20, 40, 80, 160, 320, 480, 600 mg QD or 240 mg BID was administered orally (fasted). (b) CLL: Tirabrutinib 20, 40, 80, 160, 320, 400, 500, 600 mg QD or 300 mg BID was administered orally (fasted).	Safety PK
Reference	Foreign	1765	I	Healthy adults	15	A single dose of tirabrutinib 100 mg was administered orally (fasted) in combination with rifampicin.	PK
		1767	I	Healthy adults	76 (a) 16 (b) 24 (c) 24 (d) 12	(a) A single dose of tirabrutinib 100 mg (capsule or tablet) was administered orally (fasted). (b) A single dose of tirabrutinib 100 mg-tablet or 75 mg-capsule was administered orally (fasted or fed). (c) A single dose of tirabrutinib 100 mg-tablet or 75 mg-capsule was administered orally (fasted) in combination with omeprazole. (d) A single dose of tirabrutinib 100 mg-tablet was administered orally (fasted or fed).	PK
		1768	I	Healthy adults	8	A single dose of tirabrutinib 75 mg was administered orally (fasted).	PK

Each clinical study is summarized below. Major adverse events other than death observed in each clinical study are summarized in Section "7.3 Adverse events, etc. observed in clinical studies," and clinical studies on PK in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Clinical pharmacology study

The applicant submitted results of the following clinical pharmacology study in healthy adults [see Section 6.2]. No death occurred during the study period.

7.1.1.1 Japanese Phase I study (CTD 5.3.3.4-3, Study 04 [[redacted] to [redacted] 20[redacted]])

7.1.2 Japanese clinical studies

7.1.2.1 Japanese Phase I study (CTD 5.3.3.2-2, Study 01 [ongoing since January 2015 (data cut-off January 4, 2018)])

An open-label, uncontrolled study was conducted in patients with recurrent or refractory B-NHL or CLL (maximum target sample size, 24 subjects) to investigate the safety, PK, etc. of tirabrutinib at 5 study sites in Japan.

Tirabrutinib 160, 320, or 480 mg was administered orally QD or 300 mg BID under fasting conditions until any discontinuation criterion was met.

All of the 17 patients enrolled in the study received tirabrutinib and were included in the safety analysis population. Of those in the safety analysis population, 15 patients[26] were included in dose limiting toxicity (DLT) evaluation.

During the DLT evaluation period of 28 days after the start of treatment, DLT was observed in 1 of 6 patients in the tirabrutinib 300 mg BID group (Grade 3 pneumonitis) but the maximum tolerated dose (MTD) was not reached.

No death occurred during the treatment with tirabrutinib or within 56 days after the end of treatment.

7.1.2.2 Japanese Phase I/II study (CTD 5.3.5.2-1, Study 02 [ongoing since October 2017 (data cut-off [redacted], 20[redacted])])

An open-label, uncontrolled study was conducted in patients with recurrent or refractory PCNSL[27] (target sample size, 6-12 subjects in Phase I [3-6 each in the 320 and 480 mg groups], 20 subjects in Phase II,[28] 15 subjects in the 480 mg fasted group in Phase II) to investigate the efficacy, safety, and PK of tirabrutinib at 12 study sites in Japan.

In Phase II of the study, tirabrutinib 480 mg was administered orally QD (either fasted or non-fasted) based on the results of Phase I. However, serious adverse events for which a causal relationship to tirabrutinib[29] could not be ruled out were observed in 4 of 7 patients after the start of Phase II, whereupon the enrollment in this group was stopped and switched to the 320 mg group. After the completion of patient enrollment in the 320 mg group, results of Study 04 on the food effect on tirabrutinib became available, which suggested that the PK of tirabrutinib is affected by food [see Section 6.R.1]. Therefore, the group receiving 480 mg under fasting conditions was newly added in Phase II.

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[26] 15 patients excluding 2 patients, 1 of whom with a compliance rate of <80% and the other who discontinued the treatment for a reason other than DLT

[27] Non-B-cell PCNSL was excluded.

[28] Includes patients who, in Phase I, received the dose for Phase II. Patients in Phase I who were treated according to the dosage regimen for the Phase II part were to proceed to Phase II.

[29] ILD/*Pneumocystis jirovecii* pneumonia (death) was observed in 1 of 3 patients who proceeded from the Phase I to Phase II, and erythema multiforme was observed in 3 of 4 patients newly enrolled in Phase II. (The causal relationship to tirabrutinib could not be ruled out. The symptom was serious in 2 of them.)

In the 320 mg and 480 mg groups, tirabrutinib was administered orally QD (either fasted or non-fasted). In the 480 mg fasted group, tirabrutinib was administered orally QD under fasting conditions.[30] In all treatment groups, treatment with tirabrutinib was continued until any discontinuation criterion was met.

All of the 44 patients enrolled in the study (20 in the 320 mg group, 7 in the 480 mg group, 17 in the 480 mg fasted group)[31] received tirabrutinib, and were included in the efficacy and safety analysis populations. Of patients in the safety analysis population, all of the 6 patients enrolled in Phase I (3 each in the 320 mg and 480 mg groups) underwent DLT evaluation.

The primary endpoint of the study was the response rate by centralized assessment based on International PCNSL Collaborative Group (IPCG) criteria (*J Clin Oncol*. 2005;23:5034-43). The response rate was evaluated using the pooled data from Phases I and II.

Table 25 shows the results of the primary endpoint, i.e., response rate[32] in the 320 mg group and the 480 mg fasted group, according to the centralized assessment based on IPCG criteria.

Table 25. Best overall response and response rates
(centralized assessment, efficacy analysis population, data cut-off [redacted], 20[redacted])

Best overall response	Number of patients (%)	
	320 mg n = 20	480 mg fasted n = 17
CR	2 (10.0)	1 (5.9)
CRu	3 (15.0)	5 (29.4)
PR	7 (35.0)	3 (17.6)
SD	4 (20.0)	3 (17.6)
PD	4 (20.0)	5 (29.4)
Response (CR, CRu, or PR) (response rate [95% CI] [%]*)	12 (60.0 [36.1, 80.9])	9 (52.9 [27.8, 77.0])

* Clopper-Pearson method

The response rate in patients with recurrent[33] PCNCL was 70.6% (12 of 17) in the 320 mg group and 64.3% (9 of 14) in the 480 mg fasted group The response rate in patients with refractory[34] PCNCL was 0% (0 of 3) in the 320 mg group and 0% (0 of 3) in the 480 mg fasted group.

No DLT was observed during the DLT evaluation period of 28 days after the start of administration, and tirabrutinib up to 480 mg was well tolerated.

Death occurred in 1 of 7 patients in the 480 mg group (interstitial lung disease [ILD]/*Pneumocystis jirovecii* pneumonia) during tirabrutinib treatment or within a 28-day post-treatment period.

30) Tirabrutinib was administered under fasting conditions before breakfast as a rule.
31) In the 320 mg group, 3 patients in Phase I and 17 patients in Phase II. In the 480 mg group, 3 patients in Phase I and 4 patients in Phase II. In the 480 mg fasting group, none proceeded from Phase I.
32) The threshold response rate was 14% by referring to the clinical study data of temozolomide in patients with recurrent or refractory PCNSL (*J Clin Neurosci*. 2012;19:1501-5).
33) Patients who showed partial response (PR) or better in the most recent treatment and changed to progressive disease (PD) later.
34) Patients who showed stable disease (SD) or PD in the most recent treatment.

7.1.3 Foreign clinical study

7.1.3.1 Foreign Phase I study (CTD 5.3.3.2-1, Study POE001 [August 2012 to December 2015])

An open-label, uncontrolled study was conducted in patients with recurrent or refractory B-NHL or CLL (target sample size, 54 patients for dose escalation [27 patients with B-NHL, 27 patients with CLL]; additional subjects of ≤86 for dose finding) to investigate the safety, PK, etc. of tirabrutinib at 6 study sites in foreign countries.

Patients with B-NHL received oral tirabrutinib 20, 40, 80, 160, 320, 480, or 600 mg QD or 240 mg BID and patients with CLL received oral tirabrutinib 20, 40, 80, 160, 320, 400, 500, or 600 mg QD or 300 mg BID, under fasting conditions in all treatment groups. Patients showing clinical benefit were able to continue with treatment until progressive disease (PD) or occurrence of an adverse event leading to treatment discontinuation.

All of the 62 patients with B-NHL and 28 patients with CLL enrolled in the study received tirabrutinib, and were included in the safety analysis population. Of patients in the safety analysis population, 33 patients with B-NHL and 27 patients with CLL were evaluated for DLT.

During the DLT evaluation period of 28 days after the start of treatment, among patients with B-NHL, DLT was observed in 1 of 6 patients in the 320 mg QD group (Grade 4 hypersensitivity), in 1 of 6 patients in the 480 mg QD group (Grade 3 adverse drug reaction[35)]), and in 2 of 6 patients in the 600 mg QD group (Grade 3 rash maculo-papular and Grade 3 ill-defined disorder[36)]). Accordingly, 480 mg QD was defined as MTD in patients with B-NHL. Among patients with CLL, DLT was observed in 1 of 3 patients in the 400 mg QD group (Grade 3 haematoma) and in 1 of 3 patients in the 300 mg BID group (Grade 3 international normalized ratio [INR] increased), but no MTD was reached.

Death occurred during the tirabrutinib treatment or within 30-days post-treatment period in 1 of 3 patients with CLL in the 600 mg QD group (cardiac function disturbance postoperative), but its causal relationship to tirabrutinib was ruled out. Among patients with B-NHL, death occurred in 2 of 3 patients in the 20 mg QD group, 1 of 5 patients in the 80 mg QD group, 1 of 8 patients in the 160 mg QD group, 6 of 21 patients in the 320 mg QD group, 4 of 10 patients in the 480 mg QD group, 1 of 9 patients in the 600 mg QD group, and 1 of 3 patients in the 240 mg BID group. The causes of deaths other than disease progression (1 each in the 20 mg QD, 80 mg QD, 160 mg QD, 600 mg QD, and240 mg BID groups, 6 patients in the 320 mg QD group, and 2 patients in the 480 mg QD group) were pneumonia (1 in the 20 mg QD group), cardiac arrest (1 in the 480 mg QD group), and *Pneumocystis jirovecii* pneumonia/H1N1 influenza (1 in the 480 mg QD group). A causal relationship to tirabrutinib was ruled out for all of these adverse events.

35) Rash maculo-papular was observed.
36) Whole body heat sensation and sensation of pressure at neck and tongue were noted.

7.2 Reference data

7.2.1 Clinical pharmacology studies

The applicant submitted data of the following 3 clinical pharmacology studies in healthy adults [see Section 6.2]. No death occurred during the period of these studies.

7.2.1.1 Foreign Phase I study (CTD 5.3.3.4-1, Study 1765 [■ to ■ 20■])

7.2.1.2 Foreign Phase I study (CTD 5.3.3.4-2, Study 1767 [■ to ■ 20■])

7.2.1.3 Foreign Phase I study (CTD 5.3.3.1-1, Study 1768 [■ to ■ 20■])

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA concluded that, among the evaluation data submitted, the most important clinical study for evaluating the efficacy and safety of tirabrutinib was the Japanese Phase I/II study (Study 02) conducted in patients with recurrent or refractory PCNSL, and decided to evaluate the submitted data focusing on this study.

7.R.2 Efficacy

On the basis of the following review, PMDA concluded that the efficacy of tirabrutinib had been demonstrated to a certain extent in patients with recurrent or refractory PCNSL.

7.R.2.1 Efficacy endpoints and evaluation results

In Phase II of Study 02, the response rate [95% CI] in the 320 mg group and the 480 mg fasted group was 60.0% [36.1%, 80.9%] (12 of 20) and 52.9% [27.8%, 77.0%] (9 of 17), respectively, with the lower limit of 95% CI exceeding the pre-defined threshold response rate (14%) in both groups [see Section 7.1.2.2].

The applicant's explanation about the response rate, the primary endpoint of Phase II of Study 02:
Patients with recurrent or refractory PCNSL have a poor prognosis, and there is no established standard treatment that prolongs overall survival (OS). Considering that accessory symptoms of brain lesions are ameliorated by tumor shrinkage, it is of clinical significance that these patients responded to tirabrutinib.

PMDA's view:
The applicant's explanation about the efficacy endpoint is understandable.

Efficacy in the 320 mg group of Study 02 should be evaluated carefully because the efficacy analysis of this group included those who were enrolled in Phase I. However, a certain level of efficacy was observed not only in the 320 mg group but also in the 480 mg fasted group as well, indicating a certain level of efficacy of tirabrutinib in patients with recurrent or refractory PCNSL.

PMDA's conclusion on the dosage regimen of tirabrutinib is described in Section 7.R.5.

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

PMDA's view:

Discussions in the following subsections revealed adverse events requiring particular attention in treatment with tirabrutinib, namely, bone marrow depression, infection, ILD, skin disorder, hemorrhage, hepatic dysfunction, and hypersensitivity. Caution should be exercised against these possible adverse events in using tirabrutinib.

Although the above-mentioned adverse events require attention during treatment, tirabrutinib will be well tolerated under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy who cope with adverse events appropriately by monitoring and controlling. Because of the extremely limited experience in the treatment with tirabrutinib, safety data should be further collected in the post-marketing setting [see Section 7.R.6].

7.R.3.1 Safety profile of tirabrutinib and difference in safety profile between Japanese and non-Japanese patients

The applicant's explanation about the safety profile of tirabrutinib:

Table 26 shows the outline of safety in Study 02.

Table 26. Outline of safety (Study 02)

	Number of patients (%)		
	320 mg n = 20	480 mg n = 7	480 mg fasted n = 17
All adverse events	16 (80.0)	7 (100)	15 (88.2)
Grade ≥3 adverse events	6 (30.0)	5 (71.4)	10 (58.8)
Adverse events resulting in death	0	1 (14.3)	0
Serious adverse events	1 (5.0)	5 (71.4)	3 (17.6)
Adverse events leading to treatment discontinuation	1 (5.0)	2 (28.6)	0
Adverse events leading to treatment interruption	5 (25.0)	3 (42.9)	10 (58.8)
Adverse events leading to dose reduction	0	0	1 (5.9)

Table 27 shows all-Grade adverse events with an incidence of ≥20% in any group in Study 02.

Table 27. Adverse events with an incidence of ≥20% in any group (Study 02)

SOC PT (MedDRA/J ver.21.1)	Number of patients (%)					
	320 mg n = 20		480 mg n = 7		480 mg fasted n = 17	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	16 (80.0)	6 (30.0)	7 (100)	5 (71.4)	15 (88.2)	10 (58.8)
Blood and lymphatic system disorders						
Lymphopenia	1 (5.0)	0	2 (28.6)	1 (14.3)	1 (5.9)	1 (5.9)
Eye disorders						
Cataract	0	0	2 (28.6)	1 (14.3)	0	0
Gastrointestinal disorders						
Constipation	1 (5.0)	0	0	0	4 (23.5)	0
Infections and infestations						
Urinary tract infection	0	0	2 (28.6)	0	1 (5.9)	1 (5.9)
Investigations						
White blood cell count decreased	2 (10.0)	1 (5.0)	2 (28.6)	0	2 (11.8)	1 (5.9)
Platelet count decreased	1 (5.0)	0	2 (28.6)	0	1 (5.9)	0
Blood bilirubin increased	4 (20.0)	1 (5.0)	0	0	0	0
Skin and subcutaneous tissue disorders						
Erythema multiforme	2 (10.0)	1 (5.0)	3 (42.9)	2 (28.6)	0	0
Rash	6 (30.0)	0	2 (28.6)	0	6 (35.3)	1 (5.9)

In Study 02, serious adverse events were seizure and haemorrhage intracranial in 1 each of 20 patients (5.0%) in the 320 mg group; erythema multiforme in 2 of 7 patients (28.6%), cataract, *Pneumocystis jirovecii* pneumonia, ILD, and drug eruption in 1 each of 7 patients (14.3%) in the 480 mg group; and bronchopulmonary aspergillosis, pneumonia, spinal compression fracture, seizure, and haematuria in 1 each of 17 patients (5.9%) in the 480 mg fasted group. A causal relationship to tirabrutinib could not be ruled out for erythema multiforme in 2 patients, *Pneumocystis jirovecii* pneumonia, ILD, and drug eruption in 1 patient each in the 480 mg group; and bronchopulmonary aspergillosis, pneumonia, and haematuria in 1 patient each in the 480 mg fasted group. Adverse events leading to the discontinuation of tirabrutinib were drug eruption in 1 of 20 patients (5.0%) in the 320 mg group; and *Pneumocystis jirovecii* pneumonia, ILD, and drug eruption in 1 each of 7 patients (14.3%) in the 480 mg group. A causal relationship to tirabrutinib could not be ruled out for any of these adverse events. Adverse events leading to treatment interruption in ≥2 patients were erythema multiforme in 2 of 7 patients (28.6%) in the 480 mg group and rash maculo-papular in 2 of 17 patients (11.8%) in the 480 mg fasted group. There were no adverse events leading to dose reduction in ≥2 patients.

PMDA's view:

Adverse events resulting in death, serious adverse events, or those leading to the discontinuation of tirabrutinib in Study 02 are treatment-emergent adverse events that require attention. The occurrence of these events should be communicated appropriately to healthcare professionals via the package insert, etc.

In the following sections, PMDA reviewed adverse events with a focus on those for which a causal relationship to tirabrutinib could not be ruled out, based on the safety results obtained from Study 02. Because of the extremely limited use experience of tirabrutinib, the incidences of Grade ≥3 adverse events, death, and serious adverse events observed in Study 01 and Study POE001 in patients with recurrent or refractory B-NHL or CLL were also reviewed.

7.R.3.2 Hematotoxicity

The applicant's explanation about the incidence of hematotoxicity associated with tirabrutinib:
Hematotoxicity-related adverse events were tabulated based on preferred terms (PTs) falling under standard Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQ) of "Haematopoietic erythropenia (broad)," "Haematopoietic leukopenia (narrow)," and "Haematopoietic thrombocytopenia (narrow);" and high level group term (HLGT) of "Haematological disorders NEC," "Haematology investigations (incl blood groups)," "Platelet disorders," "Red blood cell disorders," and "White blood cell disorders."

Table 28 shows the incidences of hematotoxicity in Study 02.

Table 28. Incidence of hematotoxicity (Study 02)

MedDRA PT (MedDRA/J ver.21.1)	Number of patients (%)					
	320 mg n = 20		480 mg n = 7		480 mg fasted n = 17	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Haematotoxicity	6 (30.0)	2 (10.0)	5 (71.4)	2 (28.6)	6 (35.3)	3 (17.6)
Neutrophil count decreased	3 (15.0)	1 (5.0)	1 (14.3)	0	2 (11.8)	1 (5.9)
White blood cell count decreased	2 (10.0)	1 (5.0)	2 (28.6)	0	2 (11.8)	1 (5.9)
Anaemia	1 (5.0)	0	1 (14.3)	0	2 (11.8)	0
Lymphopenia	1 (5.0)	0	2 (28.6)	1 (14.3)	1 (5.9)	1 (5.9)
Neutropenia	1 (5.0)	1 (5.0)	1 (14.3)	0	2 (11.8)	1 (5.9)
Lymphocyte count decreased	1 (5.0)	0	1 (14.3)	1 (14.3)	1 (5.9)	0
Platelet count decreased	1 (5.0)	0	2 (28.6)	0	1 (5.9)	0
Leukopenia	0	0	1 (14.3)	0	1 (5.9)	1 (5.9)
Thrombocytopenia	0	0	1 (14.3)	0	0	0

In Study 02, hematotoxicity leading to the interruption of tirabrutinib was observed in 1 patient (5.0%) in the 320 mg group. There was no hematotoxicity resulting in death, serious hematotoxicity, or hematotoxicity leading to the discontinuation or dose reduction of tirabrutinib.

In Study 01, Grade ≥3 hematotoxicity was observed in 6 patients (35.3%; neutrophil count decreased in 3; anaemia, neutropenia, and white blood cell count decreased in 2 each; and lymphocyte count decreased, febrile neutropenia, and INR increased in 1 each [including multiple events per patient]). No death or serious hematotoxicity was observed.

In Study POE001, Grade ≥3 hematotoxicity was observed in 34 patients (37.8%; thrombocytopenia and neutropenia in 13 each, anaemia in 10, lymphopenia in 5, leukopenia and febrile neutropenia in 3 each, lymphocytosis, INR increased, and neutropenic sepsis in 2 each, and neutropenic infection, lymphocytic infiltration, and immune thrombocytopenic purpura in 1 each [including multiple events per patient]). Serious hematotoxicity was observed in 8 patients (8.9%; febrile neutropenia in 3, neutropenic sepsis in 2, and anaemia, neutropenia, neutropenic infection, INR increased, activated partial thromboplastin time prolonged, and lymphocytic infiltration in 1 each [including multiple events per patient]). A causal relationship to tirabrutinib could not be ruled out for febrile neutropenia in 2 patients, neutropenic sepsis, neutropenia, and lymphocytic infiltration in 1 patient each. There was no hematotoxicity resulting in death.

PMDA's view:

In light of Grade ≥3 bone marrow depression observed in Japanese clinical studies and serious bone marrow depression for which a causal relationship to tirabrutinib could not be ruled out in the foreign clinical study, tirabrutinib treatment requires attention to bone marrow depression. Thus, the occurrence of bone marrow depression in the clinical studies should be communicated to the healthcare professionals. They should also be appropriately informed via the package insert, etc. of the importance of hematological testing to be performed regularly during treatment so that tirabrutinib is interrupted or reduced, or any appropriate measures are taken in case of abnormalities.

7.R.3.3 Infection

The applicant's explanation about the incidence of infection associated with tirabrutinib:

Adverse events related to infection were tabulated by PTs falling under the MedDRA System organ class (SOC) of "Infections and infestations."

Table 29 shows the incidences of infections in Study 02.

Table 29. Incidence of infection (Study 02)

MedDRA PT (MedDRA/J ver.21.1)	Number of patients (%)					
	320 mg n = 20		480 mg n = 7		480 mg fasted n = 17	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Infection	4 (20.0)	0	5 (71.4)	1 (14.3)	5 (29.4)	3 (17.6)
Urinary tract infection	0	0	2 (28.6)	0	1 (5.9)	1 (5.9)
Nasopharyngitis	2 (10.0)	0	0	0	0	0
Oral herpes	1 (5.0)	0	1 (14.3)	0	0	0
Bronchitis	1 (5.0)	0	0	0	0	0
Bronchopulmonary aspergillosis	0	0	0	0	1 (5.9)	1 (5.9)
Cystitis	0	0	0	0	1 (5.9)	0
CMV infection	0	0	1 (14.3)	0	0	0
Pneumonia	0	0	0	0	1 (5.9)	1 (5.9)
Tinea pedis	0	0	1 (14.3)	0	0	0
Upper respiratory tract infection	0	0	0	0	1 (5.9)	0
Pneumocystis jirovecii pneumonia	0	0	1 (14.3)	1 (14.3)	0	0

In Study 02, infection resulted in death of 1 patient in the 480 mg group (14.3%; *Pneumocystis jirovecii* pneumonia in 1), and a causal relationship of the infection to tirabrutinib could not be ruled out for the event. Serious infection was observed in 1 patient in the 480 mg group (14.3%; *Pneumocystis jirovecii* pneumonia in 1) and in 2 patients in the 480 mg fasted group (11.8%; bronchopulmonary aspergillosis and pneumonia in 1 each), and a causal relationship to tirabrutinib could be ruled out for any of them. Infection led to the discontinuation of tirabrutinib in 1 patient (14.3%) in the 480 mg group. Infection led to the interruption of tirabrutinib in 1 patient (5.0%) in the 320 mg group, 1 patient (14.3%) in the 480 mg group, and 2 patients (11.8%) in the 480 mg fasted group. There was no infection leading to dose reduction of tirabrutinib.

In Study 01, Grade ≥3 infection was observed in 1 patient (5.9%; pneumonia bacterial). Serious infection was observed in 2 patients (11.8%; hepatitis B reactivation and pneumonia bacterial in 1 each). A causal relationship to tirabrutinib could not be ruled out for hepatitis B reactivation in 1 patient. There was no infection resulting in death.

In Study POE001, Grade ≥3 infection was observed in 24 patients (26.7%; lower respiratory tract infection in 6; pneumonia, lung infection, sepsis, neutropenic sepsis, and *Pneumocystis jirovecii* pneumonia in 2 each; and upper respiratory tract infection, urinary tract infection, chronic sinusitis, infection, device related infection, bacteraemia, bronchiolitis, *Campylobacter* gastroenteritis, *Escherichia* sepsis, hepatitis E, pneumonia pneumococcal, tooth abscess, abscess neck, neutropenic infection, abdominal abscess, *Haemophilus* infection, respiratory syncytial virus infection, lower respiratory tract infection bacterial, lower respiratory tract infection fungal, and H1N1 influenza in 1 each [including multiple events per patient]). Infection resulted in death in 4 patients (4.4%; pneumonia, *Pneumocystis jirovecii* pneumonia, *Escherichia* sepsis, and abdominal abscess in 1 each). A causal relationship to tirabrutinib could not be ruled out for abdominal abscess. Serious infection was observed in 24 patients (26.7%; lower respiratory tract infection in 7, pneumonia in 3, neutropenic sepsis, *Pneumocystis jirovecii* pneumonia, and device related infection in 2 each, and bronchitis, upper respiratory tract infection, influenza, ear infection, lung infection, herpes simplex, infection, sepsis, bacteraemia, bronchiolitis, *Campylobacter* gastroenteritis, *Escherichia* sepsis, hepatitis E, pneumonia pneumococcal, *Escherichia* urinary tract infection, neutropenic infection, abdominal abscess, respiratory syncytial virus infection, respiratory tract infection viral, herpes zoster oticus, lower respiratory tract infection bacterial, lower respiratory tract infection fungal, and H1N1 influenza in 1 each [including multiple events per patient]). A causal relationship to tirabrutinib could not be ruled out for influenza, neutropenic sepsis, bronchiolitis, hepatitis E, abdominal abscess, and lower respiratory tract infection bacterial in 1 patient each.

PMDA asked the applicant to explain (a) guidelines for prophylactic medication against opportunistic infection and the occurrence of opportunistic infection and (b) the results of screening for hepatitis B virus (HBV) infection and the occurrence of HBV reactivation in the Studies 01, 02 and POE001.

The applicant's explanation:

(a) Guidelines for prophylactic medication against opportunistic infection and the occurrence of opportunistic infection

As the preventive measures against opportunistic infection, antimicrobial agents (e.g., fluoroquinolones and sulfamethoxazole/trimethoprim [ST]-combination) and acyclovir (all patients with a history of herpetic infection) was recommended in Study 02, whereas no specific prophylaxis was recommended in Study 01 or Study POE001.

Pneumocystis jirovecii infection observed was *Pneumocystis jirovecii* pneumonia in 1 patient (serious) in Study 02 and in 2 patients (serious in both) in Study POE001. A causal relationship to tirabrutinib could not be ruled out for *Pneumocystis jirovecii* pneumonia in 1 patient in Study 02. None of these patients received a prophylactic antimicrobial agent.

Cytomegalovirus (CMV) infection was observed in 1 patient (non-serious) in Study 02, and its causal relationship to tirabrutinib was ruled out. Prophylactic acyclovir was administered to the patient.

Varicella zoster virus (VZV) infections observed were herpes zoster in 8 patients (non-serious in all), herpes zoster oticus in 1 patient (serious), and herpes zoster disseminated in 1 patient (non-serious),

all in Study POE001. A causal relationship to tirabrutinib could not be ruled out for herpes zoster in 2 patients. Prophylactic acyclovir was administered to none of these patients experiencing VZV infection.

No other opportunistic infections were observed.

(b) Results of screening for HBV infection and the occurrence of HBV reactivation

Results of screening for HBV infection (anti-HBs antibody or anti-HBc antibody)[37] revealed that, in Study 02, 2 patients were positive for anti-HBs antibody only, none were positive for anti-HBc antibody only, and 5 patients were positive for both anti-HBs and anti-HBc antibodies. In Study 01, 1 patient was positive for anti-HBs antibody only, 1 patient was positive for anti-HBc antibody only, and 2 patients were positive for both anti-HBs and anti-HBc antibodies.

HBV reactivation observed in Study 01 was transaminases increased and positive HBV-DNA (serious) in 1 patient,[38] and a causal relationship to tirabrutinib could not be ruled out for these events. Entecavir hydrate was administered, and the outcome was "recovered." No HBV reactivation was observed in other studies.

PMDA's view:

Given the observed serious infections (including opportunistic infection) including death for which a causal relationship to tirabrutinib could not be ruled out in multiple patients in Japanese and foreign clinical studies, attention should be called for infections during treatment with tirabrutinib. The occurrence of infections, including opportunistic infection, in the clinical studies should be communicated to healthcare professionals.

Because of the limited number of patients who presented with HBV reactivation, the currently available findings are insufficient for drawing any definite conclusion on the relationship between tirabrutinib and HBV reactivation. Because a causal relationship to tirabrutinib could not be ruled out for the serious HBV reactivation observed, patients should be screened for HBV infection prior to tirabrutinib treatment and monitored periodically for signs of HBV reactivation through blood test for hepatic function, etc. during the treatment. This should be appropriately communicated to healthcare professionals via the package insert, etc.

Furthermore, healthcare professionals should be informed of safety measures for infection control taken in the clinical studies appropriately through written materials, etc.

7.R.3.4 ILD

The applicant's explanation of the occurrence of ILD associated with tirabrutinib:

Adverse events related to ILD were tabulated by PTs falling under the MedDRA SMQ of "Interstitial lung disease (broad)."

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[37] Results of screening of patients with the target disease of tirabrutinib

[38] The screening test showed that this patient was positive for both anti-HBs and anti-HBc antibodies.

In Study 02, all-Grade ILD was observed in 1 patient in the 480 mg group (14.3%; ILD in 1), and Grade ≥3 ILD was observed in 1 patient in the 480 mg group (14.3%; ILD in 1). ILD resulted in death of 1 patient in the 480 mg group (14.3%; ILD in 1), and its causal relationship to tirabrutinib could not be ruled out. Serious ILD was observed in 1 patient in the 480 mg group (14.3%; ILD in 1), and its causal relationship to tirabrutinib could not be ruled out. ILD leading to the discontinuation of tirabrutinib was observed in 1 patient in the 480 mg group (14.3%). There was no ILD leading to the interruption or dose reduction of tirabrutinib.

In Study 01, Grade ≥3 ILD was observed in 1 patient (5.9%; pneumonitis). There was no ILD resulting in death. Serious ILD was observed in 1 patient (5.9%; pneumonitis in 1), and its causal relationship to tirabrutinib could not be ruled out.

In Study POE001, Grade ≥3 ILD was observed in 1 patient (1.1%; bronchiolitis in 1). There was no ILD resulting in death. Serious ILD was observed in 1 patient (1.1%; bronchiolitis in 1), ant its causal relationship to tirabrutinib could not be ruled out.

PMDA's view:
Although there were only limited cases of ILD in the Japanese and foreign clinical studies, treatment with tirabrutinib requires attention to the onset of ILD because of observed serious cases (including death) for which a causal relationship to tirabrutinib could not be ruled out. The occurrence of ILD in the clinical studies should be communicated to healthcare professionals. They should also be advised appropriately via the package insert to take appropriate measures, i.e., the interruption or dose reduction of tirabrutinib, in case of abnormalities.

7.R.3.5 Skin disorder

The applicant's explanation about the incidence of skin disorders associated with tirabrutinib:
Adverse events related to skin disorder were tabulated by PTs falling under the MedDRA HLGT of "Epidermal and dermal conditions."

Table 30 shows the incidences of skin disorder in Study 02.

Table 30. Incidences of skin disorders (Study 02)

MedDRA PT (MedDRA/J ver.21.1)	Number of patients (%)					
	320 mg n = 20		480 mg n = 7		480 mg fasted n = 17	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin disorder	11 (55.0)	3 (15.0)	6 (85.7)	3 (42.9)	10 (58.8)	2 (11.8)
Rash	6 (30.0)	0	2 (28.6)	0	6 (35.3)	1 (5.9)
Erythema multiforme	2 (10.0)	1 (5.0)	3 (42.9)	2 (28.6)	0	0
Drug eruption	2 (10.0)	1 (5.0)	1 (14.3)	1 (14.3)	1 (5.9)	0
Rash maculo-papular	1 (5.0)	0	0	0	2 (11.8)	1 (5.9)
Pruritus	1 (5.0)	0	1 (14.3)	0	0	0
Blister	0	0	1 (14.3)	0	0	0
Dermatitis	0	0	0	0	1 (5.9)	0
Erythema	1 (5.0)	1 (5.0)	0	0	0	0

In Study 02, serious skin disorder was observed in 3 patients in the 480 mg group (42.9%;erythema multiforme in 2 and drug eruption in 1), and a causal relationship to tirabrutinib could not be ruled out

for either events. Skin disorder led to the discontinuation of tirabrutinib in 1 patient in the 320 mg group (5.0%) and in 1 patient in the 480 mg group (14.3%). Skin disorder led to the interruption of tirabrutinib in 2 patients in the 320 mg group (10.0%), 2 patients in the 480 mg group (28.6%), and 4 patients in the 480 mg fasted group (23.5%). Skin disorder led to the dose reduction of tirabrutinib in 1 patient in the 480 mg fasted group (5.9%). There was no skin disorder resulting in death.

In Study 01, there was no Grade ≥3, serious skin disorder, or those resulting death.

In Study POE001, Grade ≥3 skin disorder was observed in 1 patient (1.1%; rash maculo-papular). Serious skin disorder was observed in 1 patient (1.1%; rash), and its causal relationship to tirabrutinib could not be ruled out. There was no skin disorder resulting in death.

PMDA's view:
Serious skin disorder for which a causal relationship to tirabrutinib could not be ruled out was observed in multiple patients in Japanese and foreign clinical studies, warranting caution against skin disorder during the treatment with tirabrutinib. The occurrence of skin disorder in the clinical studies should be communicated to healthcare professionals. They should also be advised appropriately via the package insert, etc. to take appropriate measures, i.e., the interruption or dose reduction of tirabrutinib, in case of abnormalities.

7.R.3.6 Hemorrhage

The applicant's explanation about the incidence of hemorrhage associated with tirabrutinib:
Adverse events related to hemorrhage were tabulated by PT falling under the MedDRA SMQ of "Haemorrhage terms (excl laboratory terms) (narrow)."

In Study 02, all-Grade haemorrhage was observed in 3 patients in the 320 mg group (15.0%; conjunctival haemorrhage, haemorrhage intracranial, and subdural haematoma in 1 each) and in 2 patients in the 480 mg fasted group (11.8%; haematuria and purpura in 1 each). Grade ≥3 haemorrhage was not observed. Serious haemorrhage was observed in 1 patient in the 320 mg group (5.0%; haemorrhage intracranial in 1) and in 1 patient in the 480 mg fasted group (5.9%; haematuria in 1). A causal relationship to tirabrutinib could not be ruled out for haematuria in 1 patient in the 480 mg fasted group. Haemorrhage leading to interruption of tirabrutinib was observed in 1 patient (5.9%) in the 480 mg fasted group. There was no haemorrhage resulting in death, or that leading to the discontinuation or dose reduction of tirabrutinib.

In Study 01, serious haemorrhage was observed in 1 patient (5.9%; Mallory-Weiss syndrome in 1), and its causal relationship to tirabrutinib could not be ruled out. There was no Grade ≥3 haemorrhage and haemorrhage resulting in death.

In Study POE001, Grade ≥3 haemorrhage was observed in 5 patients (5.6%; petechiae, purpura, haematoma, oesophageal haemorrhage, small intestinal haemorrhage, and immune thrombocytopenic purpura in 1 each [including multiple events per patient]). Serious haemorrhage was observed in 5 patients (5.6%; purpura, spontaneous haematoma, ear haemorrhage, oesophageal haemorrhage, and

small intestinal haemorrhage in 1 each), and a causal relationship to tirabrutinib could not be ruled out for purpura and spontaneous haematoma in 1 patient each. There was no haemorrhage resulting in death.

PMDA's view:
Serious haemorrhage for which a causal relationship to tirabrutinib could not be ruled out were observed in multiple patients in the Japanese and foreign clinical studies, warranting caution against haemorrhage during the treatment with tirabrutinib. Thus, the occurrence of haemorrhage in the clinical studies should be communicated to healthcare professionals. They should also be advised appropriately via the package insert, etc. to perform hematological tests regularly during the treatment and take appropriate measures, i.e., the interruption or dose reduction of tirabrutinib, in case of abnormalities.

7.R.3.7 Hepatic dysfunction

The applicant's explanation about the occurrence of hepatic dysfunction associated with tirabrutinib:
Adverse events related to hepatic dysfunction were tabulated by PT falling under the MedDRA SMQs of "Liver related investigations, signs and symptoms (narrow)" or in "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow)."

In Study 02, all-Grade hepatic dysfunction was observed in 4 patients in the 320 mg group (20.0%; blood bilirubin increased in 4, aspartate aminotransferase [AST] increased in 2, and alanine aminotransferase [ALT] increased and γ-glutamyltransferase [GGT] increased in 1 each [including multiple events per patient) and in 2 patients in the 480 mg fasted group (11.8%; AST increased, ALT increased, and hepatic function abnormal in 1 each [including multiple events per patient]). Grade ≥3 hepatic dysfunction was observed in 1 patient in the 320 mg group (5.0%; blood bilirubin increased, AST increased, and ALT increased in 1 each [including multiple events per patient]) and in 1 patient in the 480 mg fasted group (5.9%; AST increased and ALT increased in 1 each [including multiple events per patient]). Hepatic dysfunction led to the interruption of tirabrutinib in 1 patient (5.0%) in the 320 mg group and in 1 patient (5.9%) in the 480 mg fasted group. There was no hepatic dysfunction resulting in death, serious hepatic dysfunction, or hepatic dysfunction leading to the discontinuation or dose reduction of tirabrutinib.

In Study 01, there was no Grade ≥3 or serious hepatic dysfunction, or hepatic dysfunction resulting in death.

In Study POE001, Grade ≥3 hepatic dysfunction was observed in 3 patients (3.3%; GGT increased in 2, blood bilirubin increased, AST increased, ALT increased, portal hypertensive gastropathy, and varices oesophageal in 1 each [including multiple events per patient]). There was no hepatic dysfunction that was serious or resulting in death.

One patient in the 320 mg group in Study 02 (blood bilirubin increased/AST increased/ALT increased/GGT increased) and 2 patients in Study POE001 (blood bilirubin increased/AST increased/ALT increased/GGT increased and hepatocellular injury in 1 patient each)[39)] met Hy's law

[39)] Blood bilirubin increased/AST increased/ALT increased/GGT increased was observed in a patient in the tirabrutinib 40 mg group, and hepatocellular injury in a patient in the tirabrutinib 500 mg group.

laboratory criteria (defined based on "Guidance for industry. Drug-Induced Liver Injury: premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009").

PMDA's view:
Hepatic dysfunction meeting Hy's law was observed in ≥2 patients in the Japanese and foreign clinical studies. Caution is called for hepatic dysfunction in treatment with ibrutinib that has a similar action mechanism as tirabrutinib. Given these, the treatment with tirabrutinib also requires attention to hepatic dysfunction. The occurrence of hepatic dysfunction in the clinical studies should be communicated to healthcare professionals. They should also be advised appropriately via the package insert, etc. to perform hepatic function test regularly during the treatment so that appropriate measures, i.e., the interruption or dose reduction of tirabrutinib, are taken in case of abnormalities.

7.R.3.8 Hypersensitivity

The applicant's explanation about the occurrence of hypersensitivity associated with tirabrutinib:
Adverse events related to hypersensitivity were tabulated by PT falling under the MedDRA SMQ of "Hypersensitivity (narrow)."[40)]

In Study 02, all-Grade hypersensitivity was observed in 1 patient in the 480 mg fasted group (5.9%; hypersensitivity in 1). There was no Grade ≥3 hypersensitivity, hypersensitivity resulting in death, serious hypersensitivity, or hypersensitivity leading to discontinuation, interruption, or dose reduction of tirabrutinib.

In Study 01, no hypersensitivity was observed.

In Study POE001, Grade ≥3 hypersensitivity was observed in 3 patients (3.3%; angioedema, dermatitis acneiform, and hypersensitivity in 1 each). Serious hypersensitivity was observed in 2 patients (2.2%; angioedema and hypersensitivity[41)] in 1 each). A causal relationship to tirabrutinib could not be ruled out for hypersensitivity in 1 patient. There was no hypersensitivity resulting in death.

PMDA's view:
In the clinical studies in and outside Japan, although in limited number, hypersensitivity was reported from ≥2 patients in the foreign study, including serious anaphylactic hypersensitivity for which a causal relationship to tirabrutinib could not be ruled out. Therefore, treatment with tirabrutinib requires caution against hypersensitivity. The occurrence of hypersensitivity in the clinical studies should be communicated appropriately to healthcare professionals via the package insert, etc.

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40) Excluding the PTs of "Dermatitis infected" and "Immune thrombocytopenic purpura" which are included in adverse events related to skin disorder [see Section 7.R.3.5]

41) A 7[redacted]-year-old woman with B-NHL in the 320 mg QD group who had primary macroglobulinemia. On Day 8, Grade 2 urticaria and face oedema were observed, and tirabrutinib was suspended from the next day. Tirabrutinib was resumed from Day 15, Grade 4 hypersensitivity symptoms (thoracoabdominal and dorsal erythema, strangled sensation of pharynx, and wheezing) developed on that day. The hypersensitivity was treated with intravenous injection of hydrocortisone and antihistamine, followed by oral prednisolone for 10 days at tapering doses. The outcome after 2 months was "recovered."

7.R.3.9 Other

Among the attention-requiring events during treatment with ibrutinib that acts similarly to tirabrutinib (see "Review Report of Imbruvica Capsules 140 mg, dated April 26, 2018"), those not mentioned in the above subsections are arrhythmia, secondary malignancy, eye disorder, tumour lysis syndrome, and Stevens-Johnson syndrome, the occurrence of which are summarized below. No Stevens-Johnson syndrome was observed in Study 02, 01, or POE001.

(a) Cardiac disorder

Adverse events related to cardiac disorder were tabulated by PT falling under the MedDRA SOC of "Cardiac disorders" and the MedDRA SMQs of "Arrhythmia (broad)," "Cardiac failure (broad)," "Cardiomyopathy (broad)," and "Ischaemic heart disease (broad)."

No cardiac disorder was observed in Study 02.

In Study 01, there was no Grade ≥3 or serious cardiac disorder or cardiac disorder resulting in death.

In Study POE001, Grade ≥3 cardiac disorder was observed in 7 patients (7.8%; dyspnoea and cardiac arrest in 2 each, cardiac failure, syncope, myocardial infarction, and tricuspid valve incompetence in 1 each [including multiple events per patient]). Cardiac disorder resulted in death of 2 patients (2.2%; cardiac arrest), its causal relationship to tirabrutinib was ruled out in both cases. Serious cardiac disorder was observed in 3 patients (3.3%; cardiac arrest, cardiac failure, and syncope in 1 each), and its causal relationship to tirabrutinib was ruled out in all cases.

(b) Secondary malignancy

Secondary malignancy was tabulated by PT falling under the MedDRA SOC of "Neoplasms benign, malignant and unspecified (incl cysts and polyps)," excluding events related to benign neoplasms.

In Study 02, no secondary malignancy was observed.

In Study 01, Grade ≥3 secondary malignancy was observed in 1 patient (5.9%; acute myeloid leukaemia in 1). Serious secondary malignancy was observed in 2 patients (11.8%; neuroendocrine carcinoma of the skin and acute myeloid leukaemia in 1 each). A causal relationship to tirabrutinib could not be ruled out for acute myeloid leukaemia. There was no secondary malignancy resulting in death.

In Study POE001, Grade ≥3 secondary malignancy was observed in 3 patients (3.3%; colorectal cancer, squamous cell carcinoma of lung, and myelodysplastic syndrome in 1 each). Serious secondary malignancy was observed in 4 patients (4.4%; squamous cell carcinoma of skin, colorectal cancer, squamous cell carcinoma of lung, and myelodysplastic syndrome in 1 each). A causal relationship to tirabrutinib was ruled out for all these events. There was no secondary malignancy resulting in death.

(c) Eye disorder

Adverse events related to eye disorder were tabulated were tabulated by PT falling under the MedDRA SOC of "Eye disorders."

In Study 02, all-Grade eye disorder was observed in 2 patients in the 320 mg group (10.0%; conjunctival haemorrhage and retinal tear in 1 each), in 2 patients in the 480 mg group (28.6%; cataract in 2), and in 1 patient in the 480 mg fasted group (5.9%; diplopia in 1). Grade ≥3 eye disorder was observed in 1 patient in the 480 mg group (14.3%; cataract in 1). Serious eye disorder was observed in 1 patient in the 480 mg group (14.3%; cataract in 1), but its causal relationship to tirabrutinib was ruled out. There was no eye disorder resulting in death or leading to the discontinuation, interruption, or dose reduction of tirabrutinib.

In Study 01, there was no Grade ≥3 or serious eye disorder, or eye disorder resulting in death.

In Study POE001, Grade ≥3 eye disorder was observed in 1 patient (1.1%; cataract in 1). There was no eye disorder that was serious or resulting in death.

(d) Tumour lysis syndrome
Events were tabulated by the MedDRA PT of "Tumour lysis syndrome."

In Study 02 or 01, there was no tumour lysis syndrome.

In Study POE001, Grade ≥3 tumour lysis syndrome was observed in 1 patient (3.6%), but its causal relationship to tirabrutinib was ruled out. There was no serious tumour lysis syndrome or tumour lysis syndrome resulting in death.

PMDA's view:
Cardiac disorder, secondary malignancy, eye disorder, and tumour lysis syndrome were observed in only a limited number of patients in Study 02, 01, or POE001, and a causal relationship to tirabrutinib was ruled out for most of the serious events observed. It is therefore practically difficult to definitely conclude the risk for these events in tirabrutinib therapy in patients with recurrent or refractory PCNSL. Thus, the occurrence of these events should be further monitored in the post-marketing setting, and new findings should be communicated appropriately to healthcare professionals once available.

7.R.4 Clinical positioning and indication

The proposed indication of tirabrutinib was "recurrent or refractory primary central nervous system lymphoma." The "Precautions for Indication" section initially noted that tirabrutinib therapy be given to patients failing to respond to ≥1 standard treatment or those experiencing relapse after such treatment. After the submission of the application, the description was deleted and replaced by the following:

- Physicians should refer to the "Clinical Studies" section to have a full understanding of the efficacy and safety of tirabrutinib before selecting eligible patients.

As a result of discussions in Sections "7.R.2 Efficacy," "7.R.3 Safety," and the following subsections, PMDA concluded that the indication should be "recurrent or refractory primary central nervous system lymphoma" as proposed, after modifying the description of the "Precautions for Indication" section as below.

- Physicians should be well-versed in the findings presented in the "Clinical Studies" section to have a full understanding of the efficacy and safety of tirabrutinib before selecting eligible patients.

7.R.4.1 Clinical positioning of tirabrutinib

There are no descriptions of tirabrutinib in the treatment of recurrent or refractory PCNSL in Japanese and foreign clinical practice guidelines[42)] or in representative international textbooks[43)] on clinical oncology, neurooncology, or hematology.

PMDA asked the applicant to explain the clinical positioning of tirabrutinib.

The applicant's explanation:
Recurrent or refractory PCNSL is an extremely rare disease with poor prognosis (e.g., *J Clin Oncol.* 2016;34:1757-63). In Japan, patients with recurrent or refractory PCNSL are treated with high-dose methotrexate, temozolomide,[44)] rituximab (genetical recombination), etc. (*Practical Guidelines for Neuro-Oncology 2019* [The Japan Society for Neuro-Oncology]), but there is no established standard treatment for the disease, and only extremely limited treatment options are available.

In this situation, Study 02 was conducted in patients with recurrent or refractory PCNSL, and the results demonstrated the clinical benefits of tirabrutinib [see Sections 7.R.2 and 7.R.3]. There are no other drugs which clinical benefits have been investigated and approved for the disease. Therefore, tirabrutinib can to be recognized as a treatment option for patients with the disease.

PMDA accepted the explanation of the applicant.

7.R.4.2 The target patients and indication of tirabrutinib

PMDA asked the applicant to explain the use of tirabrutinib to patients who were excluded from Study 02, namely, patients with (a) non-B-cell PCNSL, (b) intraocular PCNSL without brain lesion, (c) PCNSL associated with human immunodeficiency virus (HIV) infection, and (d) PCNSL with systemic lymphomatous lesion.

The applicant's explanation:
(a) Patients with non-B-cell PCNSL
Tirabrutinib is not recommended for patients with non-B-cell PCNSL because of unlikely efficacy in non-B-cell PCNSL in light of its action mechanism [see Section 3.R.1], and no available clinical study data in this patient group.

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42) National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology in Central nervous system cancers (NCCN Guidelines) (v.3.2019), Practical Guidelines for Neuro-Oncology 2019 (The Japan Society for Neuro-Oncology), and Practical Guidelines for Hematological Malignancies 2018 (Japanese Society of Hematology.)
43) DeVita, Hellman, and Rosenberg's Cancer 11th edition (Wolters Kluwer, 2019, USA), Harrison's Principles of Internal Medicine 20th edition (McGraw-Hill Education, 2018, USA), Wintrobe's Clinical Hematology, 13th Edition (Lippincott Williams & Wilkins, 2014, USA), Williams Hematology, 9th Edition (The McGraw-Hill Company, Inc, 2016, USA)
44) Not approved for PCNSL.

(b) Patients with intraocular PCNSL without brain lesion

Tirabrutinib is recommended for patients with intraocular PCNSL without brain lesion. However, in Study 02 that excluded patients with PCNSL who had intraocular lesion but no brain lesion, 3 patients with PCNSL were found to have lesions both in the brain and eye. All these patients achieved partial response with improved intraocular lesion.

(c) Patients with PCNSL associated with HIV infection

Tirabrutinib is recommended for patients with PCNSL associated with HIV infection. Patients in this population have convulsions, changing state of consciousness, and poor prognosis. Despite such differences from non-HIV-infected patients with PCNSL, the histopathological type of these patient groups are similar. Based on its action mechanism [see Section 3.R.1], tirabrutinib is expected to have efficacy not only in non-HIV-infected patients with PCNSL but also in HIV-infected patients with PCNSL.

(d) Patients with PCNSL with systemic lymphomatous lesion

The efficacy of tirabrutinib in patients with PCNSL with systemic lymphomatous lesion is unknown because of no available clinical study results of patients in this population. Nevertheless, tirabrutinib is recommended for these patients if priority is given to the treatment of central lesion because the histopathological type of PCNSL does not differ between patients with and without systemic lymphomatous lesion.

Based on the observations in (a) through (d) above, the appropriate indication should be “recurrent or refractory primary central nervous system lymphoma.” It, however, requires a note that patients with non-B-cell PCNSL were excluded from the clinical studies in the “Clinical Studies” section in the package insert, as well as advice in the “Precautions for Indication” section that urges physicians to have a full understanding of the efficacy and safety of tirabrutinib based on the “Clinical Studies” section before selecting eligible patients.

PMDA’s view:

PMDA accepted the applicant’s explanation on the patient population of (a). Treatment with tirabrutinib is not recommended for patient populations of (b) to (d) because of no available clinical study data for these patients currently.

However, (i) PCNSL is an extremely rare disease and treatment options for the disease are extremely limited, (ii) the results of Study 02 demonstrated the clinical benefits of tirabrutinib for PCNSL [see Sections 7.R.2 and 7.R.3], (iii) patients with B-cell PCNSL account for ≥95% of patients with PCNSL (*Practical Guidelines for Neuro-Oncology 2019* [The Japan Society for Neuro-Oncology.]), and (iv) tirabrutinib is prescribed by physicians with adequate knowledge and experience in cancer chemotherapy. Given these observations and the applicant’s above explanation, the patient populations of (a) to (d) need not to be excluded definitely from the target of tirabrutinib treatment Thus, the indication for tirabrutinib should remain as “recurrent or refractory primary central nervous system lymphoma” as proposed by the applicant, on the premise that information on patients in Study 02 is

provided in the "Clinical Studies" section and that the following advice is given in the "Precautions for Indication" section:

- Physicians should be well-versed in the findings presented in the "Clinical Studies" section to have a full understanding of the efficacy and safety of tirabrutinib before selecting eligible patients.

7.R.5 Dosage and administration

The proposed dosage and administration of tirabrutinib was "the usual adult dosage is 480 mg of tirabrutinib administered orally once daily under fasting conditions. The dose may be reduced according to the patient's condition," and the following precautions were proposed in the "Precautions for Dosage and Administration" section. After the submission of the application, advice on specific meal timing before a tirabrutinib dose was added in the "Precautions for Dosage and Administration" section, urging to avoid using tirabrutinib within 2 hours after a meal.

- C_{max} and AUC of tirabrutinib may increase when administered after a meal as compared with those administered under fasting conditions. Tirabrutinib should be administered under fasting conditions to avoid meal effect. Do not take a meal within 1 hour after the administration of tirabrutinib.

- Dose adjustment criteria in case of adverse drug reactions

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

As a result of discussions in the Sections "6.R.1 Timing of tirabrutinib treatment," "7.R.2 Efficacy," and "7.R.3 Safety" and the discussion in the following subsections, PMDA concluded that the dosage and administration should be defined as proposed by the applicant, after modifying the descriptions in the "Precautions for Dosage and Administration" section as follows.

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

- Due to reported increases in C_{max} and AUC of tirabrutinib administered after a meal. In order to avoid food effect, do not administer tirabrutinib from 1 hour before until 2 hours after a meal.

- If an adverse drug reaction occur after the administration of tirabrutinib, tirabrutinib should be interrupted, reduced, or discontinued according to the following criteria.

Level of tirabrutinib dose reduction

Level	Dose
Usual dose	480 mg
1-level lower dose	320 mg
2-level lower dose	160 mg

Guidelines for treatment interruption, dose reduction, and discontinuation in case of adverse drug reactions

Adverse drug reaction*		Measures to be taken
Grade ≥3 febrile neutropenia Grade 3 thrombocytopenia with haemorrhage Grade 4 neutropenia Grade 4 thrombocytopenia		Interrupt tirabrutinib until recovery to Grade ≤2 (Grade ≤3 for neutropenia). After recovery, tirabrutinib may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tirabrutinib until recovery. After recovery, tirabrutinib may be resumed at 1-level lower dose.
ILD	Grade 2 or 3	Interrupt tirabrutinib until recovery to Grade ≤1. After recovery, tirabrutinib may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tirabrutinib until recovery. After recovery, tirabrutinib may be resumed at 1-level lower dose.
	Grade 4	Discontinue tirabrutinib.
Skin disorder	Grade 2	Administer antihistamine, adrenocorticosteroid, etc. If resolved, continue tirabrutinib. If the symptom does not resolve, continue tirabrutinib at 1-level lower dose or interrupt tirabrutinib.
	Grade ≥3	Administer antihistamine, adrenocorticosteroid, etc., and interrupt tirabrutinib until recovery to Grade ≤2. After recovery, tirabrutinib may be resumed at 1-level lower dose.
Grade ≥3 Hematotoxicity (other than events listed above) and Grade ≥3 nonhematological toxicity (other than ILD and skin disorder)		Interrupt tirabrutinib until recovery to Grade ≤2. After recovery, tirabrutinib may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tirabrutinib until recovery. After recovery, tirabrutinib may be resumed at 1-level lower dose.

* Grade is defined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0.

7.R.5.1 Dosage and administration of tirabrutinib

The applicant's explanation about the dosage and administration of tirabrutinib:

Results of Studies 01 and POE001 in patients with recurrent or refractory B-NHL or CLL suggested that tirabrutinib 480 mg QD (either fasted or non-fasted) was well-tolerated. However, there was the possibility that patients with brain lesion suffer partially impaired function of the blood-brain barrier at the tumor site, possibly resulting in higher exposure of the entire brain tissue to tirabrutinib. Therefore, the starting dose of tirabrutinib in Phase I of Study 02 in patients with PCNSL was determined as 320 mg QD (either fasted or non-fasted).

Because no DLT was observed in the tirabrutinib 320 and 480 mg QD groups (either fasted or non-fasted) in Phase I of Study 02, the dosage regimen of tirabrutinib 480 mg QD was selected for Phase II (either fasted or non-fasted). However, death due to ILD occurred in 1 of 3 patients who proceeded to Phase II from the 480 mg QD group (either fasted or non-fasted) in Phase I,[45)] and erythema multiform was observed in 3 of 4 patients who were newly enrolled in Phase II.[46)] Given these observations, the dosage regimen for Phase II was changed to tirabrutinib 320 mg QD (either fasted or non-fasted). After the completion of patient enrollment in Phase II of the study, results of Study 04 investigating food effect on tirabrutinib became available, and suggested that the PK of tirabrutinib is affected by food consumption [see Section 6.R.1]. Therefore, the tirabrutinib 480 mg QD group (fasted) was included in Phase II for efficacy and safety evaluations.

Accordingly, Phase II of Study 02 was conducted and demonstrated the efficacy of tirabrutinib to a certain extent in patients with recurrent or refractory PCNSL, both at 320 mg QD (either fasted or non-

45) The ILD occurred after the DLT evaluation period (28 days after the start of treatment) and, ultimately, the event name was changed to "ILD or *Pneumocystis jirovecii* pneumonia."

46) The causal relationship of erythema multiform to tirabrutinib could not be ruled out in any of them, and the symptom was serious in 2 of them.

fasted) and at 480 mg QD (fasted) [see Section 7.R.2]. Both dosage regimens were well-tolerated [see Section 7.R.3]. Given the following points, however, to be more appropriate, meal timing should be specified in the dosage regimen. Accordingly, the dosage regimen was proposed as "tirabrutinib 480 mg QD (fasted)," also taking account of the clinical benefits demonstrated in the group treated with the regimen [see Sections 7.R.2 and 7.R.3].

- Study results suggested that the PK of tirabrutinib is affected by meal.
- Patients in the tirabrutinib 320 mg QD (either fasted or non-fasted) group had no specified meal time, which could be inconsistent within and among individuals.

PMDA accepted the explanation of the applicant.

7.R.5.2 Dose adjustment of tirabrutinib

The applicant's explanation about the justification of dose adjustment criteria for tirabrutinib in patients with recurrent or refractory PCNSL:

Study 02 defined criteria for interruption, dose reduction, and discontinuation of tirabrutinib in case of an adverse event. Tirabrutinib was administered in accordance with these criteria and well tolerated in the study. Therefore, the dose adjustment criteria for tirabrutinib were specified in the "Precautions for Dosage and Administration" section according to Study 02. However, for the following reason, the dose adjustment criteria for skin disorders need not be the same as those used in Study 02 but rather may follow those for non-hematological toxicity.

- In Study 02, dose adjustment criteria related to Grade 2 skin disorder[47)] were added because of a high incidence of skin disorder. However, in 9 of 11 patients with Grade 2 skin disorder, the event was controllable by appropriate treatment while continuing treatment with tirabrutinib.

PMDA's view:

PMDA accepted the applicant's explanation about the dose adjustment criteria in case of adverse drug reactions except for skin disorder. However, dose adjustment criteria for skin disorder should be the same as used in Study 02, taking account of the following: (a) caution should be used against skin disorder associated with tirabrutinib [see Section 7.R.3.5], and (b) tirabrutinib was well tolerated when the dose was adjusted according to the criteria used in Study 02.

7.R.6 Post-marketing investigations

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

In order to investigate the safety, etc. of tirabrutinib in post-marketing clinical use, the applicant plans to conduct post-marketing surveillance targeting patients with recurrent or refractory PCNSL who are treated with tirabrutinib.

The safety specification of the surveillance include the following events requiring caution in treatment with tirabrutinib: infection, severe skin disorder, bone marrow depression, hypersensitivity, ILD, hepatic

47) If symptoms resolve or improve by symptomatic treatments (antihistamine, corticosteroid, etc.), continue treatment with tirabrutinib. If not, continue treatment with tirabrutinib at a 1-level lower dose or interrupt at the discretion of the physician. The treatment may be resumed after interruption at the discretion of the physician.

dysfunction, and haemorrhage. Because of the limited safety information in long-term treatment with tirabrutinib, long-term safety was included in the safety specification.

The planned sample size is 100 patients, based on the incidences of events Study 02 included in in the above safety specification.

The observation period is 52 weeks, considering that most of the events included in the safety specification occurred within 52 weeks after the start of treatment in Study 02, etc.

PMDA's view:
Because of the extremely limited safety information of tirabrutinib, the surveillance should cover all patients treated with tirabrutinib for a certain period after the market launch, to collect safety data promptly in an unbiased manner and to provide healthcare professionals with obtained safety information without delay.

The safety specification of the surveillance, based on the review in Section "7.R.3 Safety," should include infection, severe skin disorder, bone marrow depression, hypersensitivity, ILD, hepatic dysfunction, and haemorrhage. Although there is only limited safety information on the long-term treatment with tirabrutinib, no specific safety concerns associated with the long-term treatment observed in the clinical studies. Therefore, there is little need to include long-term safety in the safety specification on the premise that safety information, including long-term safety, is collected appropriately during the planned follow-up period.

The sample size and the follow-up period planned by the applicant are acceptable.

7.3 Adverse events, etc. observed in the clinical studies

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

7.3.1 Japanese Phase I study (Study 04)

Adverse events were observed in 1 of 12 patients (8.3%) in the fasted group in Part A, 1 of 12 patients (8.3%) in the non-fasted group in Part A, 0 of 12 patients in the tirabrutinib alone group in Part B, 4 of 12 patients (33.3%) in the tirabrutinib/itraconazole group in Part B, 0 of 12 patients in the midazolam alone group in Part C, and 9 of 12 patients (75.0%) in the tirabrutinib/midazolam group in Part C. Adverse events for which a causal relation to the study drug could not be ruled out were observed in 1 of 12 patients (8.3%) in the fasted group in Part A, 1 of 12 patients (8.3%) in the non-fasted group in Part A and 9 of 12 patients (75.0%) receiving tirabrutinib/midazolam in Part C (0 in patients receiving tirabrutinib alone in Part B, tirabrutinib/itraconazole in Part B, or midazolam alone in Part C). Adverse events with an incidence of ≥10% were nasopharyngitis in 2 patients (16.7%) receiving tirabrutinib/itraconazole in Part B and high density lipoprotein decreased in 9 patients (75.0%) receiving tirabrutinib/midazolam in Part C (0 in the fasted group in Part A, the non-fasted group in Part A, the tirabrutinib alone group in Part B, or the midazolam alone group in Part C).

No serious adverse event was observed in any treatment group.

An adverse event led to the discontinuation of the study drug in 1 of 12 patients (8.3%) receiving the tirabrutinib/itraconazole in Part B. The event was nasopharyngitis in 1 patient, and its causal relationship to the study drug was ruled out.

7.3.2 Japanese Phase I study (Study 01)

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 2 of 3 patients (66.7%) in the 160 mg QD group, 3 of 3 patients (100%) in the 320 mg QD group, 4 of 4 patients (100%) in the 480 mg QD group, and 6 of 7 patients (85.7%) in the 300 mg BID group. Adverse events with an incidence of ≥50% were malaise and myalgia in 2 patients (66.7%) in the 160 mg QD group, neutrophil count decreased, white blood cell count decreased, and rash in 2 patients (66.7%) each in the 320 mg QD group, and anaemia, vomiting, hypokalaemia, hypophosphataemia, and rash in 2 patients (50.0%) each in the 480 mg QD group (0 in the 300 mg BID group).

Serious adverse events were observed in 1 of 3 patients (33.3%) in the 160 mg QD group, 2 of 3 patients (66.7%) in the 320 mg QD group, 2 of 4 patients (50.0%) in the 480 mg QD group, and 2 of 7 patients (28.6%) in the 300 mg BID group. These events were anal fistula and hepatitis B reactivation in 1 patient (33.3%) each in the 160 mg QD group, acute myeloid leukaemia and neuroendocrine carcinoma of the skin in 1 patient (33.3%) each in the 320 mg QD group, Mallory-Weiss syndrome and spinal column stenosis in 1 patient (25.0%) each in the 480 mg QD group, and pyrexia, pneumonia bacterial, and pneumonitis in 1 patient (14.3%) each in the 300 mg BID group. A causal relationship to the study drug could not be ruled out for hepatitis B reactivation in 1 patient in the 160 mg QD group, acute myeloid leukaemia in 1 patient in the 320 mg QD group, Mallory-Weiss syndrome in 1 patient in the 480 mg QD group, and pneumonitis in 1 patient in the 300 mg BID group.

Adverse events led to the discontinuation of the study drug in 2 of 3 patients (66.7%) in the 320 mg QD group (0 in the 160 mg QD, 480 mg QD, or 300 mg BID group). These events were acute myeloid leukaemia and neuroendocrine carcinoma of the skin in 1 patient (33.3%) each. A causal relationship to the study drug could not be ruled out for acute myeloid leukaemia in 1 patient.

7.3.3 Japanese Phase I/II study (Study 02)

Adverse events were observed in 16 of 20 patients (80.0%) in the 320 mg group, 7 of 7 patients (100%) in the 480 mg group, and 15 of 17 patients (88.2%) in the 480 mg fasted group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 15 of 20 patients (75.0%) in the 320 mg group, 7 of 7 patients (100%) in the 480 mg group, and 13 of 17 patients (76.5%) in the 480 mg fasted group. Adverse events with an incidence of ≥20% were rash in 6 patients (30.0%) and blood bilirubin increased in 4 patients (20.0%) in the 320 mg group, erythema multiforme in 3 patients (42.9%), lymphopenia, cataract, urinary tract infection, white blood cell count decreased, platelet count decreased, and rash in 2 patients (28.6%) each in the 480 mg group, and rash in 6 patients (35.3%) and constipation in 4 patients (23.5%) in the 480 mg fasted group.

Serious adverse events were observed in 1 of 20 patients (5.0%) in the 320 mg group, 5 of 7 patients (71.4%) in the 480 mg group and 3 of 17 patients (17.6%) in the 480 mg fasted group. The observed evets were seizure and haemorrhage intracranial in 1 patient (5.0%) each in the 320 mg group, erythema multiforme in 2 patients (28.6%), cataract, *Pneumocystis jirovecii* pneumonia, ILD, and drug eruption in 1 patient (14.3%) each in the 480 mg group, and bronchopulmonary aspergillosis, pneumonia, spinal compression fracture, seizure, and haematuria in 1 patient (5.9%) each in the 480 mg fasted group. A causal relationship to the study drug could not be ruled out for erythema multiforme in 2 patients, *Pneumocystis jirovecii* pneumonia, ILD, and drug eruption in 1 patient each in the 480 mg group, and bronchopulmonary aspergillosis, pneumonia, and haematuria in 1 patient each in the 480 mg fasted group.

Adverse events leading to the discontinuation of the study drug were observed in 1 of 20 patients (5.0%) in the 320 mg group and 2 of 7 patients (28.6%) in the 480 mg group (0 in the 480 mg fasted group). The observed events were drug eruption in 1 patient (5.0%) in the 320 mg group and *Pneumocystis jirovecii* pneumonia, ILD, and drug eruption in 1 patient (14.3%) each in the 480 mg group. A causal relationship to the study drug could not be ruled out for any of these events.

7.3.4 Foreign Phase I study (Study POE001)

7.3.4.1 Patients with CLL

Adverse events were observed in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 3 of 3 patients (100%) in the 20 mg group, 3 of 3 patients (100%) in the 40 mg group, 3 of 4 patients (75.0%) in the 80 mg group, 3 of 3 patients (100%) in the 160 mg group, 2 of 3 patients (66.7%) in the 320 mg group, 3 of 3 patients (100%) in the 400 mg group, 2 of 3 patients (66.7%) in the 500 mg group, 2 of 3 patients (66.7%) in the 600 mg group, and 2 of 3 patients (66.7%) in the 300 mg BID group. Adverse events with an incidence of ≥40% were constipation and pyrexia in 2 patients (66.7%) each in the 20 mg group, neutropenia in 2 patients (66.7%) in the 40 mg group, dry skin in 2 patients (50.0%) in the 80 mg group, petechiae in 3 patients (100%) and contusion in 2 patients (66.7%) in the 160 mg group, pharyngitis and traumatic haematoma in 2 patients (66.7%) each in the 320 mg group, anaemia in 2 patients (66.7%) in the 400 mg group, erythema in 2 patients (66.7%) in the 500 mg group, pyrexia in 2 patients (66.7%) in the 600 mg group, and anaemia in 2 patients (66.7%) in the 300 mg BID group.

Serious adverse events were observed in 1 of 3 patients (33.3%) in the 20 mg group, 1 of 3 patients (33.3%) in the 40 mg group, 2 of 4 patients (50.0%) in the 80 mg group, 1 of 3 patients (33.3%) in the 320 mg group, 1 of 3 patients (33.3%) in the 400 mg group, 1 of 3 patients (33.3%) in the 500 mg group, and 2 of 3 patients (66.7%) in the 600 mg group (0 in the 160 mg or 300 mg BID group). The observed events were neutropenic infection, febrile neutropenia, and pyrexia in 1 patient (33.3%) each in the 20 mg group, neutropenic sepsis, bacteraemia, lower respiratory tract infection fungal, and sepsis in 1 patient (33.3%) each in the 40 mg group, rash and squamous cell carcinoma of skin in 1 patient (25.0%) each in the 80 mg group, neutropenia and anxiety in 1 patient (33.3%) each in the 320 mg group, lymphocytic infiltration and purpura in 1 patient (33.3%) each in the 400 mg group, pneumonia pneumococcal and spontaneous haematoma in 1 patient (33.3%) each in the 500 mg group, and neutropenic sepsis, pyrexia, inguinal hernia strangulated, and cardiac function disturbance postoperative

in 1 patient (33.3%) each in the 600 mg group. A causal relationship to the study drug could not be ruled out for febrile neutropenia and pyrexia in 1 patient each in the 20 mg group, rash in 1 patient in the 80 mg group, neutropenia in 1 patient in the 320 mg group, lymphocytic infiltration and purpura in 1 patient each in the 400 mg group, and spontaneous haematoma in 1 patient in the 500 mg group.

Adverse events led to the discontinuation of the study drug in 1 of 3 patients (33.3%) in the 400 mg group, 2 of 3 patients (66.7%) in the 500 mg group, and 1 of 3 patients (33.3%) on 600 mg (0 in the 20, 40, 80, 160, or 320 mg, or 300 mg BID group). The observed events were lymphocytic infiltration and purpura in 1 patient (33.3%) each in the 400 mg group, immune thrombocytopenic purpura and spontaneous haematoma in 1 patient (33.3%) each in the 500 mg group, and cardiac function disturbance postoperative in 1 patient (33.3%) in the 600 mg group. A causal relationship to the study drug could not be ruled out for lymphocytic infiltration and purpura in 1 patient each in the 400 mg group and spontaneous haematoma and immune thrombocytopenic purpura in 1 patient each in the 500 mg group.

7.3.4.2 Patients with B-NHL

Adverse events were observed in 3 of 3 patients (100%) in the 20 mg group, 3 of 3 patients (100%) in the 40 mg group, 4 of 5 patients (80.0%) in the 80 mg group, 7 of 8 patients (87.5%) in the 160 mg group, 19 of 21 patients (90.5%) in the 320 mg group, 9 of 10 patients (90.0%) in the 480 mg group, 9 of 9 patients (100%) in the 600 mg group, and 3 of 3 patients (100%) in the 240 mg BID group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 3 of 3 patients (100%) in the 20 mg group, 3 of 3 patients (100%) in the 40 mg group, 2 of 5 patients (40.0%) in the 80 mg group, 4 of 8 patients (50.0%) in the 160 mg group, 11 of 21 patients (52.4%) in the 320 mg group, 6 of 10 patients (60.0%) in the 480 mg group, 5 of 9 patients (55.6%) in the 600 mg group, and 1 of 3 patients (33.3%) in the 240 mg BID group. Adverse events with an incidence of ≥40% were anaemia and thrombocytopenia in 2 patients (66.7%) each in the 20 mg group, asthenia and nasopharyngitis in 2 patients (66.7%) each in the 40 mg group, anaemia and thrombocytopenia in 3 patients (60.0%) each and neutropenia in 2 patients (40.0%) in the 80 mg group, anaemia in 9 patients (42.9%) in the 320 mg group, and lymphopenia in 2 patients (66.7%) in the 240 mg BID group (0 in the 160 mg, 480 mg, or 600 mg group).

Serious adverse events were observed in 2 of 3 patients (66.7%) in the 20 mg group, 2 of 5 patients (40.0%) in the 80 mg group, 1 of 8 patients (12.5%) in the 160 mg group, 6 of 21 patients (28.6%) in the 320 mg group, 2 of 10 patients (20.0%) in the 480 mg group, 5 of 9 patients (55.6%) in the 600 mg group, and 1 of 3 patients (33.3%) in the 240 mg BID group (0 in the 40 mg group). These events were *Escherichia* urinary tract infection, small intestinal haemorrhage, and urinary retention in 1 patient (33.3%) each in the 20 mg group, general physical condition decreased, anaemia, and myeloma cast nephropathy in 1 patient (20.0%) each in the 80 mg group, herpes zoster oticus and febrile neutropenia in 1 patient (12.5%) each in the 160 mg group, lower respiratory tract infection, infection, constipation, ear haemorrhage, excessive cerumen production, cardiac failure, hypersensitivity, and myelodysplastic syndrome in 1 patient (4.8%) each in the 320 mg group, *Pneumocystis jirovecii* pneumonia, H1N1 influenza, adverse drug reaction, activated partial thromboplastin time prolonged, and INR increased in 1 patient (10.0%) each in the 480 mg group, lower respiratory tract infection, influenza, upper respiratory tract infection, ill-defined disorder, and pleural effusion in 1 patient (11.1%) each in the

600 mg group, and device related infection in 1 patient (33.3%) in the 240 mg BID group. A causal relationship to the study drug could not be ruled out for hypersensitivity in 1 patient on 320 mg, adverse drug reaction in 1 patient on 480 mg, and ill-defined disorder and influenza in 1 patient each on 600 mg.

Adverse events led to the discontinuation of the study drug in 1 of 5 patients (20.0%) in the 80 mg group, 4 of 21 patients (19.0%) in the 320 mg group, 1 of 10 patients (10.0%) in the 480 mg group, 2 of 9 patients (22.2%) in the 600 mg group, and 1 of 3 patients (33.3%) in the 240 mg BID group (0 in the 20, 40, or 160 mg group). These events were myeloma cast nephropathy in 1 patient (20.0%) in the 80 mg group, infection, hypersensitivity, general physical condition abnormal, and myelodysplastic syndrome in 1 patient (4.8%) each in the 320 mg group, H1N1 influenza and *Pneumocystis jirovecii* pneumonia in 1 patient (10.0%) each in the 480 mg group, cardiac arrest and ill-defined disorder in 1 patient (11.1%) each in the 600 mg group, and device related infection in 1 patient (33.3%) in the 240 mg BID group. A causal relationship to the study drug could not be ruled out for hypersensitivity in 1 patient on 320 mg and ill-defined disorder in 1 patient on 600 mg.

7.3.5 Foreign Phase I study (Study 1765)

Adverse events were observed in 1 of 15 patients (6.7%) in the Treatment A group, 6 of 15 patients (40.0%) in the Treatment B group, 5 of 14 patients (35.7%) in the Treatment C group, and 1 in 14 patients (7.1%) in the Treatment D group. A causal relationship to the study drug could not be ruled out for adverse events in 6 of 15 patients (40.0%) in the Treatment B group, 4 of 14 patients (28.6%) in the Treatment C group, and 1 of 14 patients (7.1%) in the Treatment D group (0 in the Treatment A group). Adverse events with an incidence of ≥10% in the Treatment B and C groups were chromaturia in 6 patients (40.0%) and chromaturia in 2 patients (14.3%), respectively (0 in the Treatment A or D group).

There were no serious adverse events or adverse events leading to the discontinuation of the study drug in any treatment group.

7.3.6 Foreign Phase I study (Study 1767)

7.3.6.1 Cohort 1

Adverse events were observed in 3 of 16 patients (18.8%) in the tirabrutinib capsule 100 mg fasted group, 3 of 16 patients (18.8%) in the placebo fasted group, 1 of 16 patients (6.3%) in the tirabrutinib Tablet A 100 mg fasted group, and 3 of 16 patients (18.8%) in the tirabrutinib Tablet B 100 mg fasted group. There were no adverse events for which a causal relationship to the study drug could not be ruled out in any treatment group. Adverse events with an incidence of ≥10% were nausea in 2 patients (12.5%) in the tirabrutinib capsule 100 mg fasted group and headache in 2 patients (12.5%) in the tirabrutinib Tablet B 100 mg fasted group (0 in the placebo fasted group or tirabrutinib Tablet A 100 mg fasted group).

There were no serious adverse events or adverse events leading to the discontinuation of the study drug in any treatment group.

7.3.6.2 Cohort 2

Adverse events were observed in 0 of 12 patients in the tirabrutinib Tablet A 100 mg fasted group, 0 of 12 patients in the tirabrutinib Tablet A 100 mg non-fasted group, 2 of 12 patients (16.7%) in the tirabrutinib capsule 75 mg fasted group, and 0 of 12 patients in the tirabrutinib capsule 75 mg non-fasted group. There were no adverse events for which a causal relationship to the study drug could not be ruled out in any treatment group.

There were no adverse events with an incidence of ≥10%; serious adverse events, or adverse events leading to the discontinuation of the study drug in any group.

7.3.6.3 Cohort 3

Adverse events were observed in 0 of 12 patients in the tirabrutinib Tablet A 100 mg alone group, 4 of 24 patients (16.7%) in the omeprazole alone group, 1 of 12 patients (8.3%) in the tirabrutinib Tablet A 100 mg/omeprazole group, 0 of 12 patients in the tirabrutinib capsule 75 mg alone group, and 1 of 12 patients (8.3%) in the tirabrutinib capsule 75 mg/omeprazole group. A causal relationship to the study drug could not be ruled out for adverse events observed in 1 of 24 patients (4.2%) on omeprazole alone and 1 of 12 patients (8.3%) on tirabrutinib capsule 75 mg/omeprazole (0 in patients on tirabrutinib Tablet A 100 mg alone, tirabrutinib Tablet A 100 mg/omeprazole, or tirabrutinib capsule 75 mg alone).

There were no adverse events with an incidence of ≥10%; serious adverse events, or adverse events leading to the discontinuation of the study drug in any group.

7.3.6.4 Cohort 4

Adverse events were observed in none of the treatment groups.

7.3.7 Foreign Phase I study (Study 1768)

Adverse events were observed in 4 of 8 patients (50.0%). A causal relationship to the study drug could not be ruled out for events in 2 of 8 patients (25.0%). These events were abdominal discomfort, change of bowel habit, diarrhoea, nausea, malaise, gastroenteritis, headache, nasal congestion, and dry skin in 1 patient (12.5%) each.

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

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 inspection is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

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

The inspection is currently ongoing. Results and the conclusion of PMDA will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that tirabrutinib has a certain level of efficacy in the treatment of recurrent or refractory PCNSL, and that tirabrutinib has acceptable safety in view of its benefits. Tirabrutinib is a drug with a new active ingredient that suppresses tumor growth by inhibiting the activity of BTK, a signal transduction molecule downstream of BCR. Tirabrutinib is thus expected to be of clinical significance as a treatment option for recurrent or refractory PCNSL. The clinical positioning, indication, dosage and administration, etc. should be further evaluated.

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

Review Report (2)

February 4, 2020

Product Submitted for Approval

Brand Name	Velexbru Tablets 80 mg
Non-proprietary Name	Tirabrutinib Hydrochloride
Applicant	Ono Pharmaceutical Co., Ltd.
Date of Application	August 28, 2019

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

As a result of its discussion in Section "7.R.2 Efficacy" in the Review Report (1), PMDA concluded that a certain level of efficacy of tirabrutinib was demonstrated in patients with recurrent or refractory PCNSL, based on the "IPCG criteria-based, centrally assessed response rate [95% CI]," which was the primary endpoint in the Phase II of the Japanese Phase I/II study (Study 02) in patients with recurrent or refractory PCNSL. The result in the 480 mg fasted group was 52.9% [27.8%, 77.0%] (9 of 17) of patients, exceeding the pre-defined threshold response rate (14%).

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

1.2 Safety

As a result of the discussion in Section "7.R.3 Safety" in the Review Report (1), PMDA concluded that the use of tirabrutinib requires attention to adverse events, in particular, bone marrow depression, infection, ILD, skin disorder, hemorrhage, hepatic dysfunction, and hypersensitivity.

PMDA also concluded that although the treatment requires vigilance against the above-mentioned adverse events, tirabrutinib is tolerable as long as physicians with adequate knowledge and experience in cancer chemotherapy take appropriate measures, such as monitoring and controlling, to cope with these events.

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

- Ibrutinib has a similar action mechanism to that of tirabrutinib, and during its use, hemorrhage occurred without decreased platelet count. The relationship between decreased platelet count and hemorrhage associated with tirabrutinib should be investigated, and the necessity of cautionary advice on the use of tirabrutinib, as given for ibrutinib, should be discussed.

PMDA asked the applicant to explain the relationship between hemorrhage and decreased platelet count.

The applicant's explanation:
In Studies 02 and 01, hemorrhage[48)] was observed in 5 and 4 patients, respectively, and none of them had decreased platelet count.[49)] Among 52 patients experiencing hemorrhage in Study POE001, 13 patients (25.0%) showed decreased platelet count.[49)] Among 5 patients with serious hemorrhage in Study POE001, 3 patients showed a decrease in platelet count,[49)] but hemorrhage and decreased platelet count[49)] did not occur concurrently, suggesting that there is no clear relationship between the 2 events.

PMDA's view:
Because of the limited availability of safety findings of tirabrutinib, it is difficult to definitely conclude the relationship between hemorrhage and a decrease in platelet count. In light of hemorrhage not accompanied by decreased platelet count observed in the above clinical studies, tirabrutinib may cause hemorrhage with or without decreased platelet count, as is the case with ibrutinib. The occurrence of hemorrhage in the clinical studies, including the above observations, should be appropriately communicated to healthcare professionals using the package insert, etc. Meanwhile, ibrutinib was reported to induce massive bleeding associated with surgical treatment, suggesting a possibility that such event may also occur with tirabrutinib. The interruption of tirabrutinib should be considered for patients on tirabrutinib who will undergo surgery or other invasive procedures, and this should be communicated to healthcare professionals.

PMDA instructed the applicant to take appropriate actions, to which the applicant agreed.

1.3 Clinical positioning and indication

After the discussion in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), PMDA concluded that the indication for tirabrutinib should be defined as "recurrent or refractory primary central nervous system lymphoma" as proposed, while noting in the "Clinical Studies" section of the package insert that patients with non-B-cell PCNSL were excluded from the studies, along with the following advice in the "Precautions for Indication" section:

Precautions for Indication

- Physicians should be well-versed in the findings presented in the "Clinical Studies" section to have a full understanding of the efficacy and safety of tirabrutinib before selecting eligible patients.

48) PTs falling under the MedDRA SMQ of "Haemorrhage terms (excl laboratory terms) (narrow)"
49) MedDRA PT of "Thrombocytopenia" or "Platelet count decreased"

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

PMDA instructed the applicant to finalize the descriptions in the "Indication" and "Precautions for Indication" sections as above. The applicant agreed.

1.4 Dosage and administration

After the discussion in Section "7.R.5 Dosage and administration" in the Review Report (1), PMDA concluded that the Dosage and Administration and Precautions for Dosage and Administration sections should be described as below.

Dosage and Administration

The usual adult dosage is 480 mg of tirabrutinib administered orally once daily under fasting conditions. The dose may be reduced according to the patient's condition.

Precautions for Dosage and Administration

- The efficacy and safety of tirabrutinib in combination with other antineoplastic agents have not been established.
- C_{max} and AUC of tirabrutinib are reported to increase when administered after a meal. In order to avoid food effect, the use of tirabrutinib should be avoided from 1 hour before until 2 hours after a meal.
- Guidelines for dose adjustment in case of adverse drug reactions

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

- While tirabrutinib 480 mg QD (fasted) is the appropriate standard dosage regimen, the treatment may be started with a dose of <480 mg. The efficacy and safety results of tirabrutinib 320 mg QD (either fasted or non-fasted) are useful reference for treatment with a low dose of tirabrutinib, which should preferably be disseminated to healthcare professionals appropriately.

Taking account of the comments raised in the Expert Discussion, PMDA concluded that the results of the tirabrutinib 320 mg QD (either fasted or non-fasted) of Study 02 should be disseminated through written materials.

Thus, PMDA instructed the applicant to describe the "Dosage and Administration" and "Precautions for Dosage and Administration" sections as above, to which the applicant agreed.

1.5 Risk management plan (draft)

In order to investigate the safety of tirabrutinib in its post-marketing clinical use, the applicant plans to conduct post-marketing surveillance targeting patients with recurrent or refractory PCNSL who are on tirabrutinib. The planned sample size is 100 patients and the follow-up period is 52 months.

After the discussion in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA concluded that post-marketing surveillance should be conducted covering all patients receiving

tirabrutinib for a certain period after the market launch, throughout which safety data should be accumulated promptly and in an unbiased manner, and obtained safety findings should be provided to healthcare professionals without delay.

PMDA further concluded on the surveillance plan that:

- The safety specification of the surveillance should include infection, severe skin disorder, bone marrow depression, hypersensitivity, ILD, hepatic dysfunction, and hemorrhage.
- The planned sample size and the follow-up period proposed by the applicant are acceptable.

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

PMDA instructed the applicant to re-examine the surveillance plan based on the above discussion.

The applicant's response:

- The surveillance will be conducted covering all patients receiving tirabrutinib for a certain post-marketing period.

- The safety specification will include infection, severe skin disorder, bone marrow depression, hypersensitivity, ILD, hepatic dysfunction, and hemorrhage.

PMDA accepted the response of the applicant.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) should include the safety specification presented in Table 31, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 32 and 33.

Table 31. Safety and efficacy specifications in risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infection • Severe skin disorder • Bone marrow depression • Hypersensitivity • ILD • Hepatic dysfunction • Hemorrhage	• Embryo-fetal toxicity	Not applicable
Efficacy specification		
Not applicable		

Table 32. Summary of additional pharmacovigilance activities, efficacy surveillance and studies, and additional risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy surveillance and studies	Additional risk minimization activities
• Early post-marketing Phase vigilance • Specified drug use-results survey (all-case surveillance) • Post-marketing clinical studies (extension of Study 02 [tirabrutinib 480 mg QD (fasted) group only] and Study ONO-4059-02E*)	Not applicable	• Information provision based on the early post-marketing Phase vigilance • Preparation and distribution of materials for healthcare professionals

* A compassionate study focused mainly on the tirabrutinib 480 mg QD (fasted) group in Study 02.

Table 33. Outline of post-marketing surveillance plan (draft)

Objective	To confirm the safety of tirabrutinib in the post-marketing clinical use
Survey method	All-case surveillance
Population	All patients receiving tirabrutinib
Follow-up period	52 weeks
Planned sample size	100
Main survey items	Safety specification: infection, severe skin disorder, bone marrow depression, hypersensitivity, ILD, hepatic dysfunction, and hemorrhage Other main survey items: patient characteristics (age, sex, past illness, comorbidities, etc.), status of tirabrutinib administration, concomitant drugs, adverse events, etc.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection found inaccuracy in the attached data set, i.e., some erroneous descriptions owing to errors in statistical analyses, for which improvement was sought. However, the errors had no significant impact on the review. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application document submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that tirabrutinib may be approved for the indication and dosage and administration shown below, with the following approval conditions. The approval is, however, granted on the premise of appropriate cautionary advice given through the package insert, information provision on its proper use in the post-marketing setting, and its proper use strictly practiced under the supervision of physicians with adequate knowledge and experience in cancer chemotherapy at medical institutions capable of emergency response. Tirabrutinib is an orphan drug,

and its re-examination period is 10 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Recurrent or refractory primary central nervous system lymphoma

Dosage and Administration

The usual adult dosage is 480 mg of tirabrutinib administered orally once daily under fasting conditions. The dose may be reduced according to the patient's condition.

Approval Conditions

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

2. Because of extremely limited number of cases in Japanese clinical studies, the applicant is required to conduct a drug use-results survey involving all patients treated with the product after its market launch until obtaining data from a certain number of patients, in order to identify the characteristics of patients using the product and to promptly collect safety and efficacy data so that necessary measures are taken for the proper use of the product.

Warning

The product should be administered only to patients recognized as eligible for the treatment with the product by a physician with adequate knowledge and experience in cancer chemotherapy at a medical institution capable of an emergency response. Prior to treatment, patients or their family members should be thoroughly informed of the potential risks and benefits of the treatment and provide consent.

Contraindication

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

Precautions for Indication

Physicians should be well-versed in the findings presented in the "Clinical Studies" section to have a full understanding of the efficacy and safety of tirabrutinib before selecting eligible patients.

Precautions for Dosage and Administration

1. The Efficacy and safety of tirabrutinib in combination with other antineoplastic agents has not been established.

2. It is reported that C_{max} and AUC of tirabrutinib increase if tirabrutinib is administered after a meal. In order to avoid the food effect, use of tirabrutinib should be avoided from 1 hour before until 2 hours after a meal.

3. If adverse drug reactions occur following the treatment, tirabrutinib should be interrupted, reduced in dose, or discontinued according to the following criteria.

Level of tirabrutinib dose reduction

Level	Dose
Usual dose	480 mg
1-level lower dose	320 mg
2-level lower dose	160 mg

Guidelines for treatment interruption, dose reduction, and discontinuation in case of adverse drug reactions

Adverse drug reaction*		Measures to be taken
Grade ≥3 febrile neutropenia Grade 3 thrombocytopenia with hemorrhage Grade 4 neutropenia Grade 4 thrombocytopenia		Interrupt tirabrutinib until recovery to Grade ≤2 (Grade ≤3 for neutropenia). After recovery, tirabrutinib may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tirabrutinib until recovery. After recovery, treatment may be resumed at 1-level lower dose.
Interstitial lung disease	Grade 2 or 3	Interrupt tirabrutinib until recovery to Grade ≤1. After recovery, tirabrutinib may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tirabrutinib until recovery. After recovery, tirabrutinib may be resumed at 1 level lower dose.
	Grade 4	Discontinue tirabrutinib.
Skin disorder	Grade 2	Administer antihistamine, adrenocorticosteroid, etc. If resolved, continue tirabrutinib. If the symptom does not resolve, continue tirabrutinib at 1-level lower dose or interrupt tirabrutinib.
	Grade ≥3	Administer antihistamine, adrenocorticosteroid, etc., and interrupt tirabrutinib until recovery to Grade ≤2. After recovery, tirabrutinib may be resumed at 1-level lower dose.
Grade ≥3 hematotoxicity (other than events described above) and Grade ≥3 nonhematological toxicity (other than interstitial lung disease and skin disorder)		Interrupt tirabrutinib until recovery to Grade ≤2. After recovery, tirabrutinib may be resumed at the dose before interruption. If the symptom recurs after resumption, interrupt tirabrutinib until recovery. After recovery, tirabrutinib may be resumed at 1-level lower dose.

* Grade is defined according to NCI-CTCAE v4.0.

Appendix

List of Abbreviations

7-AAD	7-amino actinomycin D
ABC-DLBCL	activated B cell subtype diffuse large B cell lymphoma
ADP	adenosine diphosphate
A/G ratio	albumin-globulin ratio
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Application	Marketing application
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BA	bioavailability
BCR	B cell receptor
BCRP	breast cancer resistance protein
BID	bis in die
BLK	B lymphoid tyrosine kinase
BMX	bone marrow expressed kinase
B-NHL	B-cell non-Hodgkin lymphoma
BTK	Bruton's tyrosine kinase
CHO cell line	Chinese hamster ovary cell line
CI	confidence interval
CLL	chronic lymphocytic leukemia
CMV	cytomegalovirus
CPP	critical process parameter
CQA	critical quality attribute
CR	complete response
CRu	unconfirmed complete response
CYP	cytochrome P450
^{14}C-labeled tirabrutinib	^{14}C-labeled tirabrutinib hydrochloride
DLBCL	diffuse large B cell lymphoma
DLT	dose limiting toxicity
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
efflux ratio	The ratio of permeability coefficient in the secretive direction to that in the absorptive direction
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
FcγR	Fcγ receptor
FRET	fluorescence resonance energy transfer
GCB-DLBCL	germinal center B cell subtype diffuse large B cell lymphoma
GGT	γ-glutamyltransferase
GST-P	glutathione S-transferase placental form
HBV	hepatitis B virus
HER	human epidermal growth factor receptor
hERG	human ether-a-go-go related gene
HIV	human immunodeficiency virus
HLGT	high level group term
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q1E Guideline	"Guideline on the Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)

ICH Q3A Guideline	“Guideline on Impurities in New Drug Substances” (PFSB/ELD Notification No. 1216001, dated December 16, 2002)
ICH Q3B Guideline	“Guideline on Impurities in New Drug Products” (PFSB/ELD Notification No. 0624001 dated June 24, 2003)
Ig	immunoglobulin
IL	interleukin
ILD	interstitial lung disease
INR	international normalized ratio
IPCG	International PCNSL Collaborative Group
IR	infrared absorption spectrum
ITK	inducible T cell kinase
JAK	janus kinase
ka	absorption rate constant
K_i	inhibition constant
$K_{i,\ app}$	apparent inhibition constant
k_{inact}	maximum inactivation rate constant
KLH	keyhole limpet hemocyanin
LC	liquid chromatography
LCK	lymphocyte-specific protein tyrosine kinase
LC-MS/MS	Liquid chromatography/tandem mass spectrometry
MATE	multidrug and toxin extrusion
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
M-CSF	macrophage-colony stimulating factor
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
mRNA	messenger ribonucleic acid
MRP	multidrug resistance associated protein
MTD	maximum tolerated dose
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology in Central nervous system cancers
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NMR	nuclear magnetic resonance spectrum
NZW	New Zealand White
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OS	overall survival
$P_{app\ A \rightarrow B}$	apparent permeability in apical to basolateral direction
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based pharmacokinetic
PCNSL	primary central nervous system lymphoma
PD	progressive disease
P-gp	P-glycoprotein
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PS	performance status
PT	preferred term

PTP	press through packaging
QbD	quality by design
QD	quaque die
QID	quarter in die
(Q)SAR	(quantitative) structure-activity relationship
QTcF	QT interval corrected by Fridericia's method
RANKL	receptor activator of nuclear factor-κB ligand
SCID mouse	severe combined immunodeficient mouse
SD	stable disease
SMQ	standard MedDRA queries
SOC	system organ class
ST-combination	Sulfamethoxazole/trimethoprim
Study 01	Study ONO-4059-01
Study 02	Study ONO-4059-02
Study 04	Study ONO-4059-04
Study 1765	Study GS-US-401-1765
Study 1767	Study GS-US-401-1767
Study 1768	Study GS-US-401-176
Study POE001	Study ONO-4059POE001
TCR	T cell receptor
TEC	tyrosine kinase expressed in hepatocellular carcinoma
TID	ter in die
Tirabrutinib	Tirabrutinib Hydrochloride
TLR	Toll-like receptor
TNF-α	tumor necrosis factor-α
TXK	tyrosine protein kinase
UDPGA	uridine diphosphate glucuronic acid
UGT	uridine diphosphate glucuronosyl transferase
V2/F	volume of distribution of the central compartment
VZV	varicella zoster virus
ΔQTcF	Change in QTcF from baseline