Report on the Deliberation Results

December 2, 2016

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

Brand Name	(a) Treakisym Injection 25 mg, (b) Treakisym Injection 100 mg
Non-proprietary Name	Bendamustine Hydrochloride (JAN*)
Applicant	SymBio Pharmaceuticals Limited
Date of Application	(a) October 5, 2016, (b) December 24, 2015

Results of Deliberation
In its meeting held on November 24, 2016, the Second Committee on New Drugs concluded that the partial change application for 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 re-examination period for this application is the remainder of the re-examination period for the initial approval (until October 26, 2020).

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

**Japanese Accepted Name (modified INN)*

Review Report

November 16, 2016

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	(a) Treakisym Injection 25 mg, (b) Treakisym Injection 100 mg
Non-proprietary Name	Bendamustine Hydrochloride
Applicant	SymBio Pharmaceuticals Limited
Date of Application	(a) October 5, 2016, (b) December 24, 2015
Dosage Form/Strength	Lyophilized powder for injection in vials to be reconstituted before use: Each vial contains 25 or 100 mg of Bendamustine Hydrochloride
Application Classification	Prescription drug (4) Drug with a new indication (6) Drug with a new dosage
Items Warranting Special Mention	None
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 low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma and that the product has acceptable safety in view of its benefits.

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

Indications

1. ~~The following relapsed or refractory diseases~~

Low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma

2. Chronic lymphocytic leukemia

(Underline denotes additions, strike-through deletion, and double underline addition on August 26, 2016 after the submission of the application for Treakisym Injection 100 mg)

Dosage and Administration

1. ~~Relapsed or refractory~~ Low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma

(1) Untreated disease

In combination with rituximab (genetical recombination), the usual adult dosage is 90 mg/m^2 body surface area of bendamustine hydrochloride administered once daily as an intravenous infusion over 1 hour. A cycle consists of 2 consecutive days of infusion followed by a 26-day rest period and the cycle is repeated. The dose may be reduced as appropriate according to the patient's condition.

(2) Relapsed or refractory disease

The usual adult dosage is 120 mg/m^2 body surface area of bendamustine hydrochloride administered once daily as an intravenous infusion over 1 hour. A cycle consists of 2 consecutive days of infusion followed by a 19-day rest period and the cycle is repeated. The dose may be reduced as appropriate according to the patient's condition.

2. Chronic lymphocytic leukemia

The usual adult dosage is 100 mg/m^2 body surface area of bendamustine hydrochloride administered once daily as an intravenous infusion over 1 hour. A cycle consists of 2 consecutive days of infusion followed by a 26-day rest period and the cycle is repeated. The dose may be reduced as appropriate according to the patient's condition.

(Underline denotes addition, strike-through deletion, and double underline addition on August 26, 2016 after the submission of the application for Treakisym Injection 100 mg.)

Condition of Approval

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

Attachment

Review Report (1)

October 7, 2016

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	(a) Treakisym Injection 25 mg, (b) Treakisym Injection 100 mg
Non-proprietary Name	Bendamustine Hydrochloride
Applicant	SymBio Pharmaceuticals Limited
Date of Application	(a) October 5, 2016, (b) December 24, 2015
Dosage Form/Strength	Lyophilized powder for injection in vials to be reconstituted before use: Each vial contains 25 or 100 mg of Bendamustine Hydrochloride.
Proposed Indications	1. ~~The following relapsed or refractory diseases~~ Low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma 2. Chronic lymphocytic leukemia

(Underline denotes addition, strike-through deletion, and double-underline addition on August 26, 2016 after the submission of the application for Treakisym Injection 100 mg.)

Proposed Dosage and Administration

1. ~~Relapsed or refractory~~ Low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma

(1) Untreated disease

In combination with other antineoplastic agents, the usual adult dosage is 90 mg/m^2 body surface area of Bendamustine Hydrochloride administered once daily as an intravenous infusion over 1 hour. A cycle consists of 2 consecutive days of infusion followed by a 26-day rest period and the cycle is repeated. The dose may be reduced as appropriate according to the patient's condition.

(2) Relapsed or refractory disease

The usual adult dosage is 120 mg/m^2 body surface area of Bendamustine Hydrochloride administered once daily as an intravenous infusion over 1 hour. A cycle consists of 2 consecutive days of infusion followed by a 19-day rest period and the cycle is repeated. The dose may be reduced as appropriate according to the patient's condition.

2. Chronic lymphocytic leukemia

The usual adult dosage is 100 mg/m^2 body surface area of Bendamustine Hydrochloride administered once daily as an intravenous infusion over 1 hour. A cycle consists of 2 consecutive days of infusion followed by a 26-day rest period and the cycle is repeated. The dose may be reduced as appropriate according to the patient's condition.

(Underline denotes addition, strike-through deletion, and double-underline addition on August 26, 2016 after the submission of the application for Treakisym Injection 100 mg)

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List of Abbreviations

ALP	alkaline phosphatase
ALT	alanine aminotransferase
ASCT	autologous hematopoietic stem cell transplantation
AST	aspartate aminotransferase
B-NHL	B-cell non-Hodgkin lymphoma
BR	combination of bendamustine with rituximab
CI	confidence interval
CPA	cyclophosphamide
Cr	creatinine
CR	complete remission
CRu	complete remission/unconfirmed
DSMB	data and safety monitoring board
DXR	doxorubicin hydrochloride
EFS	event-free survival
ESMO guidelines	European Society for Medical Oncology Clinical Practice Guidelines
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FL	follicular lymphoma
GELF	Groupe d'Etude des Lymphomes Foliculaires
GGT	gamma-glutamyl transferase
GLSG	German Low-Grade Lymphoma Study Group
Ig	immunoglobulin
IRC	independent review committee
ITT	intent-to-treat
IWRC	International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas (1999)
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
NA	not available
NCCN Guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas
NCI-PDQ	National Cancer Institute Physician Data Query, Adult Non-Hodgkin Lymphoma Treatment
NE	not evaluated
OS	overall survival
PD	progressive disease
PFS	progression-free survival

PK	pharmacokinetics
PPK	population pharmacokinetics
PR	partial response
PSL	prednisone (unapproved in Japan)
R-CHOP	combination of rituximab with CPA, DXR, VCR, and PSL
R-CVP	combination of rituximab with CPA, VCR, and PSL
Revised RC	Revised response criteria for malignant lymphoma defined by the International Working Group (2007)
R-Hyper CVAD	combination treatment with rituximab, CPA, VCR, DXR, dexamethasone, methotrexate, and cytarabine
SD	stable disease
VCR	vincristine sulfate
WHO	World Health Organization
WHO criteria	WHO Handbook for Reporting Results of Cancer Treatment (1979)
Study 3064	Study C18083/3064/NL/MN
PMDA	Pharmaceuticals and Medical Devices Agency
Japanese clinical practice guidelines	Clinical Practice Guidelines for Hematopoietic Cancer 2013, ed. by the Japanese Society of Hematology
Bendamustine	bendamustine hydrochloride
Rituximab	rituximab (genetical recombination)

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

1.1 Overview of the product submitted for registration

Bendamustine hydrochloride (referred to as bendamustine) is a benzimidazole derivative with a nitrogen mustard moiety. It was discovered by Jenapharm GmbH in former East Germany in 1960s with an expectation of alkylation by nitrogen mustard and purine metabolism antagonistic activity derived from benzimidazole.

Bendamustine is thought to induce apoptosis and mitotic catastrophe via mitotic checkpoint inhibition, thereby exhibiting its cytotoxic action (*Clin Cancer Res.* 2008;14:309-17).

In Japan, Treakisym was approved for the indication of "relapsed or refractory low-grade B-cell non-Hodgkin's lymphoma (B-NHL) and mantle cell lymphoma (MCL)" in October 2010. After the current application, the product was approved for the indication of "chronic lymphocytic leukemia" in August 2016.

1.2 Development history etc.

For the clinical development of bendamustine for treatment of patients with untreated low-grade B-NHL or MCL, a phase III study (Study NHL 1-2003) was started by the Study Group Indolent Lymphomas, a research group on low-grade lymphoma in Germany, in patients with untreated low-grade B-NHL or MCL in September 2003. Then, a phase III study (Study 3064) was started by Cephalon, Inc. US (currently known as Teva Pharmaceutical Industries Ltd.) in patients with untreated B-NHL or MCL in April 2009.

In the US, based on the pivotal study results, namely, the interim results from Studies NHL 1-2003 and 3064, an application for marketing approval of bendamustine for patients with untreated low-grade B-NHL or MCL was submitted in [redacted] 20[redacted]. However, Study 3064 failed to demonstrate superiority of the combination of bendamustine with rituximab (BR) over the control (combination of rituximab, cyclophosphamide [CPA], doxorubicin hydrochloride [DXR], vincristine sulfate [VCR], and prednisone [PSL] [R-CHOP] or combination of rituximab with CPA, VCR, and PSL [R-CVP]) in complete remission (CR) rate in [redacted] 20[redacted] and the application was withdrawn in [redacted] 20[redacted]. In the EU, based on the pivotal data from Studies NHL 1-2003 and 3064, an application for marketing approval was submitted using the Decentralised Procedure in Germany as the reference state in [redacted] 20[redacted]. However, the application was withdrawn in [redacted]20[redacted], primarily due to additional efficacy data requested.

As of August 2016, bendamustine has been approved in 15 countries or regions for the indication of untreated low-grade B-NHL, and 2 countries for the indication of untreated MCL.

In Japan, the applicant started a Japanese phase II study (Study 2011002) in patients with untreated low-grade B-NHL or MCL in November 2011. A follow-up study (Study 2014001) began in [redacted] 20[redacted] in patients who received ≥1 dose of the study drug in Study 2011002.

Based on the data from pivotal studies of Studies NHL 1-2003 and 2011002, the applicant has recently submitted a partial change application for Treakisym for the additional indication of untreated low-grade B-NHL or MCL and dosage and administration for the additional indication.

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

Because the current application was submitted for additional indications and dosing regimens, "data relating to quality" were omitted.

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

The current application was submitted for additional indications and dosage regimens, and no new data were attached because the evaluation of "non-clinical pharmacology study data" had been completed in the review for its new drug application.

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

The current application was submitted for additional indications and dosing regimens, and no new data were submitted because the evaluation of "non-clinical pharmacokinetic study data" was completed in the review for its new drug application.

5. Toxicology and Outline of the Review Conducted by PMDA

Because the current application was submitted for additional indications and dosage regimens, "toxicology study data" were omitted.

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

The current application was submitted for additional indications and dosage regimens, and no new data were submitted because the evaluation of "biopharmaceutic studies and associated analytical methods" was completed in the review for its new drug application.

6.1 Clinical pharmacology studies

The pharmacokinetics (PK) of bendamustine was evaluated in cancer patients receiving bendamustine in combination with rituximab.

6.1.1 Japanese phase I study (CTD 5.3.3.2-1, Study 2008002 [December 2008 to February 2010])

An open-label, uncontrolled study was conducted to evaluate the PK of bendamustine, etc. in 9 patients with relapsed or refractory intermediate- or high-grade B-NHL (9 patients included in PK analysis). One treatment cycle consisted of 21 days. Subjects received intravenous infusion of rituximab 375 mg/m^2 on Day 1 and intravenous infusion of bendamustine 90 or 120 mg/m^2 on Days 2 and 3 of each cycle, and plasma bendamustine concentrations were determined [Table 1]. The exposure (C_{max} and AUC_{last}) to bendamustine generally increased with increasing dose.

Table 1. PK parameters of bendamustine after the first dose

Dose (mg/m^2)	n	C_{max} (ng/mL)	t_{max}* (h)	AUC_{last} (ng·h/mL)	$t_{1/2}$ (h)
90	3	3811 ± 1271	1.0 (1.0, 1.0)	4546 ± 1558	0.36 ± 0.06
120	6	5405 ± 1470	1.0 (1.0, 1.0)	6146 ± 1706	0.32 ± 0.07

Mean ± standard deviation. * Median (range)

6.1.2 Pharmacokinetic interactions between bendamustine and rituximab

The applicant explained that the concomitant use of bendamustine with rituximab is unlikely to cause pharmacokinetic interactions for the following reasons:

- The PK parameters of bendamustine used in combination with rituximab in Japanese phase I study (Study 2008002) [see Section "6.1.1 Japanese phase I study"] were comparable to those in patients receiving bendamustine alone in Japanese phase I study (Study 2006001) (see "Review Report for Treakisym Injection 100 mg dated August 9, 2010").
- In foreign phase III study (Study C18083/3070), the rate of elimination of rituximab from serum of patients receiving rituximab with bendamustine was comparable to that of patients receiving rituximab alone calculated based on published literature data (e.g., *Ther Drug Monit.* 2005;27:785-92).

6.1.3 PPK analysis

A population pharmacokinetics (PPK) analysis was performed using a nonlinear mixed-effects modeling (NONMEM software Ver. 6.2.0) based on the PK data of bendamustine (49 subjects, 243 time points) obtained from a foreign phase III study (Study C18083/3070). The PK of bendamustine was described by a 3-compartment model with zero-order absorption and first-order elimination.

The final model developed in the PPK analysis performed based on the PK data (78 subjects, 347 time points) obtained from a foreign phase III study (Study SDX-105-03) was used in this analysis (*Cancer*

Chemother Pharmacol. 2010;66:1039-49). None of the evaluated covariates [1)] was found to be significant during development of the model.

CL of bendamustine when combined with rituximab was estimated to be 32.9 L/h, showing no clear difference from the estimated CL of bendamustine used alone (31.8 L/h).

6.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the applicant's explanation about pharmacokinetic interactions between bendamustine and rituximab is acceptable.

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

The efficacy and safety evaluation data submitted included the results from 5 studies including a Japanese phase I study, 2 Japanese phase II studies, and 2 foreign phase III studies listed in Table 2. The results from (a) Japanese phase I study (Study 2006001) and Japanese phase II study (Study 2007002) submitted as the reference data and the results from (b) foreign phase III study (Study C18083/3070) submitted as the evaluation data are omitted from the list because they have already been submitted and evaluated for (a) the new drug application and (b) partial change application, respectively (see "Treakisym Injection 100 mg Review Report dated August 9, 2010" and "Treakisym Injection 25 mg and Treakisym Injection 100 mg Review Report dated July 26, 2016").

Table 2. List of clinical studies on the efficacy and safety of bendamustine

Data category	Region	Study ID	Phase	Patient population	Number of subjects	Dosage regimen	Main endpoints
Evaluation	Japan	2008002	I	Previously treated patients with intermediate- or high-grade B-NHL	9	Intravenous infusion of bendamustine 90 or 120 mg/m^2 per dose on Days 2 and 3 and intravenous infusion of rituximab 375 mg/m^2 on Day 1 of each 21-day treatment cycle	Safety Efficacy PK
		2011002	II	Patients with untreated low-grade B-NHL and patients with MCL who are ineligible for ASCT	70	BR*	Efficacy Safety
		2014001	II	Patients who received ≥1 dose of the study drug in Study 2011002	69	NA	Efficacy Safety
	Outside Japan	NHL 1-2003	III	Patients with untreated low-grade B-NHL or MCL	549 (a) 274 (b) 275	(a) BR* (b) R-CHOP*	Efficacy Safety
		C18083/3064/ NL/MN	III	Patients with untreated low-grade B-NHL or MCL	447 (a) 224 (b) 223	(a) BR (b) R-CHOP or R-CVP	Efficacy Safety

* Because the first dose of rituximab required particularly careful infusion rate adjustment, infusion of rituximab in Cycle 1 was to be administered on Day 0 to avoid administering rituximab and bendamustine or CHOP on the same day.

The following subsections summarize respective clinical studies. The dosage regimens of BR, R-CHOP, and R-CVP used in the clinical studies are shown in Table 3.

Table 3. Dosage regimen for combination treatment

	Dosage regimen
BR	Intravenous infusion of bendamustine 90 mg/m^2 per dose on Days 1 and 2 and intravenous infusion of rituximab 375 mg/m^2 on Day 1 of each 28-day treatment cycle
R-CHOP	Intravenous infusion of rituximab 375 mg/m^2, CPA 750 mg/m^2, DXR 50 mg/m^2, and VCR 1.4 mg/m^2 (2 mg at a maximum) on Day1 and oral PSL 100 mg on Day 1 to Day 5 of each 21-day treatment cycle
R-CVP	Intravenous infusion of rituximab 375 mg/m^2, CPA 750 or 1000 mg/m^2, and VCR 1.4 mg/m^2 on Day1 and oral PSL of 100 mg/day on Day 1 to Day 5 of each 21-day treatment cycle

1) Sex, age, race, body weight, body surface area, creatinine clearance, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and serum albumin

Major adverse events other than death in each clinical study are described in Section "7.2 Adverse events, etc. observed in clinical studies." The PK related data are presented in "6.1 Clinical pharmacology studies."

7.1 Evaluation data

7.1.1 Clinical pharmacology studies

The applicant submitted the results from 1 clinical pharmacology study in patients [see "6.1 Clinical pharmacology studies"]. No deaths were reported during the study.

7.1.1.1 Japanese phase I study (CTD 5.3.3.2-1, Study 2008002 [December 2008 to February 2010])

7.1.2 Japanese clinical study

7.1.2.1 Japanese phase II study (CTD 5.3.5.2-1, Study 2011002 [November 2011 to November 2013])

An open-label, uncontrolled study was conducted to evaluate the efficacy and safety of BR in untreated MCL who are ineligible for autologous hematopoietic stem cell transplantation (ASCT) (target sample size; 57 patients with low-grade B-NHL, 10 patients with MCL) at 21 study centers in Japan.

Subjects received BR until disease progression or discontinuation criteria met for up to 6 cycles.

Of 70 subjects enrolled in the study (60 with low-grade B-NHL, 10 with MCL), 69 subjects receiving the study drug (59 with low-grade B-NHL, 10 with MCL) were included in the full analysis set (FAS), and it was used for efficacy and safety analyses.

The primary efficacy endpoint was CR (CR or complete remission/unconfirmed [CRu]) rate by independent review committee (IRC) assessment according to International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas (IWRC) (*J Clin Oncol.* 1999;17:1244-53). The best overall response and CR rate [confidence interval (CI)] (%) according to IWRC are shown in Table 4. The threshold CR rate for low-grade B-NHL and MCL was 47% and 8%, respectively.[2)]

Table 4. Best overall response (FAS, IRC assessment)

Best overall response	Number of subjects (%)	
	Low-grade B-NHL 59	MCL 10
CR	24 (40.7)	5 (50.0)
CRu	16 (27.1)	2 (20.0)
PR	17 (28.8)	2 (20.0)
SD	1 (1.7)	1 (10.0)
PD	0	0
NE	1 (1.7)	0
CR or CRu (CR rate [CI]* in %)	40 (67.8 [54.4, 79.4])	7 (70.0 [39.3, 91.3])

* 95% CI for low-grade B-NHL and 90% CI for MCL.

The safety analysis revealed no deaths during treatment or within 26 days after the last dose of the study drug.

A follow-up study (Japanese phase II study [CTD 5.3.5.4-1, Study 2014001 (from [redacted] 20[redacted] to [redacted] 20[redacted])]) was conducted to retrospectively collect post-study data in patients who had received ≥1 dose of the study drug in Study 2011002 at 18 study centers in Japan. No deaths were reported in the study.

2) The threshold CR rate for low-grade B-NHL was 47% based on the CR rate (%) [95% CI] of 66 [47, 81] in a Japanese phase II study evaluating the efficacy and safety of R-CHOP in patients with untreated low-grade B-NHL (*Cancer sci.* 2006;97:305-12). For MCL, the threshold CR rate was set to 8% based on the CR rate (%) [95% CI] of 15 [7.4, 25.7] calculated from the data of a foreign phase II study evaluating the efficacy and safety of rituximab monotherapy in patients with untreated or treated MCL (*J Clin Oncol.* 2000;18:317-24). One-sided significance level of 2.5% was used for low-grade B-NHL and one-sided significance level of 5% was used for MCL.

7.1.3 Foreign clinical studies

7.1.3.1 Foreign phase III study (CTD 5.3.5.1-1, Study NHL 1-2003 [September 2003 to [redacted] 20[redacted]])

An open-label, randomized, controlled study was conducted to evaluate the efficacy and safety of BR versus R-CHOP in patients with untreated low-grade B-NHL or MCL (target sample size, 214) at 81 study centers in Germany.

Subjects received BR or R-CHOP until disease progression or discontinuation criteria met for up to 6 cycles.

All 549 subjects enrolled in the study (274 in the BR group, 275 in the R-CHOP group) were included in the intent-to-treat (ITT) population, and it was used for efficacy analysis. Of these, 519 subjects who received the study drug (267 in the BR group, 252 in the R-CHOP group) were included in the safety analysis set. One subject assigned to the R-CHOP group received BR by mistake and was included in the BR group for the safety analysis.

This study was designed to demonstrate non-inferiority of BR over R-CHOP in event-free survival (EFS)[3] by investigator assessment according to World Health Organization Handbook for Reporting Results of Cancer Treatment (WHO criteria), the primary endpoint. After the study began, the following modifications were made:

- The study protocol was revised on [redacted] [redacted], 20[redacted] to change the non-inferiority margin from 15% to 10%.[4] Accordingly, the target sample size was changed from 214 to 478.
- The study protocol was revised on [redacted] [redacted], 20[redacted] to change the primary endpoint from EFS to progression-free survival (PFS)[5] and EFS was redefined as a secondary endpoint.
- After the completion of the study, the statistical analysis plan was revised on [redacted] [redacted], 20[redacted] to modify the primary analysis from non-inferiority to superiority.[6]

A total of 5 interim analyses were conducted for this study and the fifth interim analysis (data cutoff date; [redacted] [redacted], 20[redacted]) was used as the final PFS analysis. The type I error rate associated with interim analyses was adjusted using a Lan-DeMets α-spending function of O'Brien-Fleming type.

The results of efficacy analysis of PFS by investigator assessment according to WHO criteria and derived Kaplan-Meier curves are shown in Table 5 and Figure 1, respectively.

Table 5. Results of PFS analysis according to WHO criteria (ITT population; investigator assessment; data cutoff date, [redacted] [redacted], 20[redacted])

	BR	R-CHOP
Number of subjects	274	275
Number of events (%)	96 (35.0)	125 (45.5)
Median [95% CI] (months)	61.4 [45.3, NA]	31.3 [25.4, 40.7]
Hazard ratio [99% CI][*1]	0.607 [0.43, 0.86]	
P-value (two-sided)[*2]	<0.0001	

[*1] Proportional hazards model adjusted by a stratification factor (histologic type), [*2] Stratified log-rank test with histologic type as a stratification factor.

3) EFS was defined as the time from randomization to disease progression, failure to achieve PR or better within 3 cycles, secondary malignancy, or all-cause death.

4) A change due to re-assessment of clinically acceptable difference in EFS from that with the control based on available clinical study data of other drugs identifying a 2-month difference in EFS as clinically significant

5) A change made in response to the recommendation in the revised response criteria for malignant lymphoma defined by the International Working Group (Revised RC) to use PFS as the primary endpoint in February 2007 (*J Clin Oncol.* 2007;25:579-86)

6) A change was made in response to the report from the American Society of Hematology 2009 on the superiority of BR over R-CHOP demonstrated by the third interim analysis of Study NHL 1-2003

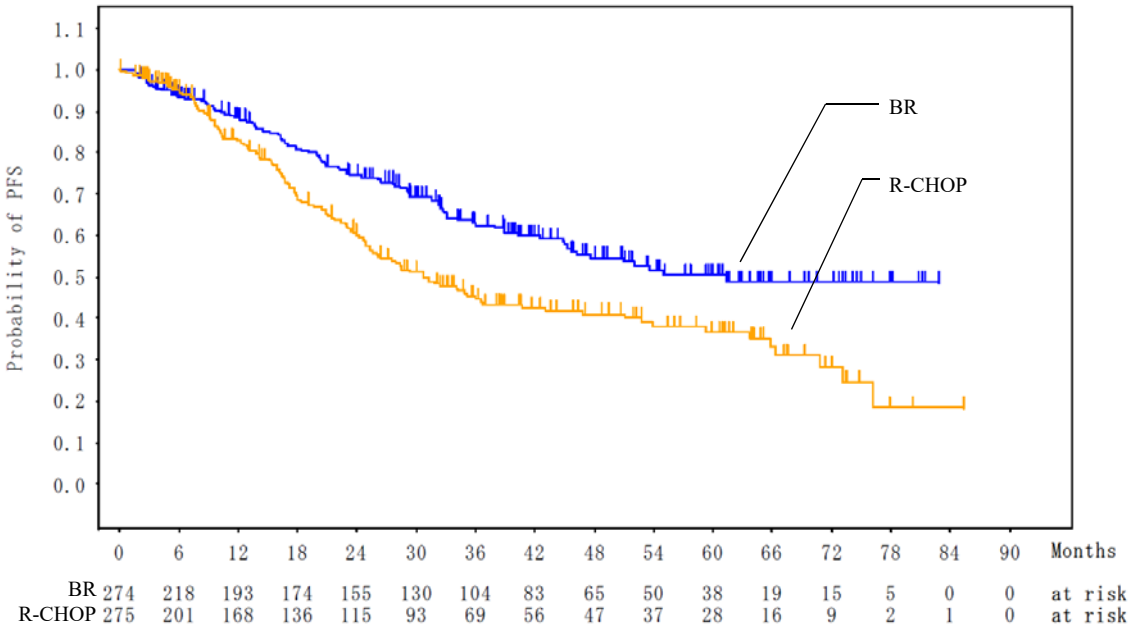

Figure 1. Kaplan-Meier curves of PFS derived using WHO criteria (ITT population; investigator assessment; data cutoff date, ■■, 20■)

The safety analysis revealed 4 of 267 subjects (1.5%) in the BR group and 4 of 252 subjects (1.6%) in the R-CHOP group died during treatment or within 30 days after the last dose of the study drug. The causes of deaths were anaemia/cardiac failure/cardiac arrest, cardiovascular insufficiency, cardiac failure acute/dyspnoea/pulmonary embolism/bronchitis bacterial, and death in 1 subject each in the BR group, and sepsis in 2 subjects and sepsis/febrile neutropenia, and bronchopulmonary aspergillosis/pneumonia in 1 subject each in the R-CHOP group. A causal relationship to the study drug could not be ruled out for anaemia/cardiac failure/cardiac arrest, cardiovascular insufficiency, and death in 1 subject each in the BR group and sepsis in 2 subjects and sepsis/febrile neutropenia, and bronchopulmonary aspergillosis/pneumonia in 1 subject each in the R-CHOP group.

7.1.3.2 Foreign phase III study (CTD 5.3.5.1-2, Study 3064 [Ongoing since April 2009 (data cutoff date, March 31, 2012)])

An open-label, randomized, controlled study was conducted to evaluate the efficacy and safety of BR versus R-CHOP or R-CVP in untreated patients with low-grade B-NHL or MCL (target sample size, 436) at 94 centers in 7 foreign countries.

Subjects received BR, R-CHOP, or R-CVP until disease progression or discontinuation criteria met for up to 8 cycles.

All 447 subjects enrolled in the study (224 in the BR group, 223 in the R-CHOP/R-CVP group) were included in the ITT population. Of these, 419 subjects who received the study drug and were evaluable for efficacy[7)] (213 in the BR group, 206 in the R-CHOP/R-CVP group) were included in the efficacy analysis. A total of 436 subjects in the ITT population who received the study drug (221 in the BR group, 215 in the R-CHOP/R-CVP group) were included in the safety analysis set.

This study was designed to demonstrate non-inferiority of BR over R-CHOP or R-CVP using the CR rate by IRC assessment according to Revised RC, a primary endpoint (*J Clin Oncol.* 2007;25:579-86). As of the start of the study, an interim analysis and a final analysis were planned.

The interim analysis was designed to analyze endpoints including the CR rate according to the Revised RC after all enrolled patients are available for response evaluation according to the Revised RC.

7) Patients who have proper baseline and post-baseline images and clinical data assessable by IRC and patients who had been withdrawn from the study treatment due to disease progression

The final analysis was planned to be conducted in 2017. Time-to-event endpoints including overall survival (OS), EFS, and PFS were to be analyzed following the completion of post-study follow-up of ≥5 years for all patients.

The following major modifications were made to the study protocol:

- On [redacted], 20[redacted], safety interim analyses were planned to be conducted by an independent data and safety monitoring board (DSMB) when a revised RC-based response evaluation becomes feasible in subjects of a number equivalent to half of the target sample size. A total of 2 interim analyses were scheduled.

- On [redacted], 20[redacted], the non-inferiority margin was changed from 15% to 0.68,[8)] the ratio of the CR rates between groups, and the target sample size was changed from 296 to 436 accordingly. In addition, the timing of the interim analyses determined on [redacted], 20[redacted] was changed to the time point when subjects of a number equivalent to approximately 30% of the target sample size or 90 subjects have completed follow-up for ≥6 months. Furthermore, the additional objective of the interim analyses was DSMB decision making on termination for futility.[9)]

- During the study, the non-inferiority margin (the ratio of CR rates between groups) was changed from 0.68 to 0.88 in response to the recommendation of the U.S. Food and Drug Administration (FDA).[10)]

DSMB concluded that the first interim analysis (data cutoff date; [redacted], 20[redacted]) revealed no safety problem. DSMB decided to continue the study without applying termination for futility.

The second interim analysis, which had not been predefined in the protocol, was conducted using a data up to the cutoff date of [redacted], 20[redacted].[11)]

Based on the results of the third interim analysis (data cutoff date; March 31, 2012), the CR rate (%) [95% CI] according to the Revised RC was 31 [25.3, 38.2] (67 of 213 subjects) in the BR group and 25 [19.5, 31.7] (52 of 206 subjects) in the R-CHOP/R-CVP group, resulting in the CR rate ratio between groups of 1.26 [0.93, 1.73].

The safety analysis revealed deaths of 2 of 221 subjects (0.9%) in the BR group and 1 of 215 subjects (0.5%) in the R-CHOP/R-CVP group during treatment or within 30 days after the last dose of the study drug. The causes of deaths were cardiac arrest and pneumonia/respiratory failure/septic shock in 1 subject each in the BR group and septic shock in 1 subject in the R-CHOP/R-CVP group. A causal relationship to the study drug could not be ruled out for all events reported in the BR group.[12)]

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA decided to focus primarily on a foreign phase III study (Study NHL 1-2003) in patients with untreated low-grade B-NHL or MCL, recognizing it as the most important clinical study for the evaluation of the efficacy and safety of bendamustine.

PMDA further decided to review efficacy and safety data of bendamustine in Japanese patients focusing on Japanese phase II study (Study 2011002) in patients with untreated low-grade B-NHL and patients with MCL who are ineligible for ASCT.

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8) The margin was changed to the between-group ratio because an FDA guidance (Guidance for Industry Non-inferiority Clinical Trials) (March 2010) state that it is not appropriate to evaluate non-inferiority using treatment difference.

9) No statistical criteria were defined regarding decision making on termination for futility.

10) A protocol amendment incorporating this change had not been made at the time of the third interim analysis (March 31, 2012), but was made in [redacted] 20[redacted].

11) The analysis was conducted in order to evaluate consistency of data between Study 3064 (e.g., remission rate in the BR group) and Study NHL 1-2003, and did not evaluate treatment difference in Study 3064.

12) Although the protocol required a causal relationship with the study drug to be evaluated for adverse events occurring in any treatment groups, causality-related data were not collected from patients receiving R-CHOP or R-CVP according to the developer's decision to place priority on the safety assessment of BR.

7.R.2 Clinical positioning of bendamustine

Explanations about bendamustine used for patients with untreated low-grade B-NHL or MCL are found in the major foreign clinical practice guidelines and textbooks on hematology or clinical oncology as shown below. The guidelines of clinical practice for hematopoietic cancer (Japanese clinical practice guidelines), the textbook, i.e., Clinical Oncology Revised Fourth Edition edited by the Japanese Society of Medical Oncology (Nankodo Co., Ltd., 2015), and Wintrobe's Clinical Hematology 13th Edition (USA, Lippincott Williams & Wilkins, 2013) have no explanations about bendamustine for the mentioned patient population.

Clinical practice guidelines

- US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Non-Hodgkin's Lymphomas (NCCN guidelines) (Version 3.2016): BR is a treatment option recommended for patients with untreated follicular lymphoma (FL) (Category 1[13]). BR is recommended as a low-intensity treatment option for patients with untreated MCL for whom high-dose chemotherapy with ASCT is not indicated (Category 2A[14]).
- European Society for Medical Oncology Clinical Practice Guidelines (ESMO guidelines) (*Ann Oncol*. 2014;25(Suppl 3):iii76–92): Combination chemotherapy with rituximab (including BR) is recommended for patients with untreated FL for the purpose to improve CR and/or PFS (level of evidence, I;[15] grade of recommendation, B[16]). The combination chemotherapy with rituximab (including BR) is recommended for elderly patients with untreated MCL (level of evidence, I; grade of recommendation, B).

- US National Cancer Institute Physician Data Query, Adult Non-Hodgkin Lymphoma Treatment (NCI-PDQ) (Version Date, June 1, 2016): Bendamustine is one of the standard treatment options against low-grade B-NHL of stage II to IV. A randomized study (Study NHL 1-2003) comparing BR and R-CHOP in patients with low-grade B-NHL or MCL showed a superior median PFS in the BR group (69 months versus 31 months) at median follow-up duration of 45 months. However, no significant difference was observed in the OS. The incidences of alopecia, hematotoxicity, stomatitis, peripheral nerve disorder, and infection were significantly lower in the BR group than in the R-CHOP group (level of evidence, 1iiDiii[17]).

Textbooks

- *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology* 10th Edition (USA, Lippincott Williams & Wilkins, 2014): A randomized phase III study (Study NHL 1-2003) comparing BR and R-CHOP in patients with advanced-stage FL, marginal zone lymphoma, lymphoplasmacytic lymphoma, or MCL showed a superior median PFS in the BR group (69.5 months versus 31.2 months). Not much toxicty was observed in patients receiving BR as evidenced by the lower incidences of Grade 3 or 4 neutropenia and leukopenia. At median follow-up of 45 months, no significant difference was observed in the OS.

- *Williams Hematology* 9th Edition (USA, McGraw-Hill Education. 2016): BR has been the most preferred regimen for patients with untreated FL in the US and EU, where approximately 65% to 70% of patients with untreated FL are treated with BR based on the results of Studies NHL 1-2003 and 3064, despite the methodological problems in these studies. BR has been the most preferred regimen for patients with MCL (especially elderly patients) because a favorable safety profile in patients with MCL was demonstrated in Studies NHL 1-2003 and 3064.

PMDA asked the applicant to explain the clinical positioning of bendamustine in the treatment of patients with untreated low-grade B-NHL or MCL.

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13) Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
14) Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
15) Evidence from at least one randomized controlled trial of good methodological quality or meta-analysis of well-conducted multiple randomized controlled trials without heterogeneity.
16) Recommended with strong or moderate evidence for efficacy but with a limited clinical benefit.
17) Evidence from a randomized, controlled, open-label clinical trial(s) with PFS as an endpoint.

The applicant's explanation:
The clinical benefit of bendamustine in the treatment of patients with untreated low-grade B-NHL or MCL was demonstrated in Studies NHL 1-2003 and 3064. The foreign clinical practice guidelines and textbooks recognize bendamustine as a treatment option for the mentioned patient population based on the results of these studies. The results of Study 2011002 in Japanese patients demonstrated comparable efficacy of bendamustine and BR in Studies NHL 1-2003 and 3064, showing no clear differences in safety between Japanese and non-Japanese patients [see Section "7.R.4 Safety"]. Thus, bendamustine is able to be recognized as a treatment option for Japanese patients.

PMDA's view:
In clinical practice guidelines and textbooks, BR is positioned as a treatment option for patients with untreated low-grade B-NHL or MCL based on the results of studies including Study NHL 1-2003.

7.R.3 Efficacy

Based on the observations in the subsections below, PMDA has concluded that a certain efficacy of bendamustine has been demonstrated in patients with untreated low-grade B-NHL or MCL.

7.R.3.1 Selection of control group

The applicant's explanation about the appropriateness of use of R-CHOP as the control in Study NHL 1-2003:
No clinical studies had demonstrated a life prolonging effect of bendamustine in patients with untreated low-grade B-NHL or MCL when the Study NHL 1-2003 protocol was being prepared. At the time, R-CHOP was commonly used in clinical practice based on the promising results from clinical studies in which R-CHOP was administered to the patient population mentioned (e.g., *J Clin Oncol.* 1999;17:268-76). The use of R-CHOP as the control in Study NHL 1-2003 was thus appropriate.

PMDA accepted the applicant's explanation.

7.R.3.2 Primary endpoint

The applicant's explanation about the appropriateness of PFS according to WHO criteria as the primary endpoint of Study NHL 1-2003:
The primary goal of treatment of low-grade B-NHL and MCL is to delay disease progression. PFS Prolongation may contribute not only to disease progression delay but also to the postponement of the start of subsequent treatment, and therefore is clinically significant. For this reason, PFS according to WHO criteria is the appropriate primary endpoint of Study NHL 1-2003.

PMDA's view:
Because the goal of treatment of low-grade B-NHL and MCL is life extension, the OS is the appropriate primary endpoint of the study to evaluate the efficacy of bendamustine in the intended patient population. Despite that, given that there are no clinical study data demonstrating survival benefit of R-CHOP, which was a standard therapy for the intended patient population around the time when Study NHL 1-2003 began, prolonged PFS in the intended patient population is of a certain clinical significance.

Accordingly, PMDA decided to review the efficacy evaluation in Study NHL 1-2003 focusing on the primary endpoint (PFS according to WHO criteria) data and to check OS as necessary.

7.R.3.3 Efficacy evaluation data

Study NHL 1-2003 in patients with untreated low-grade B-NHL or MCL demonstrated the superiority of BR over R-CHOP in the revised primary endpoint of investigator-assessed PFS according to WHO criteria [see Section "7.1.3.1 Foreign phase III study"].

The applicant's explanation about IRC-assessed PFS in Study NHL 1-2003:
A post-hoc IRC assessment was attempted while it was not predefined in the protocol. However, a complete set of image data required for the assessment were not available because of a long time interval between patient enrollment and the IRC assessment and requirements of German law on the protection of personal data. The IRC-assessed PFS according to WHO criteria were assessed in 353 IRC-evaluable patients (182 in the BR group, 171 in the R-CHOP group), and the results and derived Kaplan-Meier

curves are shown in Table 6 and Figure 2, respectively. As compared with the investigator-assessed PFS (Table 5 and Figure 1), the IRC-assessed median PFS, etc. showed a shorter survival in the BR group, but did not show inferiority of BR to R-CHOP.

Table 6. Results of PFS analysis according to WHO criteria (IRC-evaluable patient population; IRC assessment; data cutoff date, [redacted], 20[redacted])

	BR	R-CHOP
Number of subjects	182	171
Number of events (%)	85 (46.7)	97 (56.7)
Median [95% CI] (months)	30.6 [23.6, 33.3]	23.3 [16.5, 26.0]
Hazard ratio [99% CI]*1	0.735 [0.5, 1.08]	
P-value (two-sided)*2	0.0420	

*1 Proportional hazards model adjusted by a stratification factor (histologic type), *2 Stratified log-rank test with histologic type as a stratification factor.

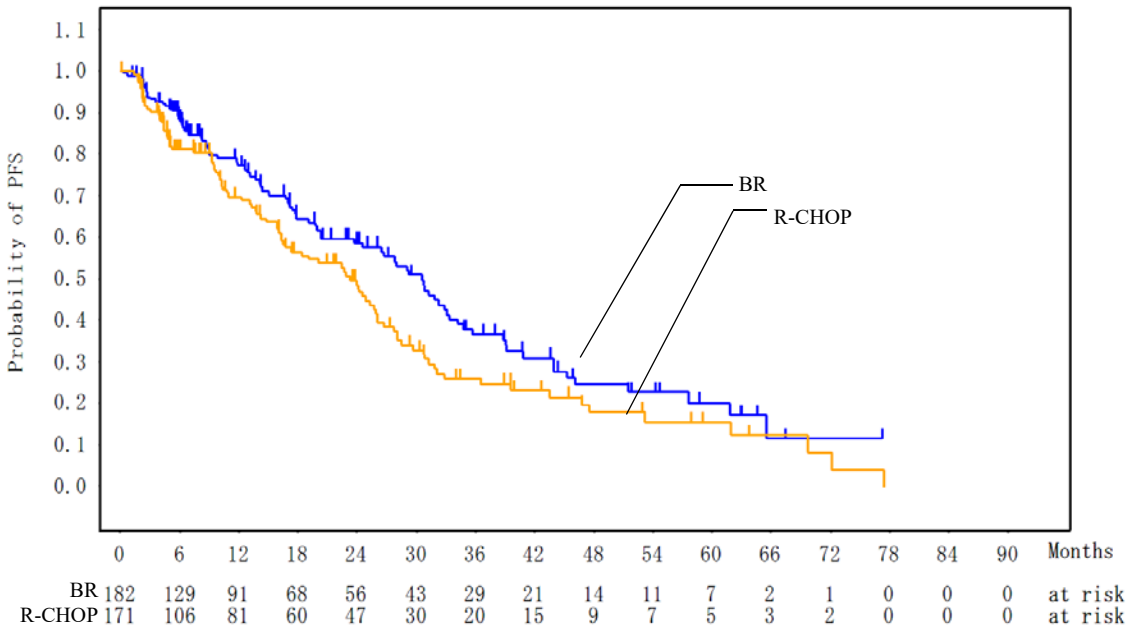

Figure 2. Kaplan-Meier curves of PFS according to WHO criteria (IRC-evaluable patient population; IRC assessment; data cutoff date, [redacted], 20[redacted])

Table 7 and Figure 3 show investigator- and IRC-assessed PFS according to WHO criteria, and derived Kaplan-Meier curves, respectively, of patients with low-grade B-NHL. Table 8 and Figure 4 present the results of patients with MCL.

Table 7. Results of PFS analysis according to WHO criteria (low-grade B-NHL) (investigator assessment in randomized patients; IRC assessment in IRC-evaluable patients; data cutoff date, [redacted], 20[redacted])

	Investigator assessment		IRC assessment	
	BR	R-CHOP	BR	R-CHOP
Number of subjects	224	223	153	137
Number of events (%)	71 (31.7)	95 (42.6)	67 (43.8)	73 (53.3)
Median [95% CI] (months)	NA [53.7, NA]	36.6 [27.6, 59.3]	26.7 [19.7, 33.3]	23.9 [16.8, 27.7]
Hazard ratio [95% CI]*1	0.611 [0.45, 0.83]		0.802 [0.58, 1.12]	
P-value (two-sided)*2	0.0015		0.1915	

*1 Proportional hazards model, *2 Log-rank test.

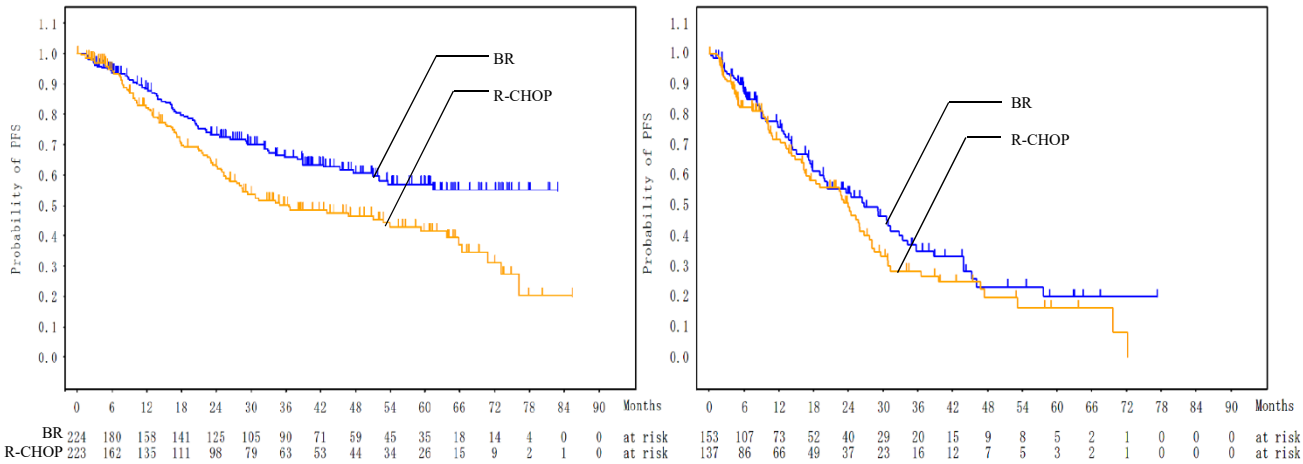

Figure 3. Kaplan-Meier curves of PFS according to WHO criteria (low-grade B-NHL) (investigator assessment in randomized patients [left]; IRC assessment in IRC-evaluable patients [right]; data cutoff date, ■■, 20■)

Table 8. Results of PFS analysis according to WHO criteria (MCL) (investigator assessment in randomized patients; IRC assessment in IRC-evaluable patients; data cutoff date, ■■, 20■)

	Investigator assessment		IRC assessment	
	BR	R-CHOP	BR	R-CHOP
Number of subjects	50	52	29	34
Number of events (%)	25 (50.0)	30 (57.7)	18 (62.1)	24 (70.6)
Median [95% CI] (months)	35.9 [31.5, 45.7]	23.7 [18.0, 31.9]	33.1 [30.7, 40.9]	16.0 [9.5, 26.0]
Hazard ratio [95% CI]*1	0.534 [0.31, 0.92]		0.551 [0.29, 1.03]	
P-value (two-sided)*2	0.0209		0.0596	

*1 Proportional hazards model, *2 Log-rank test.

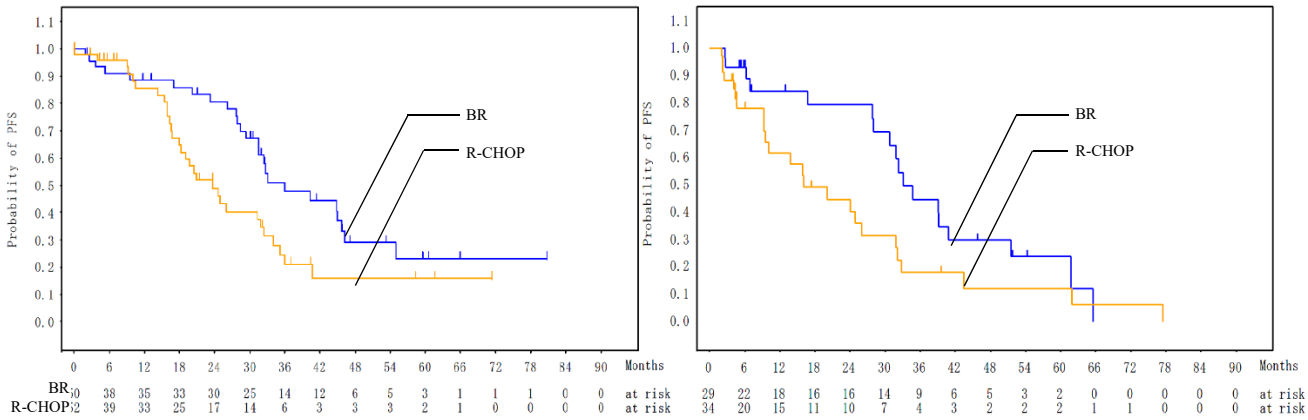

Figure 4. Kaplan-Meier curves of PFS according to WHO criteria (MCL) (investigator assessment in randomized patients [left]; IRC assessment in IRC-evaluable patients [right]; data cutoff date, ■■, 20■)

Table 9 and Figure 5 show the results of OS analysis, a secondary endpoint of Study NHL 1-2003, and derived Kaplan-Meier curves at the time of study completion (data cutoff date, ■■, 20■), respectively.

Table 9. Results of OS analysis (ITT population; data cutoff date, ■■, 20■)

	BR	R-CHOP
Number of subjects	274	275
Number of events (%)	55 (20.1)	47 (17.1)
Median [95% CI] (months)	NA [NA, NA]	NA [NA, NA]
Hazard ratio [95% CI]*1	1.131 [0.77, 1.67]	
P-value (two-sided)*2	0.5884	

*1 Proportional hazards model adjusted by a stratification factor (histologic type), *2 Stratified log-rank test with histologic type as a stratification factor.

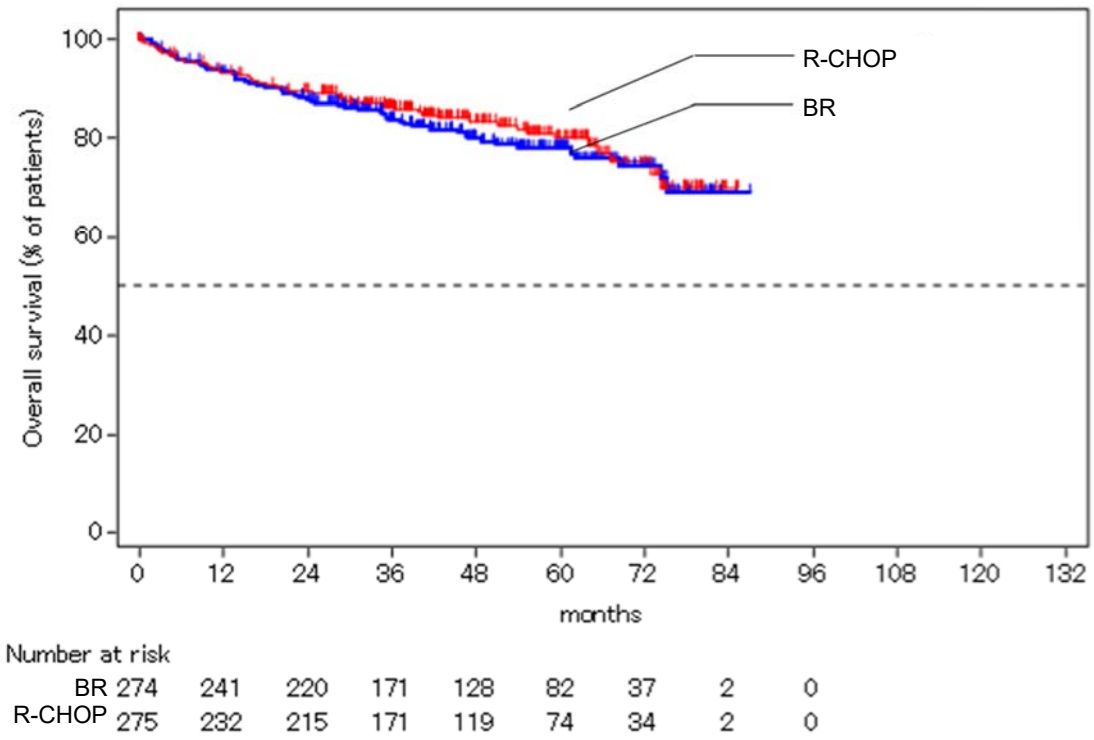

Figure 5. Kaplan-Meier curves of OS (ITT population; data cutoff date, [redacted], 20[redacted])

Table 10 is the results of a follow-up OS analysis conducted for Study NHL 1-2003 after the OS analysis explained above (data cutoff date, [redacted], 20[redacted]).The Kaplan-Meier curves are shown in Figure 6.

Table 10. Results of OS analysis (ITT population; data cutoff date, [redacted], 20[redacted])

	BR	R-CHOP
Number of subjects	274	275
Number of events (%)	69 (25.2)	79 (28.7)
Median [95% CI] (months)	NA [NA, NA]	NA [NA, NA]
Hazard ratio [95% CI]*[1]	0.846 [0.61, 1.17]	
P-value (two-sided)*[2]	0.3101	

*[1] Proportional hazards model adjusted by a stratification factor (histologic type), *[2] Stratified log-rank test with histologic type as a stratification factor.

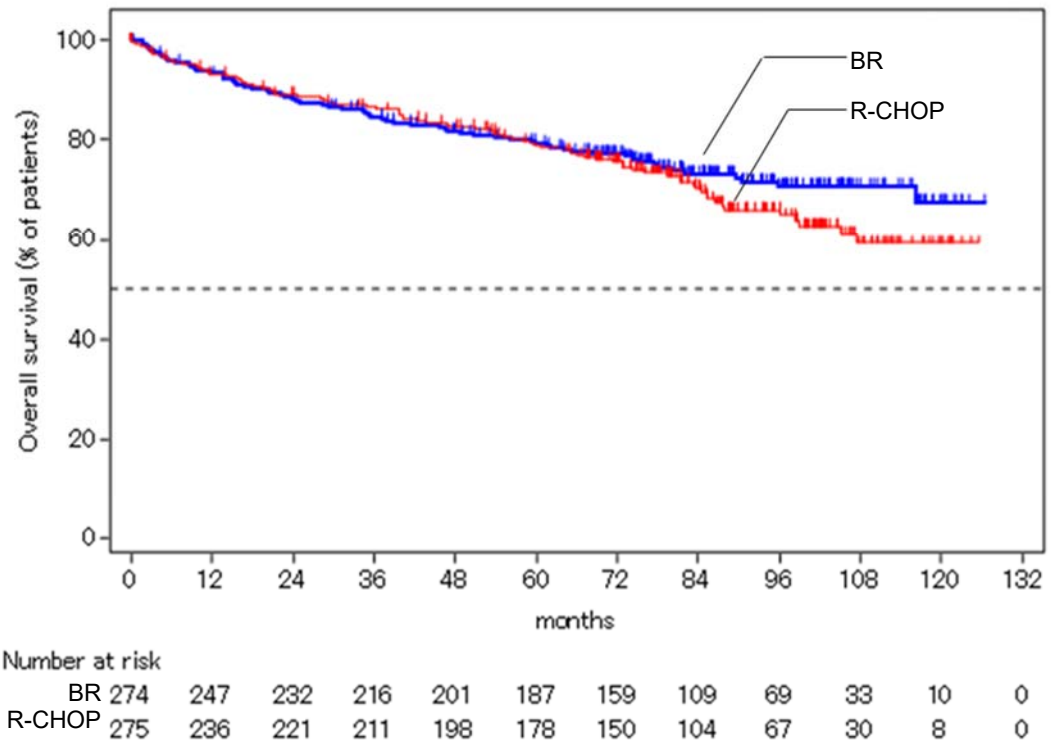

Figure 6. Kaplan-Meier curves of OS (ITT population; data cutoff date, [redacted], 20[redacted])

The applicant's explanation about the results of OS analysis:
At the time when Study NHL 1-2003 (data cutoff date; [redacted], 20[redacted]) was completed, the hazard ratio of OS in the BR group to the R-CHOP group was 1.131. It would be however difficult to evaluate the OS due to the limited number of fatal events in both groups (20% of subjects in the BR group, 17% of subjects in the R-CHOP group) and the short observation period. Meanwhile, as of the subsequent data cutoff date ([redacted], 20[redacted]) when the cumulative number of fatal events was available, the hazard ratio of OS in the BR group to the R-CHOP group was 0.846, showing a trend toward longer OS in the BR group than in the R-CHOP group.

PMDA's view:
R-CHOP was used as the control in Study NHL 1-2003 and failed to demonstrate its survival benefit in patients with untreated low-grade B-NHL or MCL, and the efficacy of R-CHOP was far from being established when the protocol of Study NHL 1-2003 was being prepared. Therefore, the study should have been designed as a superiority study rather than a non-inferiority study. The following critical problems of the study indicate a possible increase in bias and/or type I error rate in the assessment of the primary endpoint, i.e., investigator-assessed PFS according to WHO criteria. Therefore, the efficacy of bendamustine is hardly be considered demonstrated in the study.

- The evaluation of superiority in PFS was not planned originally in the study protocol. It was specified when the statistical analysis plan was revised after the completion of the study based on the results of the third interim analysis showing a superiority of BR over R-CHOP [see Section "7.1.3.1 Foreign phase III study"].
- The study did not require PFS to be assessed by IRC despite its open-label-nature. This made some image data inaccessible, thus only a part of the ITT population were able to be assessed by IRC. Therefore, the robustness of the PFS results cannot be assured.
- PFS was scheduled to be assessed after the completion of Cycle 3 and study treatment, and as necessary thereafter depending on the patient's clinical outcome (with an interval of 6 months). However, each treatment cycle of BR was 28 days long while that of R-CHOP is 21 days long. The 2 treatment groups are thus assessed at unequal intervals.

At the same time, the following observations suggest the efficacy of bendamustine in patients with untreated low-grade B-NHL or MCL. Because BR is recognized as a treatment regimen recommended

for these patients in the foreign clinical practice guidelines and textbooks based on the results of Study NHL 1-2003, etc. [see Section "7.R.2 Clinical positioning of bendamustine"], the introduction of bendamustine in Japanese clinical practice has significance. However, as mentioned, the efficacy of bendamustine is not a firm one. The package insert, etc. of bendamustine should give cautionary advice to the effect that the use of bendamustine should be determined carefully based on the good understanding of the efficacy and safety of bendamustine, and after due consideration of other treatment options. Furthermore, the results of IRC-assessed PFS according to WHO criteria should be appropriately communicated to healthcare professionals via package insert, etc.

- The post-hoc IRC-assessed PFS according to WHO criteria, the primary endpoint of Study NHL 1-2003, showed no clear inferiority of BR to the control.
- The data of PFS according to WHO criteria showed no trend toward clear inferiority of BR to the control either in patients with low-grade B-NHL or MCL.
- There is a limitation in evaluating the OS prolonging effect of bendamustine based on the OS analyses (data cutoff date; [redacted], 20[redacted] and [redacted], 20[redacted]) due to the design of Study NHL 1-2003 that does not allow a statistical evaluation of OS. Despite that, in light of additional analyses data, there was no trend toward clear inferiority of BR to the control.

7.R.3.4 Efficacy of bendamustine in Japanese patients

The applicant explained that the IRC-assessed CR (CR or CRu) rate according to IWRC, the primary endpoint of Study 2011002, was greater than the predefined threshold CR rate [see Section "7.1.2.1 Japanese phase II study"], indicating that bendamustine is expected to have efficacy in Japanese patients with untreated low-grade B-NHL or MCL.

PMDA accepted the applicant's explanation.

7.R.4 Safety [for adverse events, see Section "7.2 Adverse events, etc. observed in clinical studies"]

Based on the discussions in the following subsections, PMDA concluded that the treatment with bendamustine in patients with untreated low-grade B-NHL or MCL requires special attention to the known adverse events identified during the review for the approved indications (bone marrow depression, infection, interstitial lung disease, tumor lysis syndrome, serious dermatologic symptom, shock/anaphylaxis, and secondary malignancy). No additional attention-requiring adverse events were identified.

The use of bendamustine requires particular attention to the above-mentioned adverse events. PMDA however concluded that bendamustine is tolerated by patients with untreated low-grade B-NHL or MCL when they are followed by a physician with adequate knowledge and experience in the treatment of haematopoietic malignancies, through the monitoring and control of adverse events, dose interruption or reduction, or treatment discontinuation.

7.R.4.1 Safety profile of bendamustine and its differences between Japanese and non-Japanese patients

The applicant's explanation about the safety profile of bendamustine:
A summary of safety in Studies NHL 1-2003, 3064, and 2011002 is shown in Table 11.

Table 11. Summary of safety (Studies NHL 1-2003, 3064, and 2011002)

	Number of subjects (%)				
Study	NHL 1-2003		3064		2011002
	BR	R-CHOP	BR	R-CHOP/ R-CVP	
	N = 267	N = 252	N = 221	N = 215	N = 69
All adverse events	264 (98.9)	249 (98.8)	221 (100)	213 (99.1)	69 (100)
Grade ≥3 adverse events	159 (59.6)	221 (87.7)	129 (58.4)	125 (58.1)	69 (100)
Adverse events resulting in death	4 (1.5)	4 (1.6)	2 (0.9)	1 (0.5)	0
Serious adverse events	63 (23.6)	69 (27.4)	58 (26.2)	48 (22.3)	8 (11.6)
Adverse events leading to treatment discontinuation	7 (2.6)	7 (2.8)	10 (4.5)	0	0
Adverse events leading to dose interruption	103 (38.6)	101 (40.1)	84 (38.0)	0	9 (13.0)
Adverse events leading to dose reduction	72 (27.0)	104 (41.3)	14 (6.3)	1 (0.5)	8 (11.6)

In Study NHL 1-2003, the adverse event of any grade with ≥10% higher incidence in the BR group than in the R-CHOP group was rash (26.6% [71 subjects] in the BR group, 15.9% [40 subjects] in the R-CHOP group). There were no Grade ≥3 adverse events with ≥5% higher incidence or serious adverse events with ≥3% higher incidence in the BR group than in the R-CHOP group. As the protocol required, adverse events leading to treatment discontinuation were counted only by the number of subjects affected but not by event term.

In Study 3064, adverse events of any grade with a ≥10% higher incidence in the BR group than in the R-CHOP/R-CVP group were nausea (62.9% [139 subjects] in the BR group, 47.4% [102 subjects] in the R-CHOP/R-CVP group) and vomiting (27.1% [60 subjects] in the BR group, 13.0% [28 subjects] in the R-CHOP/R-CVP group). There were no Grade ≥3 adverse events with ≥5% higher incidence or serious adverse events or adverse events leading to treatment discontinuation with ≥3% higher incidence in the BR group than in the R-CHOP/R-CVP group.

PMDA asked the applicant to explain the differences in the safety of bendamustine between in relapsed or refractory low-grade B-NHL or MCL (the approved indication) and untreated low-grade B-NHL or MCL.

The applicant's explanation:
Pooled analysis data of patients with untreated low-grade B-NHL or MCL who received BR in Studies NHL 1-2003, 3064, and 2011002 (557 subjects) were compared with another pooled analysis data of patients with relapsed or refractory low-grade B-NHL or MCL who received bendamustine alone in Studies 2006001, 2007002, SDX-105-01, and SDX-105-03 (254 subjects).

Table 12 shows a summary of safety in patients with untreated low-grade B-NHL or MCL and that in patients with relapsed or refractory low-grade B-NHL or MCL.

Table 12. Summary of safety in patients with low-grade B-NHL or MCL

	Number of subjects (%)	
	Patients with untreated low-grade B-NHL or MCL	Patients with relapsed or refractory low-grade B-NHL or MCL
	Pooled analysis of patients who received BR in Studies NHL 1-2003, 3064, and 2011002	Pooled analysis of patients who received bendamustine alone in Studies 2006001, 2007002, SDX-105-01, and SDX-105-03
	N = 557	N = 254
All adverse events	554 (99.5)	254 (100)
Grade ≥3 adverse events*	357 (64.1)	196 (77.2)
Adverse events resulting in death	6 (1.1)	5 (2.0)
Serious adverse events	129 (23.2)	54 (21.3)
Adverse events leading to treatment discontinuation	17 (3.1)	67 (26.4)

* Grade 3 or 4 adverse events (Grade 5 was not defined in Study NHL 1-2003.)

The incidences of white blood cell count decreased and granulocyte count decreased, etc. were higher in patients with untreated low-grade B-NHL or MCL than in patients with relapsed or refractory low-grade B-NHL or MCL. All these events are however known to be characteristic of bendamustine or rituximab treatment and are not indicative of new safety problems warranting attention.

In addition, the applicant explained differences in the safety profile between Japanese and non-Japanese patients based on the data from Study 2011002 and the pooled data from the BR group in Studies NHL 1-2003, and 3064.

Adverse events of any grade with an incidence of ≥20% in the BR group in any Study 2011002 or Studies NHL 1-2003 and 3064 combined are shown in Table 13.

Table 13. Adverse events with an incidence of ≥20% in Japanese or non-Japanese patient population

Preferred term (MedDRA/J ver18.0)	Number of subjects (%)			
	Japanese Study 2011002 N = 69		Non-Japanese Pooled analysis of the BR group in Studies NHL 1-2003 and 3064 N = 488	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	69 (100)	69 (100)	485 (99.4)	288 (59.0)
White blood cell count decreased	69 (100)	57 (82.6)	224 (45.9)	98 (20.1)
Lymphocyte count decreased	67 (97.1)	67 (97.1)	5 (1.0)	5 (1.0)
Neutrophil count decreased	64 (92.8)	58 (84.1)	9 (1.8)	5 (1.0)
CD4 lymphocytes decreased*	64 (92.8)	63 (91.3)	0	0
Nausea	46 (66.7)	1 (1.4)	140 (28.7)	4 (0.8)
Constipation	45 (65.2)	0	85 (17.4)	2 (0.4)
Platelet count decreased	38 (55.1)	5 (7.2)	77 (15.8)	18 (3.7)
Malaise	37 (53.6)	0	0	0
Blood IgM decreased	32 (46.4)	0	0	0
Decreased appetite	30 (43.5)	2 (2.9)	49 (10.0)	0
Rash	29 (42.0)	2 (2.9)	104 (21.3)	4 (0.8)
Infusion related reaction	28 (40.6)	2 (2.9)	57 (11.7)	15 (3.1)
Anaemia	24 (34.8)	3 (4.3)	32 (6.6)	4 (0.8)
AST increased	22 (31.9)	2 (2.9)	3 (0.6)	1 (0.2)
Blood LDH increased	21 (30.4)	0	3 (0.6)	1 (0.2)
Blood IgA decreased	21 (30.4)	0	0	0
Blood IgG decreased	21 (30.4)	0	0	0
Vasculitis	20 (29.0)	0	1 (0.2)	0
Insomnia	19 (27.5)	1 (1.4)	37 (7.6)	0
ALT increased	18 (26.1)	2 (2.9)	6 (1.2)	1 (0.2)
C-reactive protein increased	18 (26.1)	0	3 (0.6)	2 (0.4)
Pyrexia	17 (24.6)	0	93 (19.1)	17 (3.5)
GGT increased	15 (21.7)	1 (1.4)	5 (1.0)	1 (0.2)
Vomiting	13 (18.8)	1 (1.4)	173 (35.5)	13 (2.7)
Haemoglobin decreased	7 (10.1)	0	109 (22.3)	8 (1.6)
Fatigue	6 (8.7)	1 (1.4)	155 (31.8)	8 (1.6)
Granulocyte count decreased	0	0	145 (29.7)	65 (13.3)

* Unknown in Studies NHL 1-2003 and 3064 because data were not collected for safety evaluation.

There were no serious adverse events with a ≥5% higher incidence in Study 2011002 than in the BR group in Studies NHL 1-2003 and 3064 combined.

PMDA's view:
There is a limitation in comparing the safety of bendamustine between patients with relapsed or refractory low-grade B-NHL or MCL (the approved indication) and patients with untreated low-grade B-NHL or MCL, due to the different dosage regimens and use or non-use of concomitant drugs. Despite that, PMDA accepted the applicant's explanation that all adverse events reported are known to be characteristic of bendamustine or rituximab treatment and do not raise new safety concerns requiring attention in the use of bendamustine with rituximab in patients with untreated low-grade B-NHL or MCL.

Notable observations in the safety profile of BR compared with the control in Studies NHL 1-2003 and 3064 were (a) adverse events related to bone marrow depression and gastrointestinal disorders observed particularly at high incidences in both treatment groups and (b) rash and nausea/vomiting more frequent

in the BR group. Those frequently observed in the BR group are known adverse events associated with both bendamustine and rituximab, and there is no need for additional cautionary advice about them. However, the difference in the safety profile between the BR and control groups is useful knowledge in terms of the selection of treatment in clinical practice, and it should be appropriately communicated to healthcare professionals using written materials.

On the understanding of the small number of Japanese patients treated with bendamustine, adverse events observed more frequently in Japanese patients than in non-Japanese patients require attention. However, there were no clear differences between Japanese and non-Japanese patients in the incidences of serious adverse events or adverse events leading to treatment discontinuation, and events in Japanese patients were managed by dose interruption or reduction or discontinuation of bendamustine. Therefore, bendamustine is tolerable by Japanese patients with low-grade NHL or MCL when they are followed through the monitoring and control of adverse events, dose interruption or reduction, or treatment discontinuation by a physician with adequate knowledge and experience in the treatment of haematopoietic malignancies and the good understanding of the safety profile of bendamustine.

7.R.5 Indication

The proposed indication of bendamustine was "low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma."

Based on the discussions in Sections "7.R.2 Clinical positioning of bendamustine," "7.R.3 Efficacy," and "7.R.4 Safety" and the following subsections, PMDA concluded that the proposed indication of bendamustine is acceptable. In addition, PMDA concluded that the "Precautions for Indications" section should give the following advice.

- The use of bendamustine should be determined with the good understanding of the efficacy and safety of bendamustine based on the "Clinical Studies" section, and after due consideration of other treatment options.

7.R.5.1 Histologic types of low-grade B-NHL for which bendamustine is indicated

The applicant's explanation about the efficacy of bendamustine on individual histologic types of low-grade B-NHL:

Patients with low-grade B-NHL of the following histologic types were included in Study NHL 1-2003 and received bendamustine: FL, lymphoplasmacytic lymphoma/immunocytoma, marginal zone lymphoma (nodal marginal zone lymphoma and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue), and unclassified histology.[18)] Table 14 shows the results of PFS according to WHO criteria of patients with each histologic type. The results demonstrated promising efficacy for all histologic types, with a point estimate of a hazard ratio of <1.

Table 14. Results of PFS according to WHO criteria for patients with low-grade B-NHL by histologic type (investigator assessment; randomized patient population; data cutoff date, [redacted], 20[redacted])

Histologic type	Treatment group	Number of subjects	Number of events (%)	Median [95% CI] (months)	Hazard ratio [95% CI][*1]
FL	BR	146	47 (32.2)	NA [42.5, NA]	0.652 [0.45, 0.95]
	R-CHOP	146	63 (43.2)	36.6 [27.6, 65.7]	
Lymphoplasmacytic lymphoma /immunocytoma	BR	33	9 (27.3)	NA [52.0, NA]	0.356 [0.16, 0.80]
	R-CHOP	39	18 (46.2)	25.4 [17.2, 59.3]	
Marginal zone lymphoma[*2]	BR	38	15 (39.5)	61.4 [22.9, NA]	0.872 [0.41, 1.86]
	R-CHOP	31	12 (38.7)	NA [21.4, NA]	
Unclassified histology	BR	7	0	NA [NA, NA]	NA [NA, NA]
	R-CHOP	7	2 (28.6)	53.8 [34.1, NA]	

[*1] Proportional hazards model, [*2] Nodal marginal zone lymphoma and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue.

[18)] Histologic types of low-grade B-NHL that could not be clearly classified for the reason of not meeting the WHO histological classification, etc.

Patients with the histologic type of small lymphocytic lymphoma or splenic B-cell marginal zone lymphoma were ineligible for Study NHL 1-2003. In Study 2011002, 2 patients with small lymphocytic lymphoma and the CR (CR or CRu) rate was 100% (2 of 2). In the BR group of Study 3064, 7 patients with splenic B-cell marginal zone lymphoma were included, and the CR (CR or CRu) rate was 14.3% (1 of 7).

Based on the above results and the data obtained from Study NHL 1-2003 [see Section "7.R.3 Efficacy"], bendamustine is expected to have efficacy in the treatment of all histologic types of low-grade B-NHL and MCL. Therefore, the indication of "low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma" is acceptable.

PMDA accepted the applicant's explanation.

7.R.5.2 Use of bendamustine in patients with low-grade B-NHL with a low tumor burden

Patients participated in Studies NHL 1-2003, 3064, and 2011002 had low-grade B-NHL with a high tumor burden, according to the German Low-Grade Lymphoma Study Group (GLSG) criteria (NHL 1-2003) and the Groupe d'Etude des Lymphomes Foliculaires (GELF) criteria (3064 and 2011002). PMDA asked the applicant to explain the efficacy and safety of bendamustine in patients with low-grade B-NHL with a low tumor burden.

The applicant's explanation:
There are no clinical study data of patients with low tumor burden low-grade B-NHL treated with bendamustine. Neither the Japanese clinical practice guidelines nor the NCCN guidelines recommend an early start of treatment for this patient population. However, the Japanese clinical practice guidelines state that these patients may be treated with rituximab alone or by a combination chemotherapy with rituximab, indicating no need for discouraging the use of bendamustine in patients with low tumor burden low-grade B-NHL.

PMDA's view:
According to the applicant's explanation, and for the following reasons, the use of bendamustine in patients with low-grade B-NHL with a low tumor burden should not necessarily be restricted in the "Indications" section of the package insert. However, tumor burden was one of the inclusion criteria for patients with low-grade B-NHL of Studies NHL 1-2003, 3064, and 2011002, and this should be appropriately communicated to healthcare professionals using written materials.

- The Japanese clinical practice guidelines and the NCCN guidelines state that an untreated observation should be considered for patients with low tumor burden low-grade B-NHL. The guidelines, at the same time, mention that there is neither uniform criteria to determine when to start the treatment or to define low tumor burden nor study data supporting the appropriateness of such criteria. This precludes defining low tumor burden in the "Indications" section of the package insert.
- Bendamustine is expected to be used by physicians with adequate knowledge and experience in treatment of haematopoietic malignancies.

7.R.5.3 Use of bendamustine in patients with MCL who are eligible for ASCT

Since Study 2011002 was conducted in patients with MCL who are ineligible for ASCT, PMDA asked the applicant to explain the efficacy and safety of bendamustine in patients with untreated MCL who are eligible for ASCT.

The applicant's explanation:
Japanese and foreign clinical practice guidelines recommend the treatment begin with high-intensity chemotherapy for patients with untreated MCL aged ≤65 years, who are eligible for ASCT. Responders to the therapy are then encouraged to undergo ASCT. Patients with MCL were excluded from Study 2011002 because of another chemotherapy recommended for these patients.

Meanwhile, a phase II randomized controlled study was conducted overseas in patients with untreated MCL aged ≤65 years, who are ASCT-eligible, and BR was compared with the combination of rituximab with CPA, VCR, DXR, dexamethasone, methotrexate, and cytarabine (R-Hyper CVAD) as their first treatment (*Blood Annual Meeting.* 2015;126:Abst 518). The study yielded positive outcomes of 2-year

PFS, etc. with BR. Thus bendamustine can be a treatment option for ASCT-eligible patients with untreated MCL.

PMDA's view:
No clinical study data were submitted to evaluate the effects of bendamustine on recruitment and/or engraftment of haematopoietic stem cells, and the efficacy and safety of bendamustine are thus unclear in ASCT-eligible patients with untreated MCL. However, given that the package insert highlights the target population of Study 2011002 and a need for the communication of such information to healthcare professionals, whether or not bendamustine be used in ASCT-eligible patients is not particularly necessary to be mentioned in the "Indications" section based on the following viewpoints.

- Eligibility for ASCT depends on the patient's age and complications, etc. and thus is difficult to be clearly defined. Presenting a statement in the "Indications" section about patients' eligibility for ASCT may not necessarily precisely define the target patients of bendamustine.
- Bendamustine is expected to be used by physicians with adequate knowledge and experience in treatment of haematopoietic malignancies.

7.R.6 Dosage and administration
The proposed Dosage and Administration of bendamustine was "In combination with other antineoplastic agents, the usual adult dosage is 90 mg/m^2 body surface area of bendamustine hydrochloride administered once daily as an intravenous infusion over 1 hour. A cycle consists of 2 consecutive days of infusion followed by a 26-day rest period and this cycle is repeated. The dose may be reduced as appropriate according to the patient's condition." In the current partial change application, the applicant proposed to revise the statements in the "Precautions for Dosage and Administration" section as follows:

- The use of cancer chemotherapy including bendamustine should be decided by physicians based on accurate knowledge from the "Clinical Studies" section according to the patient's condition and history of chemotherapy.

- Before using bendamustine in combination with other antineoplastic agent(s), the package insert of the concomitant drug(s) should be read carefully.

- The efficacy and safety of bendamustine monotherapy have not been established in patients with untreated low-grade B-NHL or MCL.

Based on the discussions in Sections "7.R.3 Efficacy" and "7.R.4 Safety" and the subsections below, PMDA concluded that the "Dosage and Administration" and "Precautions for Dosage and Administration" sections should be described as follows:

Dosage and Administration
In combination with rituximab (genetical recombination), the usual adult dosage is 90 mg/m^2 body surface area of bendamustine hydrochloride administered once daily as an intravenous infusion over 1 hour. A cycle consists of 2 consecutive days of infusion followed by a 26-day rest period and this cycle is repeated. The dose may be reduced as appropriate according to the patient's condition.

Precautions for Dosage and Administration
- Rituximab should be administered based on accurate knowledge from the "Clinical Studies" section, especially the dosage and administration. The package insert of the concomitant drug(s) should be read carefully.

7.R.6.1 Dosage regimen
The applicant's explanation about the dosage regimen of bendamustine for patients with untreated low-grade B-NHL or MCL:
A foreign phase II study in patients with relapsed or refractory low-grade B-NHL or MCL (*J Clin Oncol.*

2005;23:3383-89) evaluated the safety of the combination of bendamustine with rituximab.[19] Combination chemotherapies with rituximab are known to increase bone marrow depression (*Haematologica.* 2002;87:33-43). Because the combination of rituximab with bendamustine may also have enhanced toxicity, the dose of bendamustine was reduced from 120 mg/m^2, the dose for monotherapy, to 90 mg/m^2 in this study.

The dosage regimen of Study NHL 1-2003 was determined based on the regimen of the above foreign phase II study that had been confirmed to be safe. Study NHL 1-2003 demonstrated the clinical benefits of bendamustine in the treatment of patients with untreated low-grade B-NHL or MCL. Accordingly, Study 2011002 used the same dosage regimen as that in Study NHL 1-2003, and demonstrated the efficacy and safety of bendamustine in Japanese patients. The proposed Dosage and Administration for bendamustine was determined based on the dosage regimen used in Study 2011002.

While the number of cycles of bendamustine treatment was ≤6 in Studies NHL 1-2003 and 2011002 and ≤8 in Study 3064, the proposed Dosage and Administration does not define the number of treatment cycles. The applicant explained the reason as follows:
A foreign phase II study conducted in patients with relapsed or refractory low-grade B-NHL or MCL demonstrated the efficacy and safety of bendamustine given as BR up to Cycle 4 (*Proceeding of ASCO.* 2003;22:59222:592). Given this, bendamustine treatment was considered tolerable up to 6 cycles in Study NHL 1-2003.

For Study 2011002, the number of cycles of bendamustine treatment was specified as ≤6 as per Study NHL 1-2003, which demonstrated the efficacy and safety of bendamustine in ≤6-cycle treatment. Study 2011002 demonstrated the tolerability and safety of up to 6 cycles of the treatment with bendamustine, and thus the safety of bendamustine in Japanese patients was demonstrated for up to 6 cycles of the treatment. In Study 3064, based on the reported data of patients with low-grade NHL receiving R-CHOP or R-CVP as a control for 6 to 8 cycles (e.g., *Blood.* 2005;106:3725-32), the number of cycles of BR treatment was also specified as ≤8. Of 221 subjects who received BR in Study 3064, subjects who received the treatment for >6 cycles were 50 subjects (23%, 7 cycles) and 46 subjects (21%, 8 cycles). These subjects reported no specific adverse events associated with long-term treatment.

Based on the above, the treatment cycles is not necessarily be limited to ≤6 cycles as long as bendamustine is appropriately administered according to the advice given in the "Precautions for Dosage and Administration" section of the package insert, which includes the discontinuation criteria, etc. Therefore, the proposed Dosage and Administration does not define the number of treatment cycles.

The applicant's explanation about the preparation method and infusion rate of bendamustine:
In Studies NHL 1-2003 and 3064, each dose was prepared by reconstituting 90 mg/m^2 of bendamustine with saline to a volume of 500 mL, and was administered over 30 minutes. In a foreign phase II study (Study SDX-105-01) in patients with relapsed or refractory low-grade B-NHL, bendamustine was administered over 1 hour to reduce the burden on the cardiovascular system on the assumption that a change in infusion duration would have no clear impact on the plasma exposure (AUC) to bendamustine. In Study 2011002, from safety viewpoint, bendamustine solution was prepared by reconstituting 90 mg/m^2 of bendamustine with saline to a lower volume of 250 mL and administered over 1 hour. Because the efficacy and safety of bendamustine in Japanese patients were demonstrated at the above infusion rate, the duration of each infusion of bendamustine was specified as 1 hour in the proposed dosage and administration. Because the same preparation method and infusion duration as the above are used for the approved indications (i.e., relapsed or refractory low-grade B-NHL and MCL as well as chronic lymphocytic leukemia), the safety of the proposed preparation method and infusion rate are considered established.

PMDA's view:
PMDA largely accepted the applicant's explanation, despite the unclear rationales for ≤6 cycles in Study NHL 1-2003 and ≤8 cycles in Study 3064. Because there is no study data on bendamustine treatment for >6 cycles in Japanese patients, the maximum treatment cycles in Studies NHL 1-2003, 3064, and 2011002 should be appropriately communicated to healthcare professionals via the package insert, etc.

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[19] In each 28-day cycle, intravenous bendamustine 90 mg/m^2 per dose was administered on Days 1 and 2. Intravenous rituximab 375 mg/m^2 was administered on 7 days before Cycle 1, Day 0 of Cycle 1, and Day 1 of Cycle ≥2. Bendamustine was continued for up to 4 cycles and rituximab for up to 6 cycles.

7.R.6.2 Dose adjustment

The applicant's explanation about guidelines for dose interruption, reduction, or discontinuation:
In Studies NHL 1-2003 and 2011002, bendamustine was tolerable under the following criteria for starting the subsequent cycle, dose reduction, and treatment discontinuation. Study 2011002 demonstrated the efficacy and safety of bendamustine using criteria for dose adjustment that were defined based on a Japanese phase II study (Study 2007002), in which bendamustine was administered alone to patients with relapsed or refractory low-grade B-NHL or MCL. Although in the limited number of subjects, the efficacy and safety of bendamustine was demonstrated in Study 2011002, with the dose adjustment criteria used for relapsed or refractory low-grade B-NHL and MCL, the approved indication. These criteria will not create new risks in patients with untreated low-grade B-NHL or MCL [see Section "7.R.4 Safety"]. In the "Precautions for Dosage and Administration" section of the package insert, dose adjustment guidelines of bendamustine should be defined based on criteria for dose reduction, interruption, or discontinuation of bendamustine used in Study 2011002.

Criteria for starting the subsequent cycle

Study NHL 1-2003		Study 2011002*	
White blood cell count	≥2000/mm^3	Neutrophil count	≥1000/mm^3
Platelet count	≥100,000/mm^3	Platelet count	≥75,000/mm^3 with or without blood transfusion
		AST ALT	≤5 times the local upper limit of normal
		Total bilirubin Serum Cr	≤3 times the local upper limit of normal
		Others	No Grade ≥3 persisting adverse events, except Grade 3 leukopenia, lymphopenia, decreased CD4 lymphocyte count, and Grade 3 hyperglycemia

* Graded according to CTCAE v4.03-JCOG.

Criteria for dose reduction or discontinuation

Study NHL 1-2003			Study 2011002*		
White blood cell count	<1000/mm^3 for ≥2 consecutive days	Start at 90 mg/m^2 (Level 1). Reduce to Level 2 when the dose reduction criteria are met. Afterward, reduce the dose by 1 level every time when the criteria are met. Discontinue treatment when the criteria are met Level 4. Level 1: 90 mg/m^2/day Level 2: 70 mg/m^2/day Level 3: 60 mg/m^2/day Level 4: 50 mg/m^2/day	Neutrophil count	Grade 4 conditions for ≥1 week	Start at 90 mg/m^2 (Level 1). Reduce to Level 2 when the dose reduction criteria are met. Discontinue treatment when the criteria are met at Level 2. Level 1: 90 mg/m^2/day Level 2: 60 mg/m^2/day
			Febrile neutropenia	For ≥3 consecutive days	
Platelet count	<75,000/mm^3 for ≥2 consecutive days		Platelet count	<25,000/mm^3 or requires platelet transfusion	
			Others	Otherwise, when dose reduction is required at the discretion of the investigator or subinvestigator due to adverse events	

* Graded according to CTCAE v4.03-JCOG.

PMDA accepted the applicant's explanation.

7.R.6.3 Concomitant use with antineoplastic agents other than rituximab

PMDA asked the applicant to explain the possibility that bendamustine may be administered concomitantly with antineoplastic agents other than rituximab to patients with untreated low-grade B-NHL or MCL.

The applicant's response:
Because the efficacy and safety of bendamustine used concomitantly with antineoplastic agents other than rituximab have not been established in patients with untreated low-grade B-NHL or MCL, such combination treatment is unlikely to be used.

PMDA's view:
PMDA largely accepted the applicant's explanation. However, to make clear that combination therapy with an antineoplastic agent is recommended only with rituximab, the "Dosage and Administration" section of the package insert should highlight that bendamustine must be used with rituximab.

7.R.7 Post-marketing investigations

Based on the following considerations, the applicant explained that, at present, post-marketing surveillance covering patients with untreated low-grade B-NHL or MCL does not need to be conducted immediately after the approval of bendamustine because no new safety issues were identified in the current application.

- All adverse drug reactions reported in Studies 2011002, NHL1-2003, and 3064 were known events, and no events requiring further attention have been reported by untreated patients [see Section "7.R.4 Safety"].
- Since post-marketing surveillance data have been obtained for the approved indication for patients with relapsed or refractory low-grade B-NHL or MCL (583 patients included in safety analysis), a certain amount of safety information is available for Japanese patients receiving bendamustine.

PMDA's view:
The above explanation by the applicant is acceptable. There is not much need for a post-marketing surveillance covering patients with untreated low-grade B-NHL or MCL immediately after the approval of bendamustine, and the collection of safety information on bendamustine via routine pharmacovigilance activities will suffice.

7.2 Adverse events, etc. observed in clinical studies

Based on the safety clinical study data submitted death is described in Section "7.1 Evaluation data" and other major adverse events are detailed in the subsections below. The results from (a) Japanese phase I study (Study 2006001) and Japanese phase II study (Study 2007002) and (b) foreign phase III study (Study C18083/3070) are omitted because they were submitted and evaluated for (a) the initial application for marketing approval and (b) partial change application, respectively (see "Review Report for Treakisym Injection 100 mg dated August 9, 2010" and "Review Report for Treakisym Injection 25 mg and Treakisym Injection 100 mg dated July 26, 2016").

7.2.1 Japanese phase I study (Study 2008002)

Adverse events occurred in 3 of 3 subjects (100%) in the 90 mg/m^2 group and 6 of 6 subjects (100%) in the 120 mg/m^2 group. A causal relationship to the study drug could not be ruled out for the events occurring in 3 of 3 subjects (100%) in the 90 mg/m^2 group and 6 of 6 subjects (100%) in the 120 mg/m^2 group. Adverse events with an incidence of ≥40% in any group are shown in Table 15.

Table 15. Adverse events with an incidence of ≥40% in any group

System Organ Class Preferred Term (MedDRA/J 18.0)	Number of subjects 90 mg/m^2 N = 3		120 mg/m^2 N = 6	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	3 (100)	3 (100)	6 (100)	6 (100)
Gastrointestinal disorders				
Constipation	3 (100)	0	5 (83.3)	0
Diarrhoea	0	0	3 (50.0)	0
Nausea	1 (33.3)	0	3 (50.0)	0
General disorders and administration site conditions				
Injection site reaction	0	0	3 (50.0)	0
Malaise	0	0	5 (83.3)	0
Pyrexia	0	0	3 (50.0)	0
Investigations				
ALT increased	2 (66.7)	0	2 (33.3)	0
AST increased	2 (66.7)	0	4 (66.7)	0
Blood albumin decreased	0	0	6 (100)	0
Blood IgA decreased	2 (66.7)	1 (33.3)	6 (100)	0
Blood IgG decreased	3 (100)	1 (33.3)	5 (83.3)	0
Blood IgM decreased	1 (33.3)	0	4 (66.7)	0
Blood LDH increased	1 (33.3)	1 (33.3)	5 (83.3)	0
Blood potassium decreased	0	0	3 (50.0)	1 (16.7)
C-reactive protein increased	2 (66.7)	0	5 (83.3)	0
CD4 lymphocytes decreased	3 (100)	3 (100)	5 (83.3)	5 (83.3)
Haemoglobin decreased	1 (33.3)	0	5 (83.3)	0
Lymphocyte count decreased	3 (100)	3 (100)	6 (100)	6 (100)
Neutrophil count decreased	3 (100)	3 (100)	6 (100)	6 (100)
Neutrophil count increased	1 (33.3)	0	4 (66.7)	0
Platelet count decreased	3 (100)	0	5 (83.3)	2 (33.3)
Protein total decreased	0	0	5 (83.3)	0
Red blood cell count decreased	0	0	5 (83.3)	0
White blood cell count decreased	3 (100)	3 (100)	6 (100)	6 (100)
White blood cell count increased	2 (66.7)	0	4 (66.7)	0
Blood ALP increased	2 (66.7)	0	2 (33.3)	0
Metabolism and nutrition disorders				
Decreased appetite	1 (33.3)	0	4 (66.7)	0
Respiratory, thoracic and mediastinal disorders				
Hiccups	0	0	3 (50.0)	0

Serious adverse events occurred in 1 of 6 subjects (16.7%) in the 120 mg/m^2 group. The events were, namely, malaise and pyrexia, and a causal relationship to the study drug was ruled out for both events.

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

7.2.2 Japanese phase II study (Study 2011002)

Adverse events occurred in 69 of 69 subjects (100%), and a causal relationship to the study drug could not be ruled out for the events occurring in 69 of 69 subjects (100%). Adverse events with an incidence of ≥20% are shown in Table 16.

Table 16. Adverse events reported by ≥20% of subjects

System Organ Class Preferred Term (MedDRA/J 18.0)	Number of subjects (%) N = 69	
	All Grades	Grade ≥3
All adverse events	69 (100)	69 (100)
Blood and lymphatic system disorders		
Anaemia	24 (34.8)	3 (4.3)
Gastrointestinal disorders		
Constipation	45 (65.2)	0
Nausea	46 (66.7)	1 (1.4)
General disorders and administration site conditions		
Malaise	37 (53.6)	0
Pyrexia	17 (24.6)	0
Injury, poisoning and procedural complications		
Infusion related reaction	28 (40.6)	2 (2.9)
Investigations		
ALT increased	18 (26.1)	2 (2.9)
AST increased	22 (31.9)	2 (2.9)
Blood IgA decreased	21 (30.4)	0
Blood IgG decreased	21 (30.4)	0
Blood IgM decreased	32 (46.4)	0
Blood LDH increased	21 (30.4)	0
C-reactive protein increased	18 (26.1)	0
CD4 lymphocytes decreased	64 (92.8)	63 (91.3)
GGT increased	15 (21.7)	1 (1.4)
Lymphocyte count decreased	67 (97.1)	67 (97.1)
Neutrophil count decreased	64 (92.8)	58 (84.1)
Platelet count decreased	38 (55.1)	5 (7.2)
White blood cell count decreased	69 (100)	57 (82.6)
Metabolism and nutrition disorders		
Decreased appetite	30 (43.5)	2 (2.9)
Psychiatric disorders		
Insomnia	19 (27.5)	1 (1.4)
Skin and subcutaneous tissue disorders		
Rash	29 (42.0)	2 (2.9)
Vascular disorders		
Vasculitis	20 (29.0)	0

Serious adverse events occurred in 8 of 69 subjects (11.6%). They were, namely, febrile neutropenia in 3 subjects (4.3%), atrial tachycardia, pyrexia, pneumonia cytomegaloviral, tumour lysis syndrome, and dermatitis allergic in 1 subject each (1.4%). A causal relationship to the study drug could not be ruled out for febrile neutropenia (3 subjects) and pyrexia, pneumonia cytomegaloviral, and tumour lysis syndrome (1 subject each).

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

7.2.3 Japanese phase II study (Study 2014001)

It was a follow-up study for Study 2011002 to collect data on serious adverse events occurring after the completion of Study 2011002 only. No new serious adverse events were identified.

7.2.4 Foreign phase III study (Study NHL 1-2003)

Adverse events occurred in 264 of 267 subjects (98.9%) in the BR group and 249 of 252 subjects (98.8%) in the R-CHOP group. A causal relationship to the study drug could not be ruled out for events occurring in 263 of 267 subjects (98.5%) in the BR group and 249 of 252 subjects (98.8%) in the R-CHOP group. Adverse events with an incidence of ≥20% in any group are shown in Table 17.

Table 17. Adverse events reported by ≥20% of subjects in any group

System Organ Class Preferred Term (MedDRA/J 18.0)	Number of subjects			
	BR		R-CHOP	
	N = 267		N = 252	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	264 (98.9)	159 (59.6)	249 (98.8)	221 (87.7)
Gastrointestinal disorders				
Stomatitis	20 (7.5)	4 (1.5)	63 (25.0)	8 (3.2)
Vomiting	113 (42.3)	6 (2.2)	115 (45.6)	11 (4.4)
General disorders and administration site conditions				
Pyrexia	56 (21.0)	15 (5.6)	55 (21.8)	12 (4.8)
Infections and infestations				
Bacterial infection	36 (13.5)	10 (3.7)	54 (21.4)	7 (2.8)
Investigations				
Granulocyte count decreased	145 (54.3)	65 (24.3)	182 (72.2)	158 (62.7)
Haemoglobin decreased	101 (37.8)	7 (2.6)	145 (57.5)	13 (5.2)
Platelet count decreased	75 (28.1)	18 (6.7)	77 (30.6)	15 (6.0)
White blood cell count decreased	218 (81.6)	95 (35.6)	228 (90.5)	177 (70.2)
Transaminases increased	60 (22.5)	4 (1.5)	44 (17.5)	2 (0.8)
Nervous system disorders				
Peripheral sensory neuropathy	24 (9.0)	3 (1.1)	78 (31.0)	6 (2.4)
Skin and subcutaneous tissue disorders				
Alopecia	43 (16.1)	11 (4.1)	179 (71.0)	94 (37.3)
Rash	71 (26.6)	3 (1.1)	40 (15.9)	2 (0.8)

Serious adverse events occurred in 63 of 267 subjects (23.6%) in the BR group and 69 of 252 subjects (27.4%) in the R-CHOP group. Serious adverse events reported by ≥1 subject include pyrexia (11 subjects, 4.1%), general physical health deterioration (7 subjects, 2.6%), chills (5 subjects, 1.9%), pneumonia (4 subjects, 1.5%), leukopenia, vomiting, urinary tract infection, and pulmonary embolism (3 subjects each, 1.1%), and neutropenia, diarrhoea, ileus, herpes zoster, granulocyte count decreased, white blood cell count decreased, pain in extremity, dyspnoea, and rash (2 subjects each, 0.7%) in the BR group; and general physical health deterioration (10 subjects, 4.0%), pyrexia (9 subjects, 3.6%), febrile neutropenia and white blood cell count decreased (7 subjects each, 2.8%), neutropenia and sepsis (6 subjects each, 2.4%), leukopenia and pneumonia (5 subjects each, 2.0%), ileus (4 subjects, 1.6%), diarrhoea, nausea, vomiting, dyspnoea, and pleural effusion (3 subjects each, 1.2%), and abdominal pain upper, constipation, extravasation, hypersensitivity, herpes zoster, urinary tract infection, pneumonia bacterial, body temperature increased, granulocyte count decreased, dehydration, back pain, headache, and syncope (2 subjects each, 0.8%) in the R-CHOP group. A causal relationship to the study drug could not be ruled out for pyrexia (10 subjects), chills (5 subjects), general physical health deterioration and pneumonia (4 subjects each), leukopenia and urinary tract infection (3 subjects each), vomiting, pulmonary embolism, diarrhoea, herpes zoster, granulocyte count decreased, white blood cell count decreased, pain in extremity, and rash (2 subjects each), and neutropenia, ileus, and dyspnoea (1 subject each) in the BR group and general physical health deterioration (9 subjects), pyrexia, febrile neutropenia, and white blood cell count decreased (7 subjects each), neutropenia and sepsis (6 subjects each), leukopenia and pneumonia (5 subjects each), ileus (4 subjects), nausea and vomiting (3 subjects each), diarrhoea, dyspnoea, pleural effusion, constipation, hypersensitivity, herpes zoster, urinary tract infection, pneumonia bacterial, body temperature increased, granulocyte count decreased, dehydration, back pain, and headache (2 subjects each), and abdominal pain upper, extravasation, and syncope (1 subject each) in the R-CHOP group.

Adverse events leading to discontinuation of the study drug were reported by 7 of 267 subjects (2.6%) in the BR group and 7 of 252 subjects (2.8%) in the R-CHOP group.[20)]

7.2.5 Foreign phase III study (Study 3064)

Adverse events were reported by 221 of 221 subjects (100%) in the BR group and 213 of 215 subjects (99.1%) in the R-CHOP/R-CVP group. A causal relationship to the study drug could not be ruled out for events in 213 of 221 subjects (96.4%) in the BR group. Data related to a causal relationship to the

[20)] In terms of adverse events leading to treatment discontinuation, only the number of subjects was counted without recording the event term according to a protocol requirement.

study drug were not collected from patients receiving R-CHOP/R-CVP according to the developer's decision to prioritize the safety evaluation of BR. Adverse events with an incidence of ≥20% in any group are shown in Table 18.

Table 18. Adverse events with an incidence of ≥20% in any group

System Organ Class Preferred Term (MedDRA/J 18.0)	Number of subjects			
	BR		R-CHOP/R-CVP	
	N = 221		N = 215	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	221 (100)	129 (58.4)	213 (99.1)	125 (58.1)
Blood and lymphatic system disorders				
Neutropenia	74 (33.5)	59 (26.7)	85 (39.5)	78 (36.3)
Gastrointestinal disorders				
Constipation	64 (29.0)	0	90 (41.9)	3 (1.4)
Diarrhoea	46 (20.8)	2 (0.9)	49 (22.8)	0
Nausea	139 (62.9)	4 (1.8)	102 (47.4)	0
Vomiting	60 (27.1)	7 (3.2)	28 (13.0)	0
General disorders and administration site conditions				
Fatigue	113 (51.1)	8 (3.6)	107 (49.8)	3 (1.4)
Injury, poisoning and procedural complications				
Infusion related reaction	52 (23.5)	13 (5.9)	45 (20.9)	8 (3.7)
Nervous system disorders				
Headache	47 (21.3)	1 (0.5)	44 (20.5)	1 (0.5)
Neuropathy peripheral	9 (4.1)	1 (0.5)	51 (23.7)	1 (0.5)
Psychiatric disorders				
Insomnia	37 (16.7)	0	47 (21.9)	0
Skin and subcutaneous tissue disorders				
Alopecia	8 (3.6)	0	74 (34.4)	1 (0.5)

Serious adverse events were reported by 58 of 221 subjects (26.2%) in the BR group and 48 of 215 subjects (22.3%) in the R-CHOP/R-CVP group. Serious adverse events reported by ≥1 subject were infusion related reaction (8 subjects, 3.6%), febrile neutropenia and pneumonia (7 subjects each, 3.2%), pyrexia (5 subjects, 2.3%), drug hypersensitivity (4 subjects, 1.8%), neutropenia, nausea, and vomiting (3 subjects each, 1.4%), and abdominal pain, diverticulitis, viral infection, and respiratory failure (2 subjects each, 0.9%) in the BR group; and febrile neutropenia (9 subjects, 4.2%), neutropenia (5 subjects, 2.3%), infusion related reaction and pyrexia (4 subjects each, 1.9%), non-cardiac chest pain (3 subjects, 1.4%), and back pain (2 subjects, 0.9%) in the R-CHOP/R-CVP group. A causal relationship to the study drug could not be ruled out for febrile neutropenia (7 subjects), pneumonia and pyrexia (5 subjects each), neutropenia, nausea, and vomiting (3 subjects each), abdominal pain and viral infection (2 subjects each), and diverticulitis, drug hypersensitivity, and respiratory failure (1 subject each) in the BR group.

Adverse events led to discontinuation of the study drug in 10 of 221 subjects (4.5%) in the BR group. These events include neutropenia in 2 subjects (0.9%), and splenomegaly, cardiac arrest, pericardial effusion, ileus, infusion related reaction, blood lactate dehydrogenase (LDH) increased, gamma-glutamyl transferase (GGT) increased, sarcoma, and lung neoplasm malignant in 1 subject each (0.5%). A causal relationship to the study drug could not be ruled out for neutropenia (2 subjects) and cardiac arrest, pericardial effusion, ileus, and GGT increased (1 subject each).

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

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

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

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

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

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

On the basis of data submitted, PMDA has concluded that bendamustine has efficacy in the treatment of untreated low-grade B-NHL or MCL, and that bendamustine has acceptable safety in view of its benefits. Bendamustine is clinically significant as a treatment option for patients with untreated low-

grade B-NHL or MCL. Further discussions are needed on the clinical positioning, indications, dosage and administration, and post-marketing investigations of bendamustine.

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

Review Report (2)

November 15, 2016

Product Submitted for Approval

Brand Name	(a) Treakisym Injection 25 mg, (b) Treakisym Injection 100 mg
Non-proprietary Name	Bendamustine Hydrochloride
Applicant	SymBio Pharmaceuticals Limited
Date of Application	(a) October 5, 2016, (b) December 24, 2015

1. Content of the Review

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

1.1 Clinical positioning and efficacy

As mentioned in Sections "7.R.2 Clinical positioning of bendamustine" and "7.R.3 Efficacy" of the Review Report (1), clinical practice guidelines and textbooks recommend bendamustine hydrochloride (bendamustine) for patients with untreated low-grade B-cell non-Hodgkin lymphoma (B-NHL) or mantle cell lymphoma (MCL) based on the results of a foreign phase III study in patients with untreated low-grade B-NHL or MCL (Study NHL 1-2003). PMDA thus concluded that introducing bendamustine to Japanese clinical practice has significance given that clinical study data on bendamustine including statistically sound interpretation of the results of Study NHL 1-2003 are appropriately presented to healthcare professionals via the package insert, etc. [see Section "7.R.3 Efficacy" of the Review Report (1)] .

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

- There remains a concern about the quality of Study NHL 1-2003 because of changes made in the protocol while the study was underway. However, PMDA's conclusion is reasonable because progression-free survival (PFS) according to WHO criteria at least did not indicate a tendency for the combination of bendamustine with rituximab (genetical recombination) (BR) to be less effective than the combination of rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP).

- Although due attention should be paid to the risk of bone marrow depression and infections, bendamustine has clinical benefits as a new treatment option for patients with untreated low-grade B-NHL or MCL with its safety profile distinct from that of R-CHOP, a conventional therapy.

In addition, the following comments (a) and (b) were raised from the expert advisors at the Expert Discussion:

(a) For the evaluation of the original primary endpoint of event-free survival in Study NHL 1-2003, "failure to achieve partial response (PR) or better within 3 cycles" was defined as an event, and thus progression-free patients were included in the evaluation if inadequately responding to the treatment. In contrast, after the revision of the primary endpoint to PFS according to WHO criteria, patients were censored to receive post-study treatment due to inadequate response, etc. This may have led to overestimation of the efficacy of bendamustine. How the censoring due to the start of post-study treatment affected the efficacy evaluation should be examined.

(b) Whether the non-inferiority in PFS, it was the primary analysis at that time, was demonstrated by the PFS analyses results presented at the American Society of Hematology (2009) should be determined in light of the significance levels used for the previous interim analyses.

PMDA asked the applicant to explain the above points (a) and (b).

The applicant's response:

(a) A total of 328 subjects (178 in the BR group, 150 in the R-CHOP group) were censored in Study NHL 1-2003. Because reasons for censoring were not collected, it was not possible to identify subjects who were censored to receive post-study treatment. Table 19 shows the results of sensitivity analysis when the following cases were counted as events because of a possibility of being censored due to inadequate response.

- A patient underwent an objective assessment such as by imaging. The patient was censored by their attending physician on the day of assessment if achieving partial response (PR) or better according to WHO criteria, or considered had an event if failing to achieve PR.
- A patient did not undergo an objective assessment such as by imaging. The patient was censored by their attending physician on the day of the most recent evaluation if achieving PR or better, or considered had an event on the day of the most recent evaluation if failing to achieve PR.

Table 19. Results of sensitivity analysis for PFS according to WHO criteria (ITT population; investigator assessment; data cutoff date, [redacted], 20[redacted])

	BR	R-CHOP
Number of subjects	274	275
Number of events (%)	150 (54.7)	165 (60.0)
Median [95% CI] (months)	29.3 [23.0, 32.2]	23.0 [19.1, 25.6]
Hazard ratio [99% CI][*1]	0.817 [0.61, 1.09]	
P-value (two-sided)[*2]	0.0373	

[*1] Proportional hazards model adjusted by a stratification factor (histologic type), [*2] Stratified log-rank test with histologic type as a stratification factor

(b) Because the interim analyses before the presentation at the American Society of Hematology 2009 (the third interim analysis) were conducted by investigators within the framework of investigator-initiated trial, and the detailed data including the significance levels used were not able to be obtained. In addition, neither the positioning of the analysis presented at individual conferences nor discussions on the analysis plan could be identified. According to the results of PFS by investigator assessment according to WHO criteria obtained at the third interim analysis, the median PFS was 54.8 months in the BR group and 34.8 months in the R-CHOP group, with a hazard ratio [95% CI] of 0.5765 [0.4292, 0.7683] (P = 0.0002, stratified log-rank test), and the P value fell below the post-hoc significance level of 0.005469.[21)] Thus, the non-inferiority for PFS (primary analysis defined in the second amendment of the protocol) was demonstrated.

PMDA's view:

(a) The impact of censoring due to shifting to a post-study treatment on the efficacy evaluation in Study NHL 1-2003 was evaluated without being able to identify individual relevant cases. However, patients who were censored possibly due to inadequate response are more likely to undergo a post-study treatment than the other censored patients. In fact, the mentioned sensitivity analysis did not show a clear inferiority of BR relative to the control.

(b) The non-inferiority of BR over R-CHOP (endpoint for the primary objective as of the time of study data publication at the American Society of Hematology 2009) is not considered demonstrated for the following reasons:

1) Because there was no written interim analysis plan available at the time of the American Society of Hematology 2009, whether the details of interim analysis were predefined is unclear and cannot be assured:

[21)] Calculated using a Lan-DeMets α-spending function of O'Brien-Fleming type and information fraction at the interim analysis by defining the information amount of 1 as the number of events expected based on the hypothesis for event-free survival for sample size determination described in the protocol because the protocol did not define details of the interim analyses including maximal information.

- Details of interim analysis were not found in the protocol.
- The first version of the statistical analysis plan was developed in [redacted] 20[redacted] after the publication at the American Society of Hematology 2009.

2) Based on 1), validity of the post-hoc significance level calculated by the applicant is not ensured objectively.

3) The 2 interim analyses were performed before the American Society of Hematology 2009, and it is difficult to calculate a post-hoc significance level to control the type I error rate because:
   - Significance levels used for these interim analyses are not known.
   - Neither the positioning of the analysis presented at individual conferences nor discussions on analysis plan could be identified.

Study NHL 1-2003 should have designed as a superiority trial rather than a non-inferiority trial [see Section "7.R.3 Efficacy" of the Review Report (1)]. PMDA thus concluded that the superiority of bendamustine has not been demonstrated, as pointed out in Section "7.R.3 Efficacy" of the Review Report (1), also from the following view:

- Although confirmatory data for superiority of BR over R-CHOP were not yet available at the time of presentation at the American Society of Hematology 2009, the objective of final primary analysis was changed thereafter from non-inferiority testing to superiority testing. This is inappropriate in terms of clinical study methodology, and the superiority of BR over R-CHOP is therefore not considered demonstrated.

1.2 Safety

PMDA's conclusions:

Based on the results of the review in Section "7.R.4 Safety" of the Review Report (1), adverse events requiring attention during treatment with bendamustine in patients with untreated low-grade B-NHL or MCL are the known events associated with bendamustine or rituximab, and no other adverse events requiring further attention have been noted.

Bendamustine is tolerable when the patient is followed by a physician with adequate knowledge and experience in the treatment of haematopoietic malignancies, through the monitoring and control of adverse events, dose interruption or reduction, or treatment discontinuation.

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

1.3 Indication

PMDA's conclusion:

Based on the discussion in Section "7.R.5 Indication" of the Review Report (1), the proposed indication of "low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma" is appropriate. However, the following cautionary advice should be given in the "Precautions for Indications" section of the package insert.

- The use of bendamustine should be determined with the good understanding of the efficacy and safety of bendamustine based on the "Clinical Studies" section, and after due consideration of other treatment options.

The PMDA's conclusion was supported by the expert advisors at the Expert Discussion.

Accordingly, PMDA instructed the applicant to revise the "Indications" and "Precautions for Indications" sections, and the applicant agreed.

1.4 Dosage and administration

PMDA's conclusions:

Based on the discussions in Section "7.R.6 Dosage and administration" of the Review Report (1), the proposed dose level, preparation procedure, infusion rate, and dose adjustment of bendamustine are acceptable. The Dosage and Administration of bendamustine should be "In combination with rituximab (genetical recombination), the usual adult dosage is 90 mg/m^2 body surface area of bendamustine hydrochloride administered once daily as an intravenous infusion over 1 hour. A cycle consists of 2

consecutive days of infusion followed by a 26-day rest period and this cycle is repeated. The dose may be reduced as appropriate according to the patient's condition." However, the following cautionary advice should be given in the "Precautions for Dosage and Administration" section.

- Rituximab should be administered based on accurate knowledge from the "Clinical Studies" section, especially the dosage and administration. The package insert of the concomitant drug(s) should be read carefully.

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

Thus, PMDA instructed the applicant to include the above cautionary advice in the "Dosage and Administration" and the "Precautions for Dosage and Administration" sections, and the applicant agreed.

1.5 Risk management plan (draft)

PMDA's conclusions:
Based on the discussion in Section "7.R.7 Post-marketing investigations" of the Review Report (1), there is not much need for a post-marketing surveillance covering patients with untreated low-grade B-NHL or MCL immediately after the approval of bendamustine. The collection of bendamustine safety data via routine pharmacovigilance activities will suffice.

The PMDA's conclusion was supported by the expert advisors at the Expert Discussion.

Further, based on the above discussion, PMDA concluded that, at present, the draft risk management plan for Treakisym should include safety specifications listed in Table 20 and additional pharmacovigilance and risk minimization activities listed in Table 21.

Table 20. Safety specifications and efficacy specifications in risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Bone marrow depression • Infections • Toxic epidermal necrolysis and oculomucocutaneous syndrome • Tumor lysis syndrome • Shock/anaphylaxis • Interstitial lung disease	• Secondary malignancy	• None
Efficacy specification (related to the current partial change application)		
• None		

Table 21. Summary of additional pharmacovigilance and risk minimization plans

Additional pharmacovigilance activities	Additional risk minimization activities
• Drug use-results survey covering patients with chronic lymphocytic leukemia	• Preparation and distribution of materials for healthcare professionals

Underline denotes activities for the currently proposed indication.

1.6 Approval of bendamustine

PMDA's conclusions based on the above discussions:
As described in Section "7.R.3 Efficacy" of the Review Report (1), the results of Study NHL 1-2003, a pivotal study for the evaluation of the efficacy and safety of bendamustine, did not clearly demonstrate the efficacy of bendamustine but indicated a certain level of efficacy in patients with untreated low-grade B-NHL or MCL. At present, clinical practice guidelines and textbooks recommend BR based on the published data from Study NHL 1-2003. Given this situation, it is impractical to conduct a randomized controlled study to verify the efficacy of bendamustine. The approval of bendamustine will offer an advantage that the drug is supplied to medical centers with appropriate information according to a risk management plan. With all these considered, the practical approach is to approve bendamustine with the premise that a certain level of safety monitoring is performed.

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

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 inspection and data integrity assessment

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

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

The new drug application data (CTD 5.3.5.2-1, CTD 5.3.5.4-1) 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. As a whole, the clinical studies were conducted in accordance with GCP. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. However, the following areas for improvement were revealed at some study sites and the sponsor. These were of no significant impact on the overall evaluation of the studies but were notified to the heads of the sites concerned and the applicant (sponsor).

Areas for improvement

Study sites:

- Protocol deviations (non-compliance with the dose reduction criteria of the study drug and non-compliance with the provisions on the use restriction of supportive care)

Sponsor:

- Some information on serious unexpected adverse drug reactions were not appropriately communicated to the investigators and the heads of the study sites.

3. Overall Evaluation

As a result of the above review, PMDA concluded that the product may be approved for the indication, and dosage and administration modified as below, with the following condition. However, after approval, necessary cautionary advice and information for the proper use of the product must be given in the package insert appropriately. The product must be used strictly under the supervision of a physician with adequate knowledge and experience in treatment of haematopoietic malignancies at a medical facility capable of responding to emergency. The re-examination period for this application is the remainder of the re-examination period for the initial approval (until October 26, 2020).

Indication (Underline denotes addition, strike-through deletion, and double-underline addition on August 26, 2016 after the submission of the application for Treakisym Injection 100 mg.)

1. ~~The following relapsed or refractory diseases~~

Low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma

2. Chronic lymphocytic leukemia

Dosage and Administration (Underline denotes addition, strike-through deletion, and double-underline addition on August 26, 2016 after the submission of the application for Treakisym Injection 100 mg.)

1. ~~Relapsed or refractory~~ Low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma

(1) Untreated disease

In combination with rituximab (genetical recombination), the usual adult dosage is 90 mg/m^2 body surface area of bendamustine hydrochloride administered once daily as an intravenous infusion over 1 hour. A cycle consists of 2 consecutive days of infusion followed by a 26-day rest period and the cycle is repeated. The dose may be reduced as appropriate according to the patient's condition.

(2) Relapsed or refractory disease

The usual adult dosage is 120 mg/m^2 body surface area of bendamustine hydrochloride administered once daily as an intravenous infusion over 1 hour. A cycle consists of 2 consecutive days of infusion followed by a 19-day rest period and the cycle is repeated. The dose may be reduced as appropriate according to the patient's condition.

2. Chronic lymphocytic leukemia
The usual adult dosage is 100 mg/m^2 body surface area of bendamustine hydrochloride administered once daily as an intravenous infusion over 1 hour. A cycle consists of 2 consecutive days of infusion followed by a 26-day rest period and the cycle is repeated. The dose may be reduced as appropriate according to the patient's condition.

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

Warnings (No change)
(1) Treakisym should be administered to patients under a supervision of a physician with adequate knowledge and experience in the treatment of haematopoietic malignancies at a medical institution well-prepared for emergency response only when the patient is considered eligible for the treatment. Prior to treatment, consent should be obtained from the patient or his/her family member who has been fully informed of the benefits and risks of the therapy.
(2) Bone marrow depression may cause a serious adverse drug reaction such as infection. The patient's condition should be closely monitored through frequent hematological tests, etc.

Treakisym must be used after a careful reading of the package insert.

Contraindications (No change)
(1) Patients with a history of serious hypersensitivity to any ingredients of Treakisym
(2) Pregnant women or women who may possibly be pregnant

Precautions for Indications (Underline denotes addition, and double-underline addition on August 26, 2016 after the submission of the application for Treakisym Injection 100 mg.)
Untreated low-grade B-cell non-Hodgkin's and mantle cell lymphomas and chronic lymphocytic leukemia
The use of bendamustine should be determined with the good understanding of the efficacy and safety of Treakisym based on the "Clinical Studies" section, and after due consideration of other treatment options.

Precautions for Dosage and Administration (Underline denotes addition, strike-through deletion, and double-underline addition on August 26, 2016 or September 28, 2016 after the submission of the application for Treakisym Injection 100 mg.)
(1) Rituximab (genetical recombination) should be administered based on accurate knowledge from the "Clinical Studies" section, especially the dosage and administration. The package insert of the concomitant drug(s) should be read carefully.
(~~1~~2) The efficacy and safety of Treakisym have not been established when used with antineoplastic agents other than rituximab in patients with relapsed or refractory low-grade B-cell non-Hodgkin's or mantle cell lymphomas or chronic lymphocytic leukemia.
(~~2~~3) If severe bone marrow depression occurs during the treatment with Treakisym, dose interruption, reduction, or discontinuation should be considered as appropriate by referring the following guidelines.

<table>
<tr><th colspan="2">Dosing interval or dose adjustment</th><th>Threshold</th></tr>
<tr><td>Dose interruption</td><td>Do not start the next cycle until the recovery of neutrophil and platelet counts to the levels meeting the thresholds in the right column.</td><td>Neutrophil count ≥1000/mm^3
and
Platelet count ≥75,000/mm^3</td></tr>
<tr><td rowspan="5">Dose reduction or discontinuation</td><td colspan="2">Do not start the next cycle when bone marrow depression is observed with neutrophil and platelet counts meeting the thresholds shown below during treatment until recovery to levels meeting the thresholds for dose interruption. Then, consider dose reduction or discontinuation according to the following:</td></tr>
<tr><td>~~Relapsed or refractory~~ Low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma</td><td rowspan="4">Neutrophil count <500/mm^3
or
Platelet count <25,000/mm^3</td></tr>
<tr><td>• Patients who received 120 mg/m^2 in the previous cycle: reduce to 90 mg/m^2.
• Patients who received 90 mg/m^2 in the previous cycle: reduce to 60 mg/m^2.
• Patients who received 60 mg/m^2 in the previous cycle: discontinue treatment.
Once reduced, maintain the dose level and do not increase again.</td></tr>
<tr><td>Chronic lymphocytic leukemia</td></tr>
<tr><td>• Patients who received 100 mg/m^2 in the previous cycle: reduce to 75 mg/m^2.
• Patients who received 75 mg/m^2 in the previous cycle: reduce to 50 mg/m^2.
• Patients who received 50 mg/m^2 in the previous cycle: discontinue treatment.
Once reduced, maintain he dose and do not increase again.</td></tr>
</table>

(~~3~~4) When nonhematologic toxicity is observed during the treatment with Treakisym, dose interruption, reduction, or discontinuation should be considered as appropriate by referring the following guidelines.

<table>
<tr><th colspan="2">Dosing interval or dose adjustment</th><th>Threshold</th></tr>
<tr><td>Dose interruption</td><td>Do not start the next cycle until the recovery of laboratory test values, etc. to the levels meeting the thresholds in the right column.</td><td>Grade ≤2 Note nonhematologic toxicity
Total bilirubin <2.0 mg/dL
Serum creatinine <2.0 mg/dL</td></tr>
<tr><td rowspan="5">Dose reduction or discontinuation</td><td colspan="2">Do not start the next cycle following an adverse drug reaction shown as the threshold below during treatment until recovery to levels meeting the thresholds for dose interruption. Then, consider dose reduction or discontinuation according to the following:</td></tr>
<tr><td>~~Relapsed or refractory~~ Low-grade B-cell non-Hodgkin's lymphoma and mantle cell lymphoma</td><td rowspan="4">Grade ≥3 Note nonhematologic toxicity</td></tr>
<tr><td>• Patients who received 120 mg/m^2 in the previous cycle: reduce to 90 mg/m^2.
• Patients who received 90 mg/m^2 in the previous cycle: reduce to 60 mg/m^2.
• Patients who received 60 mg/m^2 in the previous cycle: discontinue treatment.
Once reduced, maintain the dose and do not increase again.</td></tr>
<tr><td>Chronic lymphocytic leukemia</td></tr>
<tr><td>• Patients who received 100 mg/m^2 in the previous cycle: reduce to 75 mg/m^2.
• Patients who received 75 mg/m^2 in the previous cycle: reduce to 50 mg/m^2.
• Patients who received 50 mg/m^2 in the previous cycle: discontinue treatment.
Once reduced, maintain the dose and do not increase again.</td></tr>
</table>

Note NCI-CTCAE Version 4.0.

(45) Preparation of daily doses

Treakisym Injection 100 mg is reconstituted in 40 mL of water for injection per vial, and Treakisym Injection 25 mg in 10 mL of water for injection per vial. The appropriate dose of the reconstituted solution is calculated from the patient's body surface area and diluted with saline to the final injection volume of 250 mL.