Report on the Deliberation Results

February 29, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Besponsa Injection 1 mg
Non-proprietary Name	Inotuzumab Ozogamicin (Genetical Recombination) (JAN*)
Applicant	Pfizer Japan Inc.
Date of Application	July 27, 2023

Results of Deliberation

In its meeting held on February 22, 2024, 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 is 6 years and 1 day.

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

Review Report

February 6, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Besponsa Injection 1 mg
Non-proprietary Name	Inotuzumab Ozogamicin (Genetical Recombination)
Applicant	Pfizer Japan Inc.
Date of Application	July 27, 2023
Dosage Form/Strength	Lyophilized powder for reconstitution for injection: each vial contains 1 mg of inotuzumab ozogamicin (genetical recombination)
Application Classification	Prescription drug, (6) Drug with a new dosage
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 401 of 2017 [*29 yaku*]; PSEHB/PED Notification No. 0324-1 dated March 24, 2017, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in the treatment of relapsed or refractory cluster of differentiation (CD)22-positive acute lymphoblastic leukemia in pediatric patients, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The following issues should be further investigated through post-marketing surveillance: liver disorder, including veno-occlusive disease/sinusoidal obstruction syndrome, myelosuppression, infections, haemorrhage, tumour lysis syndrome, infusion reaction, pancreatitis, QTc interval prolongation, inflammatory gastrointestinal events, interstitial lung disease, and reproductive and developmental toxicity.

Indication

Relapsed or refractory CD22-positive acute lymphoblastic leukemia

(No change)

Dosage and Administration

The usual ~~adult~~ dosage is inotuzumab ozogamicin (genetical recombination) 0.8 mg/m^2 (body surface area) on Day 1, 0.5 mg/m^2 (body surface area) on Day 8, and 0.5 mg/m^2 (body surface area) on Day 15, administered as an intravenous infusion over at least 1 hour, followed by a rest period. For adults, the duration of treatment cycle is 21 to 28 days in Cycle 1 and 28 days in subsequent cycles. Treatment should be repeated in cycles. For pediatric patients, the duration of treatment cycle is 21 to 42 days in Cycle 1 and 28 to 42 days in subsequent cycles. Treatment should be repeated in cycles. The number of cycles should be determined depending on whether the patient proceeds to hematopoietic stem cell transplantation. The dose should be decreased according to the patient's condition.

(Underline denotes additions. Strikethrough denotes deletions.)

Approval Conditions

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

Review Report (1)

December 15, 2023

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	Besponsa Injection 1 mg
Non-proprietary Name	Inotuzumab Ozogamicin (Genetical Recombination)
Applicant	Pfizer Japan Inc.
Date of Application	July 27, 2023
Dosage Form/Strength	Lyophilized powder for reconstitution for injection: each vial contains 1 mg of inotuzumab ozogamicin (genetical recombination)
Proposed Indication	Relapsed or refractory CD22-positive acute lymphoblastic leukemia
Proposed Dosage and Administration	The usual ~~adult~~ dosage is inotuzumab ozogamicin (genetical recombination) 0.8 mg/m^2 (body surface area) on Day 1, 0.5 mg/m^2 (body surface area) on Day 8, and 0.5 mg/m^2 (body surface area) on Day 15, administered as an intravenous infusion over at least 1 hour, followed by a rest period. The duration of treatment cycle is 21 to 28 days in Cycle 1 and 28 days in subsequent cycles. Treatment should be repeated in cycles. The number of cycles should be determined depending on whether the patient proceeds to hematopoietic stem cell transplantation. The dose should be decreased according to the patient's condition.

(Strikethrough denotes deletions.)

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

Inotuzumab ozogamicin is an antibody-drug conjugate discovered by Wyeth in the US (currently Pfizer Inc., US) and Celltech in UK (currently UCB S.A., Belgium). Inotuzumab, a humanized CD22-directed monoclonal antibody, is attached to N-acetyl calicheamicin via a linker composed of 4-(4-acetylphenoxy)-butanoic acid and 3-mercapto-3-methyl-butanoicacihydrazide. It is considered that after binding of inotuzumab ozogamicin to CD22, internalization of the complex into the cell, and hydrolysis of the linker, the disulfide bonds in N-acetyl-γ-calicheamicin dimethylhydrazide are reductively cleaved, which activates calicheamicin, inducing double stranded DNA breaks and apoptosis, thereby inhibiting tumor proliferation.

In Japan, inotuzumab ozogamicin was approved in January 2018 for the indication of "relapsed or refractory CD22-positive acute lymphoblastic leukemia," and the dosage regimen for adult patients has been established.

1.2 Development history, etc.

As part of the clinical development for pediatric patients with relapsed or refractory CD22-positive acute lymphoblastic leukemia (ALL), a phase I/II study (Study ITCC-059 [Study 059]) was conducted in pediatric patients with relapsed or refractory CD22-positive ALL and other conditions outside Japan by the Erasmus Medical Center in Europe as an investigator-initiated trial starting from January 2017.

As of December 2023, the dosage regimen of inotuzumab ozogamicin for pediatric patients with relapsed or refractory CD22-positive ALL has not been approved in any countries or regions.

In Japan, an investigator-initiated, phase I study (Study ALL-1) was conducted in pediatric patients with relapsed or refractory CD22-positive ALL at 5 study centers including the National Hospital Organization Nagoya Medical Center.

Recently, a partial change application has been filed based on the results from Studies 059 and ALL-1 as the pivotal data to add a new dosage and administration of inotuzumab ozogamicin for pediatric patients with relapsed or refractory CD22-positive ALL.

On March 24, 2017, inotuzumab ozogamicin was designated as an orphan drug (Orphan Drug Designation No. 401 of 2017 [*29 yaku*]) for the expected indication of "relapsed or refractory CD22-positive acute lymphoblastic leukemia."

2. Quality and Outline of the Review Conducted by PMDA

Since the present application relates to a new dosage, no data relating to quality were submitted.

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

Although the present application relates to a new dosage, no new data on non-clinical pharmacology were submitted, because the non-clinical pharmacology data had been evaluated during the review process for the initial approval

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

Although the present application relates to a new dosage, no new data on non-clinical pharmacokinetics were submitted, because the non-clinical pharmacokinetics data had been evaluated during the review process for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application relates to a new dosage, no data relating to toxicity were submitted.

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

Although the present application relates to a new dosage, no new data on biopharmaceutic studies and associated analytical methods were submitted, because the biopharmaceutic studies and associated analytical methods data had been evaluated during the review process for the initial approval.

6.1 Clinical pharmacology

6.1.1 PPK analysis

The population pharmacokinetic (PPK) model for inotuzumab ozogamicin developed at the initial application (see Review Report of Besponsa Injection 1 mg, dated November 2, 2017) was updated (final model) using the integrated data set. The pharmacokinetic (PK) data after intravenous administration of inotuzumab ozogamicin to pediatric patients with relapsed or refractory CD22-positive ALL obtained from Study INO-Ped-ALL-1 (Study ALL-1), a Japanese phase I study, and from Study ITCC-059 (Study 059), a foreign phase I/II study, were consolidated with the PK data set[1)] for adult patients used in the PPK analysis for the review of the initial application.

The final model included serum inotuzumab ozogamicin concentration data (N = 824; 8,978 timepoints), and a PPK analysis was performed using a nonlinear mixed effect model (software, NONMEM Version 7.5.0).[2)]

---

1) Data from 2 studies in adult patients with ALL (Studies B1931010 and B1931022) and 9 studies in adult patients with non-Hodgkin's lymphoma (NHL) (Studies B1931001, B1931002, B1931003, B1931004, B1931005, B1931006, B1931007, B1931008, and B1931016)

2) Baseline demographics and disease characteristics of patients (median [Min, Max]) or disposition of patients in the PPK analysis were as follows: Age, 59.0 years [1.00, 92.0] for all age groups (9.00 years [1.00, 17.0] for pediatric patients); body weight, 72.0 kg [9.30, 154] for all age groups (29.1 kg [9.30, 146] for pediatric patients); baseline body surface area, 1.82 m^2 [0.47, 2.81] for all age groups (1.06 m^2 [0.47, 2.21] for pediatric patients); percentage of blasts in peripheral blood at baseline, 4.00% [0%, 100%] for all age groups (6.00% [0%, 96.0%] for pediatric patients); patient type, adult NHL (531 patients), adult ALL (234 patients), pediatric ALL (59 patients); race, 107 Japanese patients, 534 Caucasian patients, 20 Black patients, 54 Asian patients, 53 other racially defined patients, 56 patients with missing racial data for all age groups (6 Japanese patients, 53 patients with missing racial data for pediatric patients); concomitant rituximab use, 384 patients used and 440 patients did not use for all age groups (59 patients used and 0 patients did not use for pediatric patients); disease/analytical method, ALL patients, for whom the high performance liquid chromatography tandem mass spectrometry (HPLC-MS/MS) method was used in 293 patients and non-ALL patients, for whom the HPLC-MS/MS method was not used in 531 patients for all age groups (ALL patients, for whom the HPLC-MS/MS method was used in 59 patients and non-ALL patients, for whom the HPLC-MS/MS method was not used in 0 patients for pediatric patients).

The PK of inotuzumab ozogamicin was described by a 2-compartment model with linear clearance (CL) and time-dependent CL components, the same as the PPK model developed at the time of initial application.

In addition to the covariates incorporated in the model used for the initial application,[3)] patient type (NHL, adult ALL, and pediatric ALL) was identified as a new covariate for the decay coefficient associated with time-dependent clearance (k_{des}).

Regarding the impact of the covariate patient type, a covariate identified for the final model, on k_{des}, the applicant explained that given that time-dependent CL is one of the components of total CL, and that its contribution decreases over time, patient type is not likely to have a clinically significant effect on the PK of inotuzumab ozogamicin.

Figure 1 shows the results for exposure parameters (C_{trough}, C_{max}, and cumulative AUC) of inotuzumab ozogamicin when administering inotuzumab ozogamicin to adult patients with ALL, Japanese pediatric patients with ALL, and non-Japanese pediatric patients with ALL at the dosage regimen approved at the initial application using the empirical Bayesian estimates of PK parameters calculated from the developed PPK model. The applicant explained that the results show that the PK of inotuzumab ozogamicin in the adult patient population is consistent with that in Japanese pediatric patients and that in non-Japanese pediatric patients.

3) The following significant covariates were included in the model: (1) disease (analytical method), baseline body surface area, and use/non-use of concomitant rituximab as significant covariates on linear CL, (2) baseline body surface area as a significant covariate on time-dependent CL and central compartment distribution volume, and (3) disease (analytical method) and baseline percentage of blasts in peripheral blood as significant covariates on k_{des}.

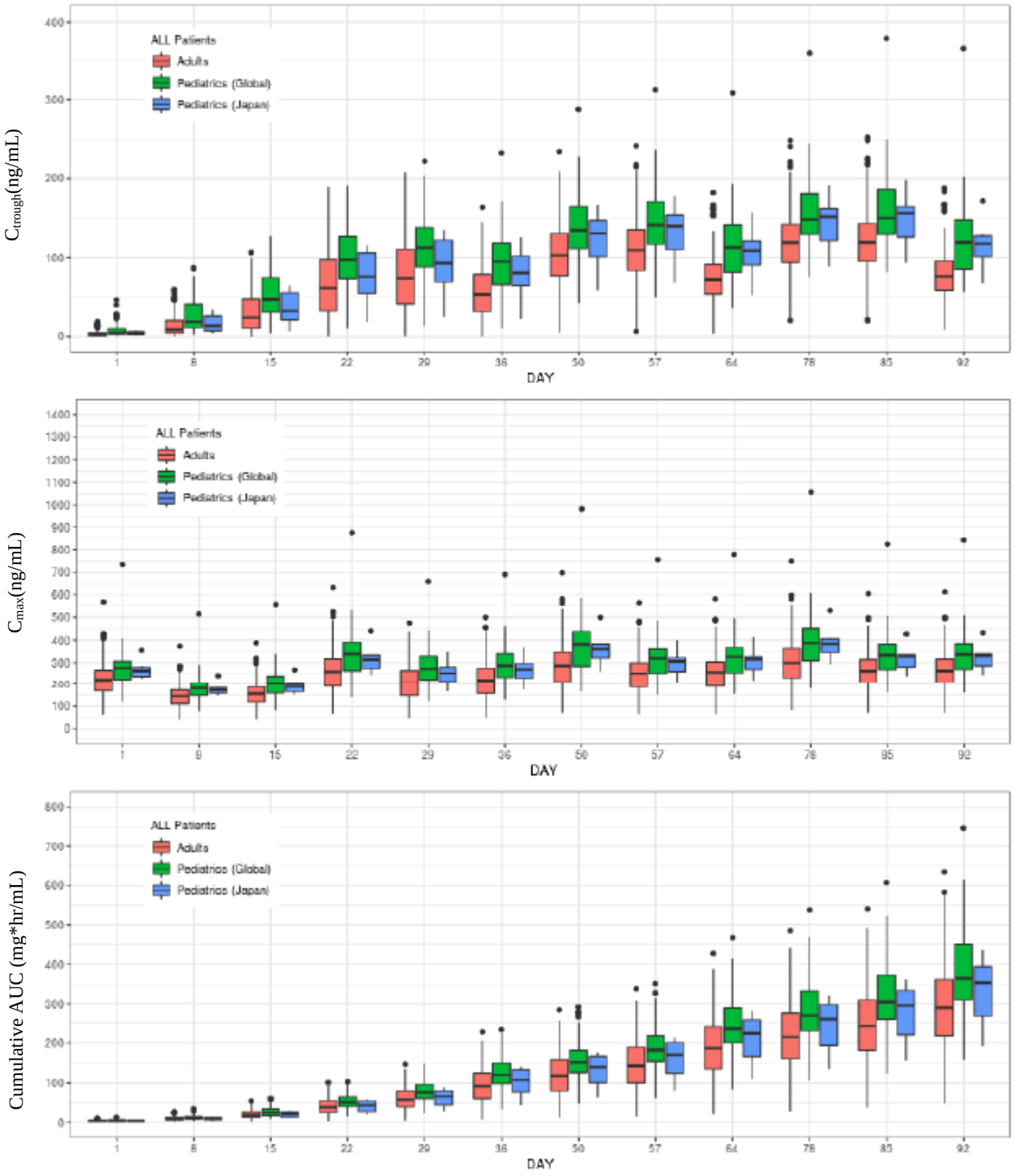

Figure 1. Results of estimated exposures to inotuzumab ozogamicin when administering inotuzumab ozogamicin to adult patients with ALL, Japanese pediatric patients with ALL, and non-Japanese pediatric patients with ALL at the dosage regimen approved at the initial application

Top, C_{trough}; middle, C_{max}; and bottom, cumulative AUC
Red, adult patients with ALL; green, non-Japanese pediatric patients with ALL; and blue, Japanese pediatric patients with ALL
Box-and-whisker plot, horizontal solid line (median); lower hinge (25th percentile); upper hinge (75th percentile): lower whisker (values within the range between the 25th percentile − 1.5 × the interquartile range), upper whisker (values within the range between the 75th percentile + 1.5 × the interquartile range), and black dot, estimated value beyond the lower or upper whisker.

6.R Outline of the review conducted by PMDA

On the basis of the submitted data and discussions in the following section, PMDA considers that the applicant's explanation about the clinical pharmacology and other aspects of inotuzumab ozogamicin is acceptable.

6.R.1 Appropriateness of the selection of the dosage regimen for pediatric patients with ALL, which is the same as that for adult patients with ALL

The applicant's explanation, from the perspective of clinical pharmacology, about the appropriateness of selecting the dosage regimen for pediatric patients with relapsed or refractory CD22-positive ALL as that of the approved dosage regimen for adult patients with ALL:

Table 1 shows the serum inotuzumab ozogamicin concentrations after intravenous infusion of inotuzumab ozogamicin 1.8 mg/m^2/cycle as divided doses in Study B1931022 (Study 1022[4)]), a global phase III study conducted in adult patients, and Study ALL-1 and the phase II part of Study 059, conducted in pediatric patients. There was no clear difference in serum inotuzumab ozogamicin concentration between non-Japanese pediatric patients and Japanese pediatric patients, or between pediatric patients and adult patients after inotuzumab ozogamicin 1.8 mg/m^2/cycle was administered as an intravenous infusion in divided doses.

Table 1. Serum inotuzumab ozogamicin concentrations (ng/mL) after intravenous infusion of inotuzumab ozogamicin 1.8 mg/m^2/cycle as divided doses to adult patients with ALL, Japanese and non-Japanese pediatric patients with ALL

Measurement timepoint	Time after administration (hours)	1022 Adult ALL		ALL-1 Japanese pediatric ALL		059 Non-Japanese pediatric ALL	
		N = 162		N = 6		N = 28	
		n	Serum concentration	n	Serum concentration	n	Serum concentration
Cycle 1 Day 1	Pre-dose	160	2.22 (754)	NC	NC	25	1.91 (500)
	1	128	211 (110)	5	330 (24)	—	—
	2	145	160 (52)	—	—	24	173 (61)
	4	145	104 (57)	—	—	26	124 (62)
Cycle 1 Day 4	72	84	10.6 (124)	5	8.53 (44)	—	—
Cycle 1 Day 8	Pre-dose	151	6.84 (276)	6	3.87 (70)	25	11.0 (197)
	1	126	194 (117)	6	219 (36)	—	—
Cycle 1 Day 15	Pre-dose	147	21.3 (168)	6	20.6 (88)	25	28.7 (92)
	1	117	170 (46)	6	183 (36)	—	—
Cycle 2 Day 1	Pre-dose	122	32.0 (147)	5	23.8 (103)	—	—
	1	107	224 (53)	4	221 (32)	—	—
	2	113	250 (41)	—	—	14	301 (33)
Cycle 2 Day 8	Pre-dose	115	61.9 (77)	—	—	14	77.5 (47)
Cycle 4 Day 1	Pre-dose	46	57.9 (51)	1	54.4	—	—

Mean (coefficient of variation, %); only serum concentration data collected at the same timepoint in ≥2 studies are shown, and the summary statistics was calculated assuming that the concentrations below the lower limit of quantitation (1.00 ng/mL) as 0; NC, not calculated because no observations were ≥ the lower limit of quantitation; "—," not applicable

The PPK analysis in adult and pediatric patients with ALL [see Section 6.1.1] predicted that PK of inotuzumab ozogamicin in adult patients would be similar to that in pediatric patients, and similar between Japanese pediatric patients and non-Japanese pediatric patients.

4) For Study 1022, see the application dossier for initial approval and "Review Report of Besponsa Injection 1 mg" dated November 2, 2017; for Studies ALL-1 and 059, see Sections 7.1.1.1 and 7.1.2.1.

The above results indicated that, it is appropriate from a clinical pharmacology perspective, to select the same dosage regimen for pediatric patients with relapsed or refractory CD22-positive ALL as that approved for adult patients.

PMDA accepted the applicant's explanation.

The appropriateness of the dosage regimen will be discussed further in Section "7.R.5 Dosage and administration."

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

The applicant submitted the efficacy and safety evaluation data shown in Table 2.

Table 2. List of clinical studies on efficacy and safety

Data category	Study location	Study ID	Phase	Study population	Number of patients enrolled	Summary of dosage regimen	Main endpoints
Evaluation	Japan	ALL-1	I	Patients with relapsed or refractory CD22-positive ALL (≥1 and ≤17 years of age)	7	The duration of treatment cycle was 21 days in Cycle 1 and 28 days in subsequent cycles. Inotuzumab ozogamicin 1.8 mg/m^2/cycle was administered intravenously as 3 divided doses on Day 1 (0.8 mg/m^2), Day 8 (0.5 mg/m^2), and Day 15 (0.5 mg/m^2) (up to a maximum of 6 cycles)	Safety Efficacy PK
	Foreign	059	I/II	Patients with relapsed or refractory CD22-positive ALL (≥1 and ≤17 years of age)	(I) 25 (II) 30	(I) Phase I part (dose escalation cohort, Stratum 1A): The duration of treatment cycle was 22 days in Cycle 1 and 28 days in subsequent cycles. Inotuzumab ozogamicin 1.4 or 1.8 mg/m^2/cycle was administered intravenously as 3 divided doses on Day 1 (0.6 or 0.8 mg/m^2), Day 8 (0.4 or 0.5 mg/m^2), and Day 15 (0.4 or 0.5 mg/m^2) (up to a maximum of 6 cycles) (II) Phase II part: The duration of treatment cycle was 22 days in Cycle 1 and 28 days in subsequent cycles. Inotuzumab ozogamicin was administered intravenously on Day 1 (0.8 mg/m^2), Day 8 (0.5 mg/m^2), and Day 15 (0.5 mg/m^2) (up to a maximum of 6 cycles)	Efficacy Safety PK

The outline of the clinical studies is discussed in the following sections. Main adverse events other than death reported in each clinical study are described in Sections "7.R.3 Safety" and "7.2 Adverse events and other findings observed in clinical studies." The results of PK studies are presented in Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA."

7.1 Evaluation data

7.1.1 Japanese clinical study

7.1.1.1 Japanese phase I study (CTD 5.3.5.2.1, Study ALL-1 [October 2018 to September 2020])

An open-label, uncontrolled study was conducted at 5 study centers in Japan in patients (≥1 and ≤17 years of age) with relapsed or refractory CD22-positive ALL (target sample size, maximum of 18 subjects) to investigate the safety, PK, and other aspects of inotuzumab ozogamicin.

The duration of treatment cycle was 21 days in Cycle 1 (can be extended up to 28 days) and 28 days in subsequent cycles (can be extended up to 56 days[5)]). Inotuzumab ozogamicin 1.8 mg/m^2/cycle was to be administered intravenously as 3 divided doses on Day 1 (0.8 mg/m^2), Day 8 (0.5 mg/m^2), and Day 15 (0.5 mg/m^2). In subsequent cycles, subjects who had achieved complete remission (CR) or CR without hematologic recovery (CRi) were to receive inotuzumab ozogamicin 1.5 mg/m^2/cycle in 3 divided doses on Days 1, 8, and 15 (0.5 mg/m^2 each). Treatment was to be continued until disease progression or until the treatment discontinuation criteria were met,[6)] up to a maximum of 3 cycles[7)] (for patients who were to proceed to allogeneic hematopoietic stem cell transplantation [HSCT]) or a maximum of 6 cycles (for patients who were not to proceed to HSCT). Table 3 shows the definitions used for the response evaluation in Study ALL-1.

Table 3. Definitions used for response evaluation (Study ALL-1)

Evaluation	Definition
CR	All of the following 5 criteria are met: (1) <5% blasts in the bone marrow; (2) no evidence of blasts in peripheral blood; (3) neutrophil counts ≥1,000/μL; (4) platelet counts ≥100,000/μL; and (5) resolution of any extramedullary disease.
CRi	One or both of the criteria (3) and (4) above are not met (i.e., neutrophil counts <1,000/μL and/or platelet counts <100,000/μL), but the rest of the criteria for CR are met.
PR	Bone marrow blast count is decreased by ≥50%, and the bone marrow blast percentage is ≥5% and ≤25%; and meeting either one or both of the criteria for extramedullary disease C2,* i.e., not meeting one or both of the above criteria (1) and (5); and meeting other criteria for CR.
Treatment failures	Not qualified for CR, CRi, or PR, the patient survived ≥7 days after the end of treatment and died under one of the following conditions: (1) resistant (the most recent test results indicate blasts in peripheral blood or bone marrow, or evidence of extramedullary disease after the end of treatment); or (2) the most recent test results indicate no blasts in bone marrow and the patient had cytopenia.
PD	Blasts in peripheral blood increased two-fold or more, and the absolute value of the blast count is >5,000/μL, or progression or emergence of extramedullary disease.

*, C2 is defined as the condition where C1 is not applicable. C1 is defined as complete resolution of extramedullary disease, except for the following: (1) no new lesions are present; (2) not palpable because the swollen organ has become smaller; (3) for measurable lesions, all nodular lesions >1.5 cm in the greatest transverse diameter have been reduced to ≤1.5 cm, and all nodular lesions ≥1 cm and ≤1.5 cm in the greatest transverse diameter have been reduced to <1 cm, or the sum of the product of diameters of the lesions has been reduced by ≥75%.

5) If the criteria for starting each cycle are not met, the treatment cycle was allowed to be extended for up to 56 days per cycle. In subsequent cycles, the key criteria for starting a new cycle were as follows:
- If the baseline neutrophil count was ≥1,000/μL or platelet count was ≥50,000/μL, neutrophil count recovers to ≥1,000/μL or platelet count recovers to ≥50,000/μL;
- If the baseline neutrophil count was <1,000/μL or platelet count was <50,000/μL, neutrophil count and platelet count recover to at least the baseline values, or the most recent bone marrow evaluation indicates stable or improvement of disease, regardless of neutrophil or platelet counts, and the decrease in neutrophil and platelet counts are considered to be due to the underlying disease;
- For patients who were not to proceed to HSCT, in Cycles 4, 5, and 6, blast percentage in bone marrow is <5% and resolution of extramedullary disease has been achieved.

6) If CR or CRi has not been achieved by the end of Cycle 3 (Day 28), treatment was to be discontinued in Cycle 3 unless there is no choice but to continue the treatment.

7) For patients who were to proceed to HSCT, treatment was to be limited to 2 cycles or the number of cycles necessary to achieve CR or CRi.

Of the 7 subjects enrolled in Study ALL-1, 1 subject was excluded due to ineligibility, and the remaining 6 subjects received inotuzumab ozogamicin, and data on the 6 subjects were analyzed for dose limiting toxicity (DLT), efficacy, and safety.
In Cycle 1, which was the evaluation period for DLT, no DLT occurred.

The remission rate in the overall treatment period of inotuzumab ozogamicin (CR + CRi rate) [95% confidence interval (CI)] was 83.3% [35.9%, 99.6%] (5 of 6 subjects).

During the treatment period or within 28 days of the completion of treatment with inotuzumab ozogamicin, 1 subject died, with the reported cause being disease progression.

7.1.2 Foreign clinical study

7.1.2.1 Foreign phase I/II study (CTD 5.3.5.2.2, Study 059 [ongoing since January 2017, data cut-off date: phase I part, Stratum 1A, on September 30, 2022; phase II part, on October 7, 2022])

An open-label, uncontrolled study was conducted in patients with relapsed or refractory CD22-positive ALL (≥1 and ≤17 years of age) at 22 study centers outside Japan (target sample size: phase I part Stratum 1A, dose escalation cohort, 6 to 36 subjects; phase II part, 25 subjects[8)]) to investigate the efficacy, safety, and various aspects of inotuzumab ozogamicin. In the dose escalation cohort in the phase I part, patients in Stratum 1B were treated with inotuzumab ozogamicin in combination with chemotherapy. The present application is intended for addition of a dosage regimen for pediatric patients as a monotherapy of inotuzumab ozogamicin, equivalent to the dosage regimen for adult patients; therefore, the following sections of the review report discuss only the information on the phase I part Stratum 1A and phase II part, in which inotuzumab ozogamicin alone was administered.

The dosage regimens were as follows:

Dose escalation cohort Stratum 1A in phase I part

The treatment cycle was 22 days for Cycle 1 and 28 days for subsequent cycles (all cycles including Cycle 1 could be extended to a maximum of 42 days[9)]). At dose level 1, inotuzumab ozogamicin 1.4 mg/m^2/cycle was to be administered intravenously in 3 divided doses on Day 1 (0.6 mg/m^2), Day 8 (0.4 mg/m^2), and Day 15

8) The calculation of the target sample size in the phase II part was based on the remission rate (proportion of responders CR + CRp + CRi), the primary endpoint. It was calculated based on an expected response rate of 55% and a threshold response of 30%, using a one-sided significance level of 0.05 and statistical power of at least 80% by the exact binomial test. The required sample size was calculated as 25 patients. The threshold response rate was set based on data including the proportion of patients achieving CR or CRi (29.4%) in Study 1022, which evaluated the efficacy and other aspects of inotuzumab ozogamicin in adult patients with relapsed or refractory CD22-positive ALL, and the proportion of patients achieving CR or CRp (20%) in a foreign phase II study conducted to evaluate the efficacy and other aspects of clofarabine in pediatric patients with relapsed or refractory ALL (*J Clin Oncol.* 2006;24:1917-23, etc.).

9) If the criteria for starting each cycle were not met, each treatment cycle could be extended to a maximum of 42 days. The key criteria for starting Cycle 2 were meeting one of the criteria shown below. However, Cycle 2 could be started if the bone marrow blast percentage was <5% and if the criteria for neutrophil or platelet counts in (1) below were not met due to hematological adverse events associated with inotuzumab ozogamicin.
(1) A bone marrow blast percentage of <5% and neutrophil counts ≥500/μL and platelet counts ≥50,000/μL (Stratum 1A) or neutrophil counts ≥500/μL and platelet counts ≥30,000/μL (phase II part)
(2) For patients with a bone marrow blast percentage of ≥25%, improvement to <25%
(3) For patients with a bone marrow blast percentage of ≥5% and <25%, improvement to <5%
The key criteria for starting Cycle 3 and subsequent cycles were meeting the following criteria:
- A bone marrow blast percentage <5% and neutrophil counts ≥500/μL and platelet counts ≥30,000/μL, and resolution of any extramedullary disease

(0.4 mg/m^2). At dose level 2, inotuzumab ozogamicin 1.8 mg/m^2/cycle was to be administered intravenously in 3 divided doses on Day 1 (0.8 mg/m^2), Day 8 (0.5 mg/m^2), and Day 15 (0.5 mg/m^2).

Phase II part

The treatment cycle was 22 days for Cycle 1 and 28 days for subsequent cycles (all cycles including Cycle 1 could be extended to a maximum of 42 days[9)]). Inotuzumab ozogamicin 1.8 mg/m^2/cycle was to be administered intravenously in 3 divided doses on Day 1 (0.8 mg/m^2), Day 8 (0.5 mg/m^2), and Day 15 (0.5 mg/m^2).

In both the phase I and phase II parts, if CR, complete remission without platelet recovery (CRp), or CRi was achieved, the dose on Day 1 of the next cycle was to be reduced; at dose level 1 in the phase I part, inotuzumab ozogamicin 1.2 mg/m^2/cycle was to be administered in 3 divided doses on Days 1, 8, and 15 (0.4 mg/m^2 each), at dose level 2 in the phase I part and in the phase II part, inotuzumab ozogamicin 1.5 mg/m^2/cycle was to be administered in 3 divided doses on Days 1, 8, and 15 (0.5 mg/m^2 each). In both phase parts, unless disease progression occurred or the treatment discontinuation criteria were met, patients not proceeding to HSCT were to continue treatment up to a maximum of 6 cycles while patients proceeding to HSCT were to receive 2 cycles of treatment as a general rule (or up to 3 cycles for patients who were not minimal residual disease [MRD]-negative[10)] at the end of Cycle 2).

Table 4 shows the definitions used for the response evaluation in Study 059.

Table 4. Definitions used for response evaluation (Study 059)

Evaluation	Definition
CR	All of the following 5 criteria are met: (1) <5% blasts in the bone marrow; (2) no evidence of blasts in peripheral blood; (3) neutrophil counts ≥500/μL; (4) platelet counts ≥50,000/μL; and (5) resolution of any extramedullary disease.
CRp	Criterion (3) above is not met (i.e., platelet counts <50,000/μL) but the rest of the criteria for CR are met.
CRi	Criterion (4) above is not met (i.e., neutrophil counts <500/μL) but all criteria (1), (2), and (5) are met.
PR	Fail to qualify for CR, CRp, or CRi, and bone marrow blast count is decreased by ≥50%.
SD	Fail to qualify for CR, CRp, CRi, PR, or PD.
PD	An increase in the number of blasts in bone marrow or peripheral blood by 25%, progression or emergence of extramedullary disease, or laboratory or clinical evidence of disease progression.

Of the 55 patients enrolled in Study 059, 2 subjects (phase II part) who did not receive inotuzumab ozogamicin were excluded, and the remaining 53 subjects (25 subjects in Stratum 1A in the phase I part and 28 subjects in the phase II part) were included in the efficacy and safety analysis sets. Data from all 28 subjects in the phase II part were used in the primary efficacy analysis. Of the 25 subjects enrolled in Stratum 1A, 2 subjects[11)] (1.8 mg/m^2/cycle group) who had received only 1 dose of inotuzumab ozogamicin in Cycle 1 were excluded, and the remaining 23 subjects (12 subjects in the 1.4 mg/m^2/cycle group and 11 subjects in the 1.8 mg/m^2/cycle group) were evaluated for DLT.

10) Patients were considered MRD-negative if the bone marrow or peripheral blood sample had <1 tumor cell per 10^4 nucleated cells by real-time quantitative reverse transcription polymerase chain reaction (RQ-PCR) and by flow cytometry at the central laboratory.

11) A male pediatric patient aged 1[redacted] years who developed sepsis (Grade 4) on Day 4, and a male pediatric patient aged [redacted] years who developed graft versus host disease (GVHD, Grade 3) on Day 8 did not receive 3 divided doses of inotuzumab ozogamicin in Cycle 1, and were excluded from the study population for DLT evaluation according to the prespecified criteria. No adverse events classified as DLT were reported in either of the patients.

In cycle 1 in Stratum 1A of the phase I part, established as the DLT evaluation period, DLT occurred in 1 of 6 subjects in the 1.4 mg/m^2/cycle group (Grade 4 alanine aminotransferase [ALT] increased) and 2 of 5 subjects in the 1.8 mg/m^2/cycle group (Grade 4 ALT increased and neutrophil count decreased[12)] in 1 subject each). Taking account of the results, a cohort[13)] was added in which criteria for monitoring of liver enzymes (hepatocellular leakage enzymes) and treatment delay were provided (protocol amendment ver.2, dated August 31, 2018). In this cohort, no DLT was reported in the 1.4 mg/m^2/cycle group (0 of 6 subjects), while DLT occurred in 1 of 6 subjects in the 1.8 mg/m^2/cycle group (Grade 4 platelet count decreased[14)]). On the basis of the above results, it was determined that 1.8 mg/m^2/cycle is tolerable as long as the patient is monitored for liver enzymes and the treatment is provided in adherence to the criteria for treatment delay.

Table 5 shows the remission rates for the overall inotuzumab ozogamicin treatment period (proportion of responders CR + CRp + CRi) [90% CI] in the phase II part, the primary efficacy endpoint, as assessed by the investigator.

Table 5. Results of best overall response and remission
(Phase II part in Study 059, data cut-off date on October 7, 2022)

Best overall response	n (%) N = 28
CR	18 (64.3)
CRp	1 (3.6)
CRi	3 (10.7)
PR	3 (10.7)
SD	1 (3.6)
PD	2 (7.1)
Remission (CR + CRp + CRi) (remission rate [90% CI][*1])	22 (78.6% [62.0%, 90.2%])
P-value[*2]	<0.0001

*1, Clopper-Pearson method; *2, exact binomial test with a threshold response rate of 30%, one-sided significance level of 0.05

Reported deaths during treatment or within 10 weeks of the end of treatment with inotuzumab ozogamicin are shown below.

In the phase I part, 4 of 12 subjects (33.3%) in the 1.4 mg/m^2/cycle group, 2 of 13 subjects (15.4%) in the 1.8 mg/m^2/cycle group, and 7 of 28 subjects (25.0%) in the phase II part died. Four subjects died due to "disease progression" (2 subjects, 0 subjects, and 2 subjects in the 1.4 mg/m^2/cycle group, 1.8 mg/m^2/cycle group, and the phase II part, respectively). Causes of death other than "disease progression" were "other causes" in 2 subjects[15)] in the 1.4 mg/m^2/cycle group, "other causes" in 2 subjects,[16)] in the 1.8 mg/m^2/cycle group, and

12) This was defined as neutrophil count decreased without blood count recovery at 42 days after the last dose of inotuzumab ozogamicin.
13) In the additional cohort, the criteria for monitoring of liver enzymes (hepatocellular leakage enzymes) and those for Day 8 treatment delay in case of elevated liver enzymes in Cycle 1 were established.
14) This was defined as platelet count decreased without blood count recovery at 42 days after the last dose of inotuzumab ozogamicin.
15) On Day 96, a female pediatric patient aged 1[redacted] years died due to sepsis (post HSCT). On Day 174, a female pediatric patient aged 1[redacted] years died due to multi-organ failure and cardiac arrest.
16) On Day 64, a male pediatric patient aged 1[redacted] years died due to respiratory infection. On Day 68, a male pediatric patient aged 1[redacted] years died due to multi-organ failure.

"other causes" in 4 subjects[17] and "treatment toxicity"[18] in 1 subject in the phase II part. Among these cases, a causal relationship to inotuzumab ozogamicin was denied for treatment toxicity.[19]

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

PMDA considered that, among the submitted evaluation data, Study 059, the foreign phase I/II study, and Study ALL-1, the Japanese phase I study, both of which were conducted in pediatric patients with relapsed or refractory CD22-positive ALL, are the pivotal studies in evaluating the efficacy and safety of inotuzumab ozogamicin. Therefore, PMDA decided to focus on these studies in its review.

7.R.2 Efficacy

On the basis of the following discussions, PMDA concluded that inotuzumab ozogamicin has a certain level of efficacy in the treatment of pediatric patients with relapsed or refractory CD22-positive ALL.

7.R.2.1 Efficacy endpoints

The applicant's explanation about the primary efficacy endpoints in Study 059:

Taking account of the following points, the remission rate (proportion of responders CR + CRp + CRi) was selected as the primary efficacy endpoint for Study 059.

- Allogeneic hematopoietic stem cell transplantation is recommended as a curative treatment for pediatric patients with relapsed or refractory ALL, and it has been reported that HSCT is more effective in patients who have achieved remission before undergoing HSCT, compared with those not in remission (Guidelines on Hematopoietic Cell Transplantation in Pediatric Patients with ALL. Third edition [in Japanese], ed. by The Japan Society for Hematopoietic Cell Transplantation). Therefore, achieving remission is clinically significant. In addition to the above, there have been reports on the status of MRD at HSCT. Compared with MRD-positive patients, patients who achieved MRD negativity have more favorable HSCT results (e.g., *Leukemia.* 2008;22:2193-200, *J Clin Oncol.* 2013;31:2736-42). Also in patients who are not appropriate to receive HSCT, effects resulting from a reduction in tumor cells such as mitigation of symptoms can be expected if remission is achieved.
- The status of CRp or CRi is the same as that for CR except that neutrophil count or platelet count recovery is insufficient. Among patients with relapsed or refractory ALL with prior treatment including HSCT, those with CRp or CRi are considered to have delayed recovery of hematopoietic capacity; therefore, achievement of CRp or CRi is clinically significant.

PMDA's discussion:

The applicant's explanation about the selection of a remission rate (proportion of responders CR + CRp + CRi) as the primary efficacy endpoint for inotuzumab ozogamicin in Study 059 is acceptable to some extent.

[17] On Day 127, a male pediatric patient aged 1[redacted] years died due to multi-organ failure. On Day 92, a male pediatric patient aged 1[redacted] years died of undetermined cause. On Day 54, a male pediatric patient aged [redacted] years died due to pneumonia and disease progression. On Day 69, a female pediatric patient aged [redacted] years died due to multi-organ failure (post HSCT).

[18] On Day 78, a male pediatric patient aged 1[redacted] years died due to encephalitis.

[19] No information on causal relationship to inotuzumab ozogamicin was collected for other cases of death.

However, it is difficult to determine whether the tumor cells in patients with CRp or CRi have not been sufficiently reduced and the patient is prone to early relapse compared with those with CR. In addition, the patient may be in a condition in which the reduction of tumor cells equivalent to CR has been achieved but recovery of hematopoietic capacity has been delayed; therefore, the clinical significance of achieving CRp or CRi is unclear. Conversely, in cases of CRp or CRi, if <5% blasts in bone marrow has been achieved, and MRD negativity has also been achieved, then it can be assumed that hematopoietic recovery has been delayed. Therefore, in addition to the results for the primary efficacy endpoint, defined as the remission rate (proportion of responders CR + CRp + CRi), the efficacy of inotuzumab ozogamicin should be evaluated in a comprehensive manner based on data including the MRD results.

7.R.2.2 Efficacy evaluation results

The applicant's explanation about the efficacy of inotuzumab ozogamicin:

In the phase II part of Study 059, which was conducted in patients with relapsed or refractory CD22-positive ALL, the results for the primary endpoint, the remission rate in the overall treatment period of inotuzumab ozogamicin (proportion of responders CR + CRp + CRi) [90% CI] was 78.6% [62.0%, 90.2%], indicating that the lower limit of the 90% confidence interval exceeded the prespecified threshold (30%[8)]).

Table 6 shows the proportion of patients who achieved MRD negativity[20)] among those who had achieved CR, CRp, or CRi in the phase II part of Study 059.

Table 6. MRD results in patients who had achieved CR, CRp, or CRi (Study 059, phase II part, data cut-off on October 7, 2022)

Proportion of patients who achieved MRD negativity	n (%) N = 22*
MRD negativity in the overall treatment period	19 (86.4)
MRD negativity at the end of Cycle 1	15 (68.2)

*, Number of patients who achieved CR, CRp, or CRi

Table 7 shows the remission rate results in the overall treatment period of inotuzumab ozogamicin (proportion of responders CR + CRi) in Study ALL-1. Among patients who had achieved CR or CRi in Study ALL-1, those who achieved MRD negativity[21)] accounted for 60.0% (3 of 5 subjects).

Table 7. Results of best overall response and remission (Study ALL-1, data cut-off on February 8, 2021)

Best overall response	n (%) N = 6
CR	4 (66.7)
CRi	1 (16.7)
Treatment failures (resistant)	1 (16.7)
Remission (CR + CRi) (Remission rate [95% CI]*)	5 (83.3% [35.88%, 99.58%])

*, Clopper-Pearson method

[20)] The proportion of patients who achieved MRD negativity was defined as the proportion of patients who achieved MRD negativity in the overall study treatment period or at the end of Cycle 1 in the total number of patients who achieved CR, CRp, or CRi.

[21)] The proportion of patients who achieved MRD negativity was defined as the proportion of patients who achieved MRD negativity as the best overall response in the total number of patients who achieved CR or CRi. Patients were considered MRD-negative if the bone marrow sample had less than 1 tumor cell per 10^4 nucleated cells detected by RQ-PCR.

In Study ALL-1, 50.0% (3 of 6) of subjects underwent HSCT, while in Study 059, 32.0% (8 of 25) of subjects in Stratum 1A in the phase I part and 64.3% (18 of 28) of subjects in the phase II part underwent HSCT.

PMDA's discussion:
PMDA concluded that inotuzumab ozogamicin demonstrated a certain level of efficacy in pediatric patients with relapsed or refractory CD22-positive ALL, based on the remission rate results in the overall treatment period of inotuzumab ozogamicin (proportion of responders CR + CRp + CRi) in the phase II part of Study 059, which exceeded the prespecified threshold, backed up by the following findings:

- When CR alone is considered, because the clinical significance of achieving CRp or CRi is unclear compared with that of achieving CR, the results for best overall response in the phase II part of Study 059 show that CR is 18 of 28 subjects (proportion of responders with CR [95% CI] is 64.3% [44.1%, 81.4%]), indicating that the results are clinically significant.
- A certain portion of patients who had achieved remission in the phase II part of Study 059 achieved MRD negativity.

In addition, while only a small number of Japanese patients was evaluated in Study ALL-1, the remission rate results in the overall treatment period of inotuzumab ozogamicin (proportion of responders CR + CRi) in the study are clinically significant, suggesting that inotuzumab ozogamicin can also be expected to show its efficacy in Japanese patients.

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

On the basis of the discussions in the following sections, PMDA considered that adverse events requiring particular caution when administering inotuzumab ozogamicin to pediatric patients with relapsed or refractory CD22-positive ALL are the adverse events of special interest referred to in the previous review of the application for the approved indication (adults): liver disorder, including veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS), myelosuppression, infections, haemorrhage, tumour lysis syndrome (TLS), infusion reaction, pancreatitis, QTc interval prolongation, inflammatory gastrointestinal events, and interstitial lung disease (ILD). PMDA concluded that patients should be closely monitored for these adverse events when using inotuzumab ozogamicin.

Although the use of inotuzumab ozogamicin requires particular caution due to the adverse events mentioned above, PMDA concluded that inotuzumab ozogamicin is tolerable as long as appropriate actions including monitoring and control of adverse events are taken by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

7.R.3.1 Safety profile of inotuzumab ozogamicin

The applicant's explanation about the safety profile of inotuzumab ozogamicin in pediatric patients with relapsed or refractory CD22-positive ALL:

Table 8 shows the summary of safety data in Studies 059[22] and ALL-1.[23]

Table 8. Summary of safety data (Studies 059 and ALL-1)

	n (%)			
	059			ALL-1
	Phase I part, Stratum 1A		Phase II part	
	1.4 mg/m^2 N = 12	1.8 mg/m^2 N = 13	1.8 mg/m^2 N = 28	1.8 mg/m^2 N = 6
All adverse events	12 (100)	13 (100)	28 (100)	6 (100)
Grade ≥3 adverse events	11 (91.7)	13 (100)	26 (92.9)	5 (83.3)
Adverse events leading to death	2 (16.7)	1 (7.7)	4 (14.3)	1 (16.7)
Serious adverse events	8 (66.7)	8 (61.5)	17 (60.7)	3 (50.0)
Adverse events leading to treatment discontinuation of inotuzumab ozogamicin	2 (16.7)	6 (46.2)	4 (14.3)	1 (16.7)
Adverse events leading to dose interruption of inotuzumab ozogamicin	1 (8.3)	0	5 (17.9)	3 (50.0)
Adverse events leading to dose reduction of inotuzumab ozogamicin	0	0	0	0

Table 9 shows the incidence of adverse events in Studies 059 and ALL-1.

[22] Adverse events occurring within 10 weeks of the last dose or by the time inotuzumab ozogamicin-related toxicity completely resolved, whichever occurred later, were reported. When another antineoplastic treatment was initiated within the period, only serious adverse events that were likely to be related to inotuzumab ozogamicin were reported. However, as for VOD/SOS, all cases of VOD/SOS occurring within 1 year of study enrollment were reported as serious adverse events.

[23] Adverse events occurring from the start of treatment with inotuzumab ozogamicin up to 9 weeks after the last dose were reported. When another antineoplastic therapy for the treatment of underlying disease or a conditioning regimen for HSCT was initiated within the period, only serious adverse events were reported. Except for Grade 5, FN and neutropenic sepsis were reported as serious adverse events only when a causal relationship to inotuzumab ozogamicin was assessed by the investigator as related. However, as for VOD/SOS, if HSCT was performed by 16 weeks after the last dose of inotuzumab ozogamicin, all cases of VOD/SOS occurring up to 16 weeks post-HSCT were reported as serious adverse events.

Table 9. Adverse events occurring in ≥20% of subjects in any part (Studies 059 and ALL-1)

SOC PT (MedDRA ver.25.1)	n (%)					
	059				ALL-1	
	1.4 mg/m^2/cycle[*1] N = 12		1.8 mg/m^2/cycle[*2] N = 41		1.8 mg/m^2/cycle N = 6	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	12 (100)	11 (91.7)	41 (100)	39 (95.1)	6 (100)	5 (83.3)
Blood and lymphatic system disorders						
Anaemia	6 (50.0)	5 (41.7)	18 (43.9)	15 (36.6)	1 (16.7)	1 (16.7)
FN	3 (25.0)	3 (25.0)	12 (29.3)	12 (29.3)	1 (16.7)	1 (16.7)
Eye disorders						
Periorbital oedema	3 (25.0)	0	0	0	0	0
Gastrointestinal disorders						
Abdominal pain	3 (25.0)	0	5 (12.2)	1 (2.4)	1 (16.7)	0
Mouth haemorrhage	3 (25.0)	0	3 (7.3)	0	0	0
Nausea	3 (25.0)	0	14 (34.1)	0	1 (16.7)	0
Oral pain	3 (25.0)	0	0	0	0	0
Vomiting	5 (41.7)	0	19 (46.3)	1 (2.4)	3 (50.0)	0
Stomatitis	1 (8.3)	1 (8.3)	4 (9.8)	2 (4.9)	2 (33.3)	0
General disorders and administration site conditions						
Pyrexia	7 (58.3)	0	19 (46.3)	2 (4.9)	2 (33.3)	0
Infections and infestations						
Skin infection	0	0	3 (7.3)	2 (4.9)	3 (50.0)	1 (16.7)
Investigations						
ALT increased	2 (16.7)	2 (16.7)	8 (19.5)	6 (14.6)	4 (66.7)	1 (16.7)
AST increased	2 (16.7)	2 (16.7)	10 (24.4)	7 (17.1)	4 (66.7)	1 (16.7)
Neutrophil count decreased	6 (50.0)	6 (50.0)	15 (36.6)	15 (36.6)	0	0
Platelet count decreased	7 (58.3)	7 (58.3)	20 (48.8)	17 (41.5)	1 (16.7)	1 (16.7)
White blood cell count decreased	3 (25.0)	3 (25.0)	14 (34.1)	12 (29.3)	0	0
Metabolism and nutrition disorders						
Hypokalaemia	2 (16.7)	1 (8.3)	7 (17.1)	5 (12.2)	2 (33.3)	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	5 (41.7)	1 (8.3)	5 (12.2)	0	0	0
Nervous system disorders						
Headache	4 (33.3)	0	7 (17.1)	0	2 (33.3)	0
Respiratory, thoracic and mediastinal disorders						
Cough	3 (25.0)	0	6 (14.6)	0	0	0
Vascular disorders						
Haematoma	2 (16.7)	0	6 (14.6)	1 (2.4)	2 (33.3)	0

*1, Phase I part, Stratum 1A, 1.4 mg/m^2/cycle group; *2, pooled data from the phase I part, Stratum 1A, 1.8 mg/m^2/cycle group and the phase II part

In Study 059, adverse events leading to death in the 1.4 mg/m^2/cycle group were disease progression (1 subject, 8.3%) and sepsis (1 subject, 8.3%), while those leading to death in the 1.8 mg/m^2/cycle group (Stratum 1A 1.8 mg/m^2 group and the phase II part) were multiple organ dysfunction syndrome (2 subjects, 4.9%), encephalopathy (1 subject, 2.4%), hypoxia (1 subject, 2.4%), pneumonia (1 subject, 2.4%), and disease progression (1 subject, 2.4%). A causal relationship to inotuzumab ozogamicin was denied for all cases. Serious adverse events occurring in >1 subject were pyrexia (3 subjects, 25.0%) and febrile neutropenia (FN) (2 subjects, 16.7%) in the 1.4 mg/m^2/cycle group; and FN (7 subjects, 17.1%), VOD (4 subjects, 9.8%), venoocclusive disease (3 subjects, 7.3%), sepsis (3 subjects, 7.3%), and device related infection (2 subjects, 4.9%) in the 1.8 mg/m^2/cycle group. Among these events, a causal relationship to inotuzumab ozogamicin could not be ruled out for FN (1 subject) in the 1.4 mg/m^2/cycle group and FN (4 subjects), venoocclusive disease (3 subjects), VOD (3 subjects), and sepsis (1 subject) in the 1.8 mg/m^2/cycle group. Grade ≥3 adverse events occurring in ≥10% of subjects were platelet count decreased (7 subjects, 58.3%), neutrophil count

decreased (6 subjects, 50.0%), anaemia (5 subjects, 41.7%), FN (3 subjects, 25.0%), white blood cell count decreased (3 subjects, 25.0%), disease progression (2 subjects, 16.7%), ALT increased (2 subjects, 16.7%), aspartate aminotransferase (AST) increased (2 subjects, 16.7%), γ-glutamyl transferase (GGT) increased (2 subjects, 16.7%), and lymphocyte count decreased (2 subjects, 16.7%) in the 1.4 mg/m^2/cycle group; and platelet count decreased (17 subjects, 41.5%), anaemia (15 subjects, 36.6%), neutrophil count decreased (15 subjects, 36.6%), FN (12 subjects, 29.3%), white blood cell count decreased (12 subjects, 29.3%), AST increased (7 subjects, 17.1%), ALT increased (6 subjects, 14.6%), lymphocyte count decreased (5 subjects, 12.2%), TLS (5 subjects, 12.2%), and hypokalaemia (5 subjects, 12.2%) in the 1.8 mg/m^2/cycle group. Adverse events leading to treatment discontinuation of inotuzumab ozogamicin that occurred in >1 subject were platelet count decreased (2 subjects, 4.9%) and ALT increased (2 subjects, 4.9%) in the 1.8 mg/m^2/cycle group. Adverse events leading to dose interruption of inotuzumab ozogamicin that occurred in >1 subject were ALT increased (4 subjects, 9.8%) and AST increased (2 subjects, 4.9%) in the 1.8 mg/m^2/cycle group.

In Study ALL-1, an adverse event (ALL) led to death in 1 subject (16.7%), and a causal relationship to inotuzumab ozogamicin was denied. Serious adverse events were pyrexia, VOD, and ALL (1 subject each, 16.7%). Among these events, a causal relationship to inotuzumab ozogamicin could not be ruled out for VOD. Grade ≥3 adverse events were anaemia, FN, VOD, skin infection, ALT increased, AST increased, platelet count decreased, ALL, and tumour pain (1 subject each, 16.7%). An adverse event (ALL) led to treatment discontinuation of inotuzumab ozogamicin in 1 subject (16.7%). Adverse events leading to dose interruption were ALT increased (2 subjects, 33.3%), AST increased (2 subjects, 33.3%), blood bilirubin increased (1 subject, 16.7%), and blood alkaline phosphatase (ALP) increased (1 subject, 16.7%).

The applicant's explanation about the difference in the safety of inotuzumab ozogamicin between Japanese and non-Japanese populations based on the results from Studies 059 and ALL-1:
Table 10 shows the adverse events occurring at a higher incidence in Japanese patients (Study ALL-1) than in non-Japanese patients in the 1.8 mg/m^2/cycle group (1.8 mg/m^2/cycle group in Stratum 1A of the phase I part and phase II part of Study 059) by ≥20%. While the incidence of Grade ≥3 events of ALT increased and that of AST increased in Japanese patients were similar to those in non-Japanese patients, the incidence of any Grade events of ALT increased and that of AST increased were higher in Japanese patients than in non-Japanese patients. The upper limits used in the testing were lower in Study ALL-1 than in Study 059,[24)] which may account for the difference.

[24)] In Study ALL-1, a uniform standard across the study centers was used (upper limit of normal [ULN] was defined according to age, ULN for ALT and AST were 41 and 57 IU/L at maximum, respectively) while in Study 059, an individual standard for each study center (the maximum ULN for ALT and AST were 91.2 and 70.8 IU/L, respectively) was used.

Table 10. Adverse events occurring at a higher incidence in Japanese patients than in non-Japanese patients by ≥20% (Studies ALL-1 and 059)

PT (MedDRA ver.25.1)	n (%)			
	Japanese patients ALL-1 N = 6		Non-Japanese patients 059* N = 41	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	6 (100)	5 (83.3)	41 (100)	39 (95.1)
AST increased	4 (66.7)	1 (16.7)	10 (24.4)	7 (17.1)
ALT increased	4 (66.7)	1 (16.7)	8 (19.5)	6 (14.6)
Skin infection	3 (50.0)	1 (16.7)	3 (7.3)	2 (4.9)
Stomatitis	2 (33.3)	0	4 (9.8)	2 (4.9)

*, The 1.8 mg/m^2/cycle group in Stratum 1A of the phase I part and the phase II part

Adverse events leading to death that occurred at a higher incidence in Japanese patients than in non-Japanese patients by ≥5% were ALL (1 Japanese subject [16.7%] and 0 non-Japanese subjects). Serious adverse events occurring at a higher incidence in Japanese patients than in non-Japanese patients by ≥5% were ALL (1 Japanese subject [16.7%] and 0 non-Japanese subjects) and pyrexia (1 Japanese subject [16.7%] and 0 non-Japanese subjects). An adverse event leading to treatment discontinuation that occurred at a higher incidence in Japanese patients than in non-Japanese patients by ≥5% was ALL (1 Japanese subject [16.7%] and 0 non-Japanese subjects). Adverse events leading to dose interruption that occurred at a higher incidence in Japanese patients than in non-Japanese patients by ≥5% were AST increased (2 Japanese subjects [33.3%] and 4 non-Japanese subjects [9.8%]), ALT increased (2 Japanese subjects [33.3%] and 2 non-Japanese subjects [4.9%]), blood bilirubin increased (1 Japanese subject [16.7%] and 0 non-Japanese subjects), and blood ALP increased (1 Japanese subject [16.7%] and 0 non-Japanese subjects).

PMDA's discussion:

Adverse events leading to death, serious adverse events, and Grade ≥3 adverse events reported in Studies 059 and ALL-1 are adverse events that require caution following treatment with inotuzumab ozogamicin. Although it is difficult to reach a definitive conclusion on the difference in safety between Japanese pediatric patients and non-Japanese pediatric patients due to limited number of Japanese patients evaluated in Study ALL-1, adverse events occurring at a higher incidence in Japanese patients than in non-Japanese patients require caution. However, given that the adverse events mentioned above are already known to be associated with inotuzumab ozogamicin treatment, inotuzumab ozogamicin is tolerable in pediatric patients with relapsed or refractory CD22-positive ALL as long as appropriate actions including monitoring and control of adverse events are taken by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

7.R.3.2 Safety by age

The applicant's explanation about the difference in safety between pediatric patients with relapsed or refractory CD22-positive ALL and adult patients with the same condition:

Table 11 shows the summary of safety data from Study 059 (1.8 mg/m^2/cycle group in Stratum 1A of the phase I part and the phase II part) and Study ALL-1, both studies conducted in pediatric patients with relapsed or

refractory ALL, and from Study 1022[25] (inotuzumab ozogamicin group) conducted in adult patients with relapsed or refractory ALL.

Table 11. Summary of safety data in adult and pediatric patients (Studies 059, ALL-1, and 1022)

	n (%)	
	Pediatric patients	Adult patients
	Pooled data of Studies 059* and ALL-1 N = 47	Study 1022 N = 164
All adverse events	47 (100)	162 (98.8)
Grade ≥3 adverse events	44 (93.6)	144 (87.8)
Adverse events leading to death	6 (12.8)	19 (11.6)
Serious adverse events	28 (59.6)	71 (43.3)
Adverse events leading to treatment discontinuation of inotuzumab ozogamicin	11 (23.4)	31 (18.9)
Adverse events leading to dose interruption of inotuzumab ozogamicin	8 (17.0)	72 (43.9)
Adverse events leading to dose reduction of inotuzumab ozogamicin	0	3 (1.8)

*, Patients in the 1.8 mg/m^2/cycle group in Stratum 1A of the phase I part and patients in the phase II part

Table 12 shows adverse events of any grade and Grade ≥3 adverse events occurring at a higher incidence in pediatric patients than in adult patients by ≥10%. In the table below, laboratory test-related events (platelet count decreased, neutrophil count decreased, white blood cell count decreased, lymphocyte count decreased, and blood bilirubin increased) occurred in pediatric patients at an incidence significantly higher than in adult patients. This difference is likely to be attributable to the difference[26] between the studies, i.e., whether abnormal laboratory value-related events were included in adverse events.

[25] Study 1022 is a global phase III study in patients with relapsed or refractory CD22-positive ALL. In the inotuzumab ozogamicin group, patients were to receive inotuzumab ozogamicin intravenously on Day 1 (0.8 mg/m^2), Day 8 (0.5 mg/m^2), and Day 15 (0.5 mg/m^2). The duration of treatment cycle was 21 days for Cycle 1 and 28 days for subsequent cycles. It was recommended that patients should receive no more than 6 cycles (for patients proceeding to HSCT, 2 cycles or minimum number of cycles needed) (see Review Report of Besponsa Injection 1 mg, dated November 2, 2017).

[26] Decreased blood counts and blood bilirubin increased were reported as adverse events based on abnormal laboratory values in Studies 059 and ALL-1, but were reported as individual adverse events in Study 1022. In fact, the incidences of adverse events: thrombocytopenia, neutropenia, leukopenia, lymphopenia, and hyperbilirubinaemia were higher in adult patients than in pediatric patients by ≥10%.

Table 12. Adverse events occurring at a higher incidence in pediatric patients than in adult patients by ≥10% (Studies 059, ALL-1, and 1022)

PT (MedDRA ver. 25.1)	n (%)			
	Pediatric patients Pooled data of Studies 059* and ALL-1 N = 47		Adult patients Study 1022 N = 164	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	47 (100)	44 (93.6)	162 (98.8)	144 (87.8)
Vomiting	22 (46.8)	1 (2.1)	25 (15.2)	2 (1.2)
Platelet count decreased	21 (44.7)	18 (38.3)	2 (1.2)	2 (1.2)
Pyrexia	21 (44.7)	2 (4.3)	52 (31.7)	5 (3.0)
Anaemia	19 (40.4)	16 (34.0)	54 (32.9)	36 (22.0)
Neutrophil count decreased	15 (31.9)	15 (31.9)	1 (0.6)	1 (0.6)
AST increased	14 (29.8)	8 (17.0)	37 (22.6)	7 (4.3)
White blood cell count decreased	14 (29.8)	12 (25.5)	10 (6.1)	10 (6.1)
ALT increased	12 (25.5)	7 (14.9)	25 (15.2)	6 (3.7)
Haematoma	8 (17.0)	1 (2.1)	0	0
Skin infection	6 (12.8)	3 (6.4)	1 (0.6)	0
Rash maculo-papular	6 (12.8)	1 (2.1)	4 (2.4)	2 (1.2)
Lymphocyte count decreased	5 (10.6)	5 (10.6)	4 (2.4)	1 (0.6)
Blood bilirubin increased	5 (10.6)	3 (6.4)	0	0

*, Patients in the 1.8 mg/m^2/cycle group in Stratum 1A of the phase I part and patients in the phase II part

Adverse events leading to death that occurred at a higher incidence in pediatric patients (a pooled analysis of Study 059 [1.8 mg/m^2 group in Stratum 1A of the phase I part and phase II part] and Study ALL-1) than in adult patients (Study 1022) by ≥3% were multiple organ dysfunction syndrome (2 pediatric subjects [4.3%] and 0 adult subjects). Serious adverse events occurring at a higher incidence in pediatric patients than in adult patients by ≥3% were FN (7 pediatric subjects [14.9%] and 18 adult subjects [11.0%]), VOD (5 pediatric subjects [10.6%] and 4 adult subjects [2.4%]), venoocclusive disease (3 pediatric subjects [6.4%] and 0 adult subjects), sepsis (3 pediatric subjects [6.4%] and 3 adult subjects [1.8%]), and device related infection (2 pediatric subjects [4.3%] and 1 adult subject [0.6%]). Adverse events leading to treatment discontinuation of inotuzumab ozogamicin that occurred at a higher incidence in pediatric patients than in adult patients by ≥3% were ALT increased (2 pediatric subjects [4.3%] and 0 adult subjects) and platelet count decreased (2 pediatric subjects [4.3%] and 0 adult subjects). Adverse events leading to dose interruption of inotuzumab ozogamicin that occurred at a higher incidence in pediatric patients than in adult patients by ≥3% were ALT increased (6 pediatric subjects [12.8%] and 5 adult subjects [3.0%]) and AST increased (4 pediatric subjects [8.5%] and 7 adult subjects [4.3%]).

The applicant's explanation about the safety by age[27)] in pediatric patients:

Table 13 shows the summary of safety data by age in the pooled analysis of data from Study 059 (1.8 mg/m^2/cycle group in the Stratum 1A of the phase I part and the phase II part) and Study ALL-1.

27) The age classification in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E11 Guidelines (≥1 month and <2 years; ≥2 and <12 years; ≥12 years and ≤18 years) was used as a reference.

Table 13. Summary of safety data by age in pediatric patients (Studies 059 and ALL-1)

	n (%)		
	Pooled data from Studies 059* and ALL-1		
	Overall pediatric N = 47	≥1 and ≤11 years N = 29	≥12 and ≤17 years N = 18
All adverse events	47 (100)	29 (100)	18 (100)
Grade ≥3 adverse events	44 (93.6)	27 (93.1)	17 (94.4)
Adverse events leading to death	6 (12.8)	4 (13.8)	2 (11.1)
Serious adverse events	28 (59.6)	17 (58.6)	11 (61.1)
Adverse events leading to treatment discontinuation of inotuzumab ozogamicin	11 (23.4)	8 (27.6)	3 (16.7)
Adverse events leading to dose interruption of inotuzumab ozogamicin	8 (17.0)	4 (13.8)	4 (22.2)
Adverse events leading to dose reduction of inotuzumab ozogamicin	0	0	0

*, Patients in the 1.8 mg/m^2/cycle group in Stratum 1A of the phase I part and patients in the phase II part

Adverse events that had a different incidence between "patients aged ≥1 and ≤11 years" and "patients aged ≥12 and ≤17 years" by ≥20% were ALT increased (4 subjects [13.8%] and 8 subjects [44.4%] in patients aged ≥1 and ≤11 years and patients aged ≥12 and ≤17 years, respectively; the same applies hereinafter) and GGT increased (2 subjects [6.9%] and 6 subjects [33.3%]). Grade ≥3 adverse events that had a different incidence between the pediatric age classes by ≥20% were ALT increased (2 subjects [6.9%] and 5 subjects [27.8%]) and GGT increased (0 subjects and 4 subjects [22.2%]). Serious adverse events occurring in >1 subject in either group that had a different incidence between the pediatric age classes by ≥5% were FN (3 subjects [10.3%] and 4 subjects [22.2%]), VOD (2 subjects [6.9%] and 3 subjects [16.7%]), and venoocclusive disease (3 subjects [10.3%] and 0 subjects). An adverse event leading to dose interruption of inotuzumab ozogamicin in >1 subject in either group that had a different incidence between the pediatric age classes by ≥5% was ALT increased (2 subjects [6.9%] and 4 subjects [22.2%]). There were no adverse events leading to death or treatment discontinuation that occurred in >1 subject in either group that had a different incidence between the pediatric age classes by ≥5%.

PMDA's discussion:

While the limited number of patients evaluated in the pooled analysis of data from Study 059 (1.8 mg/m^2/cycle group in Stratum 1A of the phase I part and the phase II part) and Study ALL-1 precludes rigorous evaluation, there was no trend towards different types of adverse events between pediatric patients and adult patients, or between different pediatric age classes (patients aged ≥1 and ≤11 years and patients aged ≥12 and ≤17 years). Therefore, currently no clear age-related differences in the safety profile have been identified. However, given that the number of patients evaluated in each age group is small, PMDA concluded that the applicant should continue to collect information on adverse events by age through post-marketing surveillance and provide information on any new findings to healthcare professionals.

In the following sections, PMDA conducted a review focusing on liver disorder, including VOD/SOS, which were regarded as adverse events of special interest in the review for the previous approval (for adults), and the occurrences of serious cases were reported in Study 059.

7.R.3.3 Liver disorder, including VOD/SOS

The applicant's explanation about the incidence of liver disorder, including VOD/SOS[28)] associated with inotuzumab ozogamicin treatment:

Adverse events related to liver disorder, including VOD/SOS were preferred terms (PTs) retrieved in standardised Medical Dictionary for Regulatory Activities (MedDRA) queries (MedDRA SMQ) for "cholestasis and jaundice of hepatic origin (narrow)," "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow)," "hepatitis, non-infectious (narrow)," "liver related investigations, signs and symptoms (narrow and broad)," as well as hepatic vein occlusion, hepatic vein thrombosis, portal vein thrombosis, Budd-Chiari syndrome, chronic GVHD in liver, acute GVHD in liver, veno-occlusive liver disease, and venoocclusive disease.

Table 14 shows the incidence of liver disorder, including VOD/SOS in Studies 059 and ALL-1.

Table 14. Incidence of liver disorder, including VOD/SOS (Studies 059 and ALL-1)

PT (MedDRA ver. 25.1)	n (%)					
	059				ALL-1	
	1.4 mg/m^2/cycle*1 N = 12		1.8 mg/m^2/cycle*2 N = 41		1.8 mg/m^2/cycle N = 6	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Liver disorder, including VOD/SOS	4 (33.3)	4 (33.3)	16 (39.0)	15 (36.6)	5 (83.3)	2 (33.3)
ALT increased	2 (16.7)	2 (16.7)	6 (14.6)	6 (14.6)	4 (66.7)	1 (16.7)
AST increased	2 (16.7)	2 (16.7)	7 (17.1)	7 (17.1)	4 (66.7)	1 (16.7)
GGT increased	2 (16.7)	2 (16.7)	4 (9.8)	4 (9.8)	1 (16.7)	0
Blood bilirubin increased	1 (8.3)	1 (8.3)	3 (7.3)	3 (7.3)	1 (16.7)	0
VOD	1 (8.3)	1 (8.3)	4 (9.8)	3 (7.3)	1 (16.7)	1 (16.7)
Venoocclusive disease	1 (8.3)	1 (8.3)	4 (9.8)	3 (7.3)	0	0
Blood ALP increased	0	0	1 (2.4)	1 (2.4)	1 (16.7)	0

*1, The 1.4 mg/m^2/cycle group in Stratum 1A of the phase I part; *2, the 1.8 mg/m^2/cycle group in Stratum 1A of the phase I part and the phase II part

In Study 059, serious liver disorder, including VOD/SOS, occurred in 1 subject in the 1.4 mg/m^2/cycle group (8.3%; venoocclusive disease and VOD) and 8 subjects in the 1.8 mg/m^2/cycle group (1.8 mg/m^2/cycle group in Stratum 1A of the phase I part and the phase II part) (19.5%; venoocclusive disease [4 subjects], VOD [4 subjects], and blood bilirubin increased [1 subject], some subjects had more than 1 event). A causal relationship to inotuzumab ozogamicin could not be ruled out for venoocclusive disease (1 subject) and VOD (1 subject) in the 1.4 mg/m^2/cycle group, and venoocclusive disease (4 subjects), VOD (3 subjects), and blood bilirubin increased (1 subject) in the 1.8 mg/m^2/cycle group. Liver disorder, including VOD/SOS, leading to treatment discontinuation of inotuzumab ozogamicin occurred in 1 subject in the 1.4 mg/m^2/cycle group (8.3%; ALT increased) and 4 subjects in the 1.8 mg/m^2/cycle group (9.8%; ALT increased [2 subjects], AST increased [1 subject], GGT increased [1 subject], blood bilirubin increased [1 subject], and venoocclusive disease [1 subject], some subjects had more than 1 event). Liver disorder, including VOD/SOS, leading to dose interruption of

28) In Study ALL-1, VOD/SOS was defined as cases in which at least 2 of the following 5 criteria (1) through (5) were met:
(1) total bilirubin >2 mg/dL; (2) hepatomegaly; (3) right upper quadrant pain; (4) retention of ascites; (5) weight gain >2% of baseline
In Study 059, VOD/SOS was defined as cases in which at least 2 of the following 3 criteria (1), (2), and (3) were met:
(1) total bilirubin >2 mg/dL; (2) hepatomegaly or right upper abdominal pain; (3) weight gain >2% of baseline

inotuzumab ozogamicin occurred in 2 subjects in the 1.8 mg/m^2/cycle group (4.9%; ALT increased [2 subjects] and AST increased [1 subject], 1 subject had more than 1 event). There were no cases of liver disorder, including VOD/SOS, leading to death or leading to dose reduction of inotuzumab ozogamicin.

In Study 059, 1 subject met the laboratory test criteria for Hy's law (defined based on the Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, by U.S. Department of Health and Human Services, Food and Drug Administration, July 2009). This patient, a male pediatric patient aged [redacted] years in the phase II part, had AST 3.85 μkat/L (226.5 U/L), ALT 3.37 μkat/L (198.2 U/L),[29] total bilirubin 63.3 μmol/L (3.7 mg/dL)[30] on Day 8 and developed Grade 3 VOD, which led to treatment discontinuation of inotuzumab ozogamicin. On Day 14, VOD and hepatic function abnormal resolved. A causal relationship to inotuzumab ozogamicin could not be ruled out.

In Study ALL-1, serious liver disorder, including VOD/SOS, occurred in 1 subject (16.7%; VOD), and a causal relationship to inotuzumab ozogamicin could not be ruled out. Liver disorder, including VOD/SOS, leading to dose interruption of inotuzumab ozogamicin occurred in 3 subjects (50.0%; ALT increased [2 subjects], AST increased [2 subjects], blood bilirubin increased [1 subject], and blood ALP increased [1 subject], some subjects had more than 1 event). There were no cases of liver disorder, including VOD/SOS, leading to death, treatment discontinuation, or dose reduction of inotuzumab ozogamicin.

Table 15 shows the details of patients who developed VOD/SOS after administration of inotuzumab ozogamicin in Studies 059 and ALL-1. Table 16 shows the details of patients who developed VOD/SOS after HSCT following administration of inotuzumab ozogamicin.

Table 15. List of patients who developed VOD/SOS after administration of inotuzumab ozogamicin (Studies ALL-1 and 059)

Study	Age	Sex	Cohort dose*1	Grade	Prior treatment*2	HSCT prior to inotuzumab ozogamicin treatment	Ongoing or prior liver disease at baseline	Number of salvage therapy regimens	Number of treatment cycles at the time of onset	HSCT after inotuzumab ozogamicin treatment	Time to onset*3	Outcome*4	Causal relationship
ALL-1	[redacted]	M	1.8	3	1	No	Yes	0	1	Yes	36	Resolved	Related
059	[redacted]	F	1.8	3	Refractory	No	No	0	2	Yes	45	Resolved	Related
	[redacted]	M	1.8	3	≥2	Yes	No	≥1	1	No	8	Resolved	Related
	[redacted]	M	1.8	4	≥2	Yes	No	≥1	1	Yes	40	Resolved	Related
	[redacted]	F	1.8	3	≥2	Yes	No	≥1	1	Yes	24	Not resolved	Related
	1[redacted]	F	1.4	3	Refractory	No	Yes	0	2	No	60	Not resolved	Related
	1[redacted]	M	1.8	4	Refractory	No	No	0	1	No	45	Not resolved	Related
	1[redacted]	M	1.8	2	Refractory	No	No	0	2	Yes	33	Resolved	Related
	1[redacted]	M	1.8	4	Refractory	No	Yes	0	3	Yes	40	Not resolved	Not related

*1, Total dose in Cycle 1 (1.4 mg/m^2/cycle or 1.8 mg/m^2/cycle); *2, classified into "1," first relapse, "≥2," second relapse or more, and "refractory"; *3, time to onset (days) of VOD/SOS since the last dose of inotuzumab ozogamicin; and *4, reported outcome of VOD/SOS

[29] AST and ALT values were converted based on the following formula: AST or ALT (U/L) = AST or ALT (μkat/L) / 0.017.
[30] Total bilirubin value was converted based on the following formula: total bilirubin (mg/dL) = total bilirubin (μmol/L) / 17.1.

Table 16. List of patients who developed VOD/SOS after undergoing HSCT following administration of inotuzumab ozogamicin (Studies ALL-1 and 059)

Study	Age	Prior HSCT	Pre-HSCT total bilirubin (μmol/L [mg/dL]*)	Days to HSCT after last dose of inotuzumab ozogamicin (days)	Time to onset of VOD/SOS after HSCT (days)	Conditioning therapy
ALL-1	[redacted]	No	5.8 (0.34)	21	16	BU/MEL
059	[redacted]	No	3.0 (0.18)	28	18	BU/FLU/THIO
	[redacted]	Yes	9.0 (0.53)	36	5	VP-16/TBI
	[redacted]	Yes	5.1 (0.30)	21	4	FLU/THIO/TREO
	1[redacted]	No	4.0 (0.23)	23	11	FLU/TBI
	1[redacted]	No	8.6 (0.50)	23	18	VP-16/TBI

BU, Busulfan; MEL, melphalan; FLU, fludarabine phosphate; TIO, thiotepa; TREO, treosulfan (not approved in Japan); VP-16, etoposide; *, The total bilirubin value was converted based on the following formula: total bilirubin (mg/dL) = total bilirubin (μmol/L) / 17.1.

In the 1.8 mg/m^2/cycle group in Study 059 (1.8 mg/m^2/cycle group in Stratum 1A of the phase I part and the phase II part), VOD/SOS occurred in 3 of 21 subjects (14.3%) who had prior HSCT before the start of inotuzumab ozogamicin and in 4 of 20 subjects (20.0%) who did not; and VOD/SOS occurred in 5 of 23 subjects (21.7%) who underwent HSCT after treatment with inotuzumab ozogamicin and in 2 of 18 subjects (11.1%) who did not. In the 1.8 mg/m^2/cycle group in Study 059, VOD/SOS occurred in 4 of 20 subjects (20.0%) in Cycle 1, 2 of 14 subjects (14.3%) in Cycle 2, 1 of 5 subjects (20.0%) in Cycle 3, and 0 of 2 subjects (0%) in Cycle 4 or more.

The applicant's explanation about the risk factors for VOD/SOS associated with inotuzumab ozogamicin treatment:

On the basis of the result data from Study 059, the risk factors for VOD/SOS associated with inotuzumab ozogamicin treatment in pediatric patients with relapsed or refractory CD22-positive ALL were evaluated.[31)]

In addition to risk factors identified at the time of review of data for the previous approval, the factors[32)] reported in the published literature (*J Clin Oncol.* 2022;40:956-67 and *Leukemia.* 2019;33:884-92) were evaluated, including "time to HSCT from the last dose of inotuzumab ozogamicin," "conditioning therapy containing busulfan or clofarabine," and "prior HSCT before the start of inotuzumab ozogamicin." The study results suggested that (1) time to HSCT after the last dose of inotuzumab ozogamicin being <2 months[33)] and (2) a greater number of prior treatments before the start of inotuzumab ozogamicin (patients with a greater number of relapses or refractory)[34)] are the potential risk factors in the studied patients who had received inotuzumab ozogamicin; however, due to the limited number of patients studied, clear risk factors were not identified.

31) Because VOD/SOS occurred only in 1 subject in Study ALL-1, no analysis was performed to identify the risk factors.

32) On the basis of the risk factors evaluated at the time of review for the previous approval, published literature (*J Clin Oncol*. 2022;40:956-67 and *Leukemia*. 2019;33:884-92), and other data, the following factors were evaluated: age; performance status (Lansky or Karnofsky score); prior treatment (first relapse, refractory, and second or subsequent relapses after HSCT); ALT, AST, or bilirubin increased at baseline; HSCT donor type after treatment with inotuzumab ozogamicin; pre-HSCT platelet count; number of treatment cycles of inotuzumab ozogamicin; use/non-use of prophylactic defibrotide sodium; use/non-use of prophylactic ursodeoxycholic acid; pre-HSCT ALT or AST increase; pre-HSCT bilirubin increase; use/non-use of total body irradiation (TBI)-based conditioning; use/non-use of conditioning regimen containing ≥2 alkylating agents; proceeding to or not proceeding to HSCT after inotuzumab ozogamicin treatment.

33) VOD/SOS occurred in 5 of 13 subjects (38.5%) who proceeded to HSCT within 2 months of the last dose of inotuzumab ozogamicin and 0 of 10 subjects (0%) who proceeded to HSCT ≥2 months after the last dose of inotuzumab ozogamicin.

34) VOD/SOS occurred in 0 of 10 subjects (0%) who experienced the first relapse after HSCT, 3 of 24 subjects (12.5%) who experienced second or subsequent relapses, and 4 of 7 subjects (57.1%) with refractory ALL.

Taken together, although interpretation of the data has limitations due to a limited number of patients studied, pediatric patients should be closely monitored for the development of VOD/SOS, when undergoing HSCT after inotuzumab ozogamicin treatment in a manner equivalent to that implemented for adult patients, given that no new findings were obtained regarding the safety profile in relation to liver disorder, including VOD/SOS, or the risk factors of VOD/SOS, and that based on the evaluation in adult patients with relapsed or refractory CD22-positive ALL, cautionary statements regarding the risk of developing VOD/SOS are included in the package insert and other materials (see Review Report of Besponsa Injection 1 mg, dated November 2, 2017).

PMDA's discussion:
In Studies 059 and ALL-1, there were reports of serious cases of liver disorder, including VOD/SOS, for which a causal relationship to inotuzumab ozogamicin could not be ruled out. On the basis of this and other factors, when administering inotuzumab ozogamicin, patients should be closely monitored for liver disorder, including VOD/SOS. Therefore, PMDA concluded that the applicant should provide information on the incidence of liver disorder in clinical studies to healthcare professionals in an appropriate manner, and include appropriate cautionary statements for healthcare professionals in the package insert and other materials to ensure that liver function and other tests are performed on a regular basis when using inotuzumab ozogamicin and if any abnormalities are detected, appropriate steps can be taken, equivalent to those implemented for the previous approval (for adults).

Although risk factors in pediatric patients have not been clearly determined based on the results of Study 059, given that the incidence of VOD/SOS in pediatric patients tends to be higher in those who underwent HSCT after receiving inotuzumab ozogamicin than in those who did not, the information should be provided to healthcare professionals in an appropriate manner. In addition, the applicant should continue to investigate the risk factors for developing VOD/SOS and other factors through the post-marketing surveillance, and should provide information to healthcare professionals in an appropriate manner if new findings become available [see Section 7.R.6].

7.R.4 Clinical positioning and indication

Inotuzumab ozogamicin has already been approved for the indication of relapsed or refractory CD22-positive ALL. In the present partial change application, while no change was made to the indication, the "Precautions Concerning Indication" section was modified as shown in the table below as requested by the applicant (underline denotes additions to and strikethrough denotes deletions from the descriptions in the previous approval).

Indication	Precautions Concerning Indication
Relapsed or refractory CD22-positive acute lymphoblastic leukemia	• Inotuzumab ozogamicin should be used in patients whose presence of CD22 antigen expression was confirmed by examinations such as flow cytometry. • Whether a patient is appropriate to receive treatment with inotuzumab ozogamicin should be decided after becoming completely familiar with the details of the "Clinical Studies" section regarding prior treatment and other data on patients enrolled in clinical studies, and gaining a thorough understanding of the efficacy and safety of inotuzumab ozogamicin. • ~~Data have suggested that the magnitude of impact of inotuzumab ozogamicin on post-hematopoietic stem cell transplantation (HSCT) overall survival may not be similar to that obtained with existing chemotherapies.~~ For patients proceeding to hematopoietic stem cell transplantation (HSCT), the use of inotuzumab ozogamicin should be determined carefully after thoroughly considering treatment options other than inotuzumab ozogamicin. In adults, data have suggested that the magnitude of impact of inotuzumab ozogamicin on post-HSCT overall survival may not be similar to that obtained with existing chemotherapies.

On the basis of the discussions in Sections "7.R.2 Efficacy," "7.R.3 Safety," and in the section below, PMDA concluded that the indication does not require revision, and that the proposed "Precautions Concerning Indication" section is acceptable as proposed by the applicant.

7.R.4.1 Clinical positioning of inotuzumab ozogamicin, intended patient population, and indication

In the major clinical practice guidelines and major textbooks on hematology and oncology published in Japan and other countries, the following descriptions of inotuzumab ozogamicin regarding the treatment of relapsed or refractory CD22-positive ALL were found.

Clinical practice guidelines

- National Comprehensive Cancer Network (NCCN) Guidelines (pediatric ALL) (v3.2024): Inotuzumab ozogamicin is a treatment option for pediatric patients with relapsed or refractory B-cell ALL regardless of prior HSCT or Philadelphia chromosome (Ph) status (Category 2A[35)]).

Textbooks

- Pizzo and Poplack's Pediatric Oncology 8th edition (Wolters Kluwer, 2020, USA): The efficacy of inotuzumab ozogamicin in pediatric patients with multiple-relapsed or refractory B-cell ALL has been reported. It is expected that inotuzumab ozogamicin can be used as bridging to HSCT or Chimeric antigen receptor T-cell (CAR-T cell) therapy. Conversely, there is concern regarding the risk of liver disorder, including VOD/SOS.

The applicant's explanation about the clinical positioning of inotuzumab ozogamicin in pediatric patients with relapsed or refractory ALL:

In pediatric patients with relapsed or refractory ALL, standard curative therapy is HSCT. Since improvement of treatment outcome can be expected in patients who are able to proceed to HSCT, it is important for patients to undergo HSCT while in remission rather than when they are not in remission (e.g., Guidelines on Hematopoietic Cell Transplantation in Pediatric Patients with ALL. Third edition [in Japanese], ed. by the Japan Society for Hematopoietic Cell Transplantation). For this reason, treatment such as salvage chemotherapies have been performed so that the patient can achieve remission before proceeding to HSCT;

35) It is based on relatively lower-level evidence, with a uniform NCCN consensus as to the intervention is appropriate.

however, no standard salvage chemotherapies for relapsed or refractory pediatric ALL have been established. In patients who do not proceed to HSCT, although no standard therapies have been established, when remission is achieved by salvage chemotherapy, mitigation of symptoms due to reduction in tumor cells is expected.

Among patients with ALL, treatment outcome of patients with Philadelphia chromosome (Ph)-positive ALL is improving after receiving treatment such as salvage chemotherapies in combination with imatinib (A Practical Guidelines for Pediatric Leukemia and Lymphoma 2016, The Japanese Society of Pediatric Hematology/Oncology); however, standard therapy for relapsed or refractory Ph-positive ALL has not been established.

Given that the results of Studies 059 and ALL-1 demonstrated that inotuzumab ozogamicin is clinically useful [see Sections 7.R.2 and 7.R.3] under the circumstances described above, inotuzumab ozogamicin can be considered as a treatment option for pediatric patients with relapsed or refractory ALL. While blinatumomab and CAR-T cell therapies[36)] can also be used in pediatric patients with relapsed or refractory ALL, given that the remission rates of patients receiving inotuzumab ozogamicin in Studies 059 and ALL-1 were comparable or higher than the rate in the clinical study of blinatumomab,[37)] inotuzumab ozogamicin can be used in a wide range of patients with various conditions.

The applicant's explanation about the intended patient population of inotuzumab ozogamicin:
As shown above, inotuzumab ozogamicin can be recommended as a treatment option for relapsed or refractory CD22-positive pediatric ALL. However, considering the risk of VOD/SOS after HSCT, whether to use inotuzumab ozogamicin in patients proceeding to HSCT should be determined carefully after a thorough consideration of other treatment options. A cautionary statement to this effect should be included in the "Precautions Concerning Indication" section, equivalent to those cautioned for adult patients.

In addition, the impact on post-HSCT overall survival (OS) as expressed in the previous approval for adults (the statement to the effect that the magnitude of impact of inotuzumab ozogamicin on post-HSCT OS may not be similar to that obtained with existing chemotherapies) should be revised so that it is clear that the statement is on the impact on post-HSCT OS in adult patients, because it is difficult to make a similar statement based on the results from Studies 059 and ALL-1,[38)] which were open-label uncontrolled studies in pediatric patients.

In Studies 059 (phase II part) and ALL-1,[39)] pediatric patients with relapsed or refractory Ph-positive ALL were not enrolled; however, these patients should be included in the intended population of inotuzumab ozogamicin equivalent to adult patients, based on the following:

---

36) Tisagenlecleucel

37) In a foreign phase I/II study, which evaluated the efficacy of blinatumomab in pediatric patients with relapsed or refractory ALL, a remission rate of 39% was reported (*J Clin Oncol*. 2016;34:4381-9).

38) Overall survival in patients who underwent HSCT was as follows: in Study ALL-1, all 3 subjects were alive as of Day 180; in the 1.8 mg/m^2/cycle group in Study 059, 8 of 23 subjects died as of Day 365.

39) The protocol of Study 059 specified no specific provision regarding the enrollment of patients with Ph-positive ALL, while in Study ALL-1, eligible patients were those who had received second or third generation tyrosine kinase inhibitors (TKIs) and at least 1 prior standard treatment as remission induction therapy, and who had treatment resistant ALL.

- Inotuzumab ozogamicin demonstrated its efficacy (CR in best overall response) in 1 subject with Ph-positive ALL in the 1.4 mg/m^2/cycle group Stratum 1A of the phase I part of Study 059.
- In the published literature, of 51 pediatric patients with relapsed or refractory ALL, 3 patients with Ph-positive ALL received inotuzumab ozogamicin, and all 3 achieved CR or CRi; in addition, there were no concerns in relation to the safety profiles (*Leukemia*. 2019;33:884-92).

PMDA's discussion:
PMDA largely accepted the applicant's explanation about the clinical positioning of inotuzumab ozogamicin and intended patient population. However, no results have been obtained from clinical studies that compared the efficacy and safety of inotuzumab ozogamicin with those of other approved treatments; therefore, it is considered that the use of inotuzumab ozogamicin or other antineoplastic agents should be determined according to the patient's condition or other factors.

PMDA considers that the applicant's explanation about the change of the expressions used in the "Precautions Concerning Indication" section is acceptable, and that the statement should be as follows:

Precautions Concerning Indication

- For patients proceeding to HSCT, the use of inotuzumab ozogamicin should be determined carefully after thoroughly considering treatment options other than inotuzumab ozogamicin. In adults, data have suggested that the magnitude of impact of inotuzumab ozogamicin on post-HSCT overall survival may not be similar to that obtained with existing chemotherapies.

7.R.5 Dosage and administration

On the basis of the applicant's proposal after filing the application for partial change, the dosage and administration and the "Precautions Concerning Dosage and Administration" section were defined as in the table below (underline denotes additions to and strikethrough denotes deletions from the descriptions in the previous approval).

Dosage and Administration	Precautions Concerning Dosage and Administration
The usual ~~adult~~ dosage is inotuzumab ozogamicin (genetical recombination) 0.8 mg/m^2 (body surface area) on Day 1, 0.5 mg/m^2 (body surface area) on Day 8, and 0.5 mg/m^2 (body surface area) on Day 15, administered as an intravenous infusion over at least 1 hour, followed by a rest period. For adults, the duration of treatment cycle is 21 to 28 days in Cycle 1 and 28 days in subsequent cycles. Treatment should be repeated in cycles. For pediatric patients, the duration of treatment cycle is 21 to 42 days in Cycle 1 and 28 to 42 days in subsequent cycles. Treatment should be repeated in cycles. The number of cycles should be determined depending on whether the patient proceeds to hematopoietic stem cell transplantation. The dose should be decreased according to the patient's condition.	• In adults, the duration of treatment cycle is, in principle, 21 days in Cycle 1, and can be extended up to 28 days if remission is achieved (regardless of blood count recovery). For pediatric patients, the duration of treatment cycle is, in principle, 21 days in Cycle 1, and 28 days in subsequent cycles. However, if remission is achieved (regardless of blood count recovery), the treatment cycle may be extended up to 42 days. If remission is achieved (regardless of blood count recovery), the dose on Day 1 of each subsequent cycle should be inotuzumab ozogamicin (genetical recombination) 0.5 mg/m^2 (body surface area). If <5% blasts in the bone marrow, the absence of peripheral blood leukemic blasts, and resolution of any extramedullary disease are achieved, it should be considered that the patient is in remission (regardless of blood count recovery). • Number of treatment cycles • Dose modification criteria of inotuzumab ozogamicin in case of adverse reactions • Premedication to reduce infusion reaction[40)] • Combination treatment with other antineoplastic agents[41)]

On the basis of the discussions in Sections "7.R.2 Efficacy," "7.R.3 Safety," and in the section below, PMDA concluded that the dosage and administration and the "Precautions Concerning Dosage and Administration" section proposed by the applicant should be defined as shown below without modification.

Dosage and Administration

The usual dosage is inotuzumab ozogamicin (genetical recombination) 0.8 mg/m^2 (body surface area) on Day 1, 0.5 mg/m^2 (body surface area) on Day 8, and 0.5 mg/m^2 (body surface area) on Day 15, administered as an intravenous infusion over at least 1 hour, followed by a rest period. For adults, the duration of treatment cycle is 21 to 28 days in Cycle 1 and 28 days in subsequent cycles. Treatment should be repeated in cycles. For pediatric patients, the duration of treatment cycle is 21 to 42 days in Cycle 1 and 28 to 42 days in subsequent cycles. Treatment should be repeated in cycles. The number of cycles should be determined depending on whether the patient proceeds to hematopoietic stem cell transplantation. The dose should be decreased according to the patient's condition.

Precautions Concerning Dosage and Administration

- In adults, the duration of treatment cycle is, in principle, 21 days in Cycle 1, and can be extended up to 28 days if remission is achieved (regardless of blood count recovery). For pediatric patients, the duration of treatment cycle is, in principle, 21 days in Cycle 1, and 28 days in subsequent cycles. However, if remission is achieved (regardless of blood count recovery), the treatment cycle may be extended up to 42 days. If remission is achieved (regardless of blood count recovery), the dose on Day 1 of each subsequent cycle should be inotuzumab ozogamicin (genetical recombination) 0.5 mg/m^2 (body surface area). If <5% blasts in the bone marrow, the absence of peripheral blood leukemic blasts, and resolution of any

[40)] Premedication regimens to reduce infusion reaction were as follows: methylprednisolone was recommended in Study 059, while agents such as corticosteroids and antihistamine were recommended in Study ALL-1. Inotuzumab ozogamicin was tolerable when the protocols were followed; therefore, the same statement from the previous approval (for adults) was included without modification.

[41)] There are no data on the clinical usefulness of inotuzumab ozogamicin in combination with other antineoplastic agents evaluated in a clinical study in pediatric patients with relapsed or refractory CD22-positive ALL. Therefore, the same statement from the previous approval (for adults) was included without modification.

extramedullary disease are achieved, it should be considered that the patient is in remission (regardless of blood count recovery).

- Number of treatment cycles of inotuzumab ozogamicin should be as follows:
  - For patients proceeding to HSCT: due to an increased risk of post-HSCT VOD/SOS with increase in the number of treatment cycles, it is recommended that patients be treated with the fewest number of cycles needed to elicit a response to inotuzumab ozogamicin. Treatment should be discontinued by the end of Cycle 3 unless there is no choice but to continue the treatment.
  - For patients not proceeding to HSCT: up to a maximum of 6 cycles may be administered. However, any patients who do not have a response to inotuzumab ozogamicin by the end of Cycle 3 should discontinue treatment.
- The efficacy and safety of inotuzumab ozogamicin administered ≥7 cycles have not been established.
- The guidelines below should be used for dose interruption, dose reduction, or treatment discontinuation due to adverse reactions. If the dose is reduced, the dose must not be re-escalated.

Hematological toxicities

Levels prior to inotuzumab ozogamicin treatment	Action(s) taken
Absolute neutrophil count (ANC) was ≥1,000/μL	If ANC decreases at the start of Cycle 2 or subsequent cycles, interrupt administration until ANC recovers to ≥1,000/μL.
Platelet count was ≥50,000/μL*	If platelet count decreases at the start of Cycle 2 or subsequent cycles, interrupt administration until platelet count recovers to ≥50,000/μL.
ANC was <1,000/μL or platelet count was <50,000/μL*	If ANC or platelet count decreases at the start of Cycle 2 or subsequent cycles, interrupt administration until at least one of the below occurs. Stable or improved disease based on the most recent bone marrow test, and the ANC and platelet count decrease are considered to be due to the underlying disease rather than being inotuzumab ozogamicin-related adverse reactions; administration may be resumed. • ANC and platelet count recover to at least pre-inotuzumab ozogamicin treatment levels • ANC recovers to ≥1,000/μL and platelet count recovers to ≥50,000/μL

*, Platelet count used for the assessment for the start of the next cycle must be independent of blood transfusion.

Non-hematological toxicities

Adverse reaction	Action(s) taken
VOD/SOS or other severe liver toxicities	Permanently discontinue treatment.
Total bilirubin elevation >1.5 × institutional ULN or AST/ALT elevation >2.5 × institutional ULN*1	Interrupt administration until recovery of total bilirubin to ≤1.5 × institutional ULN or AST/ALT to ≤2.5 × institutional ULN prior to each dose.
Infusion reaction	Interrupt the infusion and provide appropriate medical treatment such as administration of corticosteroids, antihistamines. Depending on the severity of the infusion reaction, administration may be resumed. For severe infusion reactions, permanently discontinue treatment.
Grade ≥2*2 non-hematological toxicity	Interrupt administration until recovery to Grade 1 or pre-treatment grade levels prior to each dose.

*1, Not applicable if adverse reactions are attributed to Gilbert's disease or hemolysis.
*2, Severity grade is determined in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Dose modification criteria

Duration of dose interruption due to adverse reaction	Dose modification
<7 days	Delay the next dose within the cycle. (maintain a minimum of 6 days between doses)
≥7 days	Do not administer doses within the cycle.
≥14 days	First occurrence: decrease the dose in the next cycle by 25%. Occurrence after decreasing each dose in the next cycle by 25%: administer 2 doses in the next cycle. Occurrence after modifying to 2 doses in 1 cycle: permanently discontinue treatment.
>28 days	Consider permanent treatment discontinuation.

- Premedication with corticosteroids, antipyretic, or antihistamines should be considered to reduce infusion reaction.
- The efficacy and safety of inotuzumab ozogamicin in combination with other antineoplastic agents have not been established.

7.R.5.1 Dosage regimen of inotuzumab ozogamicin

The applicant's explanation about the rationale for selection of the dosage regimen of inotuzumab ozogamicin:
In Stratum 1A of the phase I part in Study 059, a study conducted in pediatric patients with relapsed or refractory CD22-positive ALL, the 3 divided doses of inotuzumab ozogamicin 1.8 mg/m^2/cycle was determined to be tolerable [see Section 7.1.2.1]. On the basis of this and other data, the following was selected as the dosage regimen of inotuzumab ozogamicin in the phase II part of Study 059 and Study ALL-1: the duration of treatment cycle was 21 or 22 days in Cycle 1 and 28 days in subsequent cycles. Inotuzumab ozogamicin 1.8 mg/m^2/cycle was administered intravenously in 3 divided doses on Day 1 (0.8 mg/m^2), Day 8 (0.5 mg/m^2), and Day 15 (0.5 mg/m^2) (patients who achieved remission were to receive a reduced dose of 1.5 mg/m^2/cycle in the subsequent cycles, administered in 3 divided doses).

The phase II part of Study 059 and Study ALL-1 were conducted using the above dosage regimen, and the studies demonstrated that inotuzumab ozogamicin is clinically useful [see Sections 7.R.2 and 7.R.3]; therefore, based on the dosage regimen, the proposed dosage regimen and the "Precautions Concerning Dosage and Administration" for inotuzumab ozogamicin were established.

The duration of treatment cycle (days) for inotuzumab ozogamicin treatment defined for pediatric patients is different from that for adult patients based on the following consideration:
In Study 059, in principle, the duration of treatment cycle (days) was 22 days in Cycle 1 and 28 days in subsequent cycles. The cycle can be extended up to a maximum of 42 days to provide time for remission or recovery from adverse events. In Study ALL-1, the duration of treatment cycle (days) was 21 days in Cycle 1 and 28 days in subsequent cycles. The cycle can be extended up to a maximum of 28 days in Cycle 1 and a maximum of 56 days in subsequent cycles to provide time for remission or recovery from adverse events.

In Study 059 (1.8 mg/m^2/cycle group) and Study ALL-1, the proportion of patients whose treatment cycle[42] was extended was 36.6% (15 of 41 subjects) and 50.0% (3 of 6 subjects), respectively. The remission rate results in the overall treatment period with/without treatment cycle extension in Studies 059 and ALL-1 are shown in Tables 17 and 18, respectively.

Table 17. Results of best overall response and remission rate with/without treatment cycle extension (Study 059)

Best overall response	n (%) Patients with extension of treatment cycle* N = 15	Patients without extension of treatment cycle N = 26
CR	13 (86.7)	16 (61.5)
CRp	0	1 (3.8)
CRi	1 (6.7)	2 (7.7)
Remission rate (proportion of responders CR + CRp + CRi)	14 (93.3)	19 (73.1)

*, The number of patients with extension of treatment cycle and the median treatment cycle [Min, Max] in each cycle were 15 subjects and 27.0 days [23, 33] in Cycle 1; 6 subjects and 31.0 days [29, 42] in Cycle 2; and 1 subject and 29 days in Cycle 3.

Table 18. Results of best overall response and remission rate with/without treatment cycle extension (Study ALL-1)

Best overall response	n (%) Patients with extension of treatment cycle* N = 3	Patients without extension of treatment cycle N = 3
CR	1 (33.3)	3 (100)
CRi	1 (33.3)	0
Remission rate (proportion of responders CR + CRi)	2 (66.7)	3 (100)

*, The number of patients with extension of treatment cycle and the median treatment cycle [Min, Max] in each cycle were 3 subjects and 43 days [26, 49] in Cycle 1; 3 subjects and 36 days [34, 48] in Cycle 2; and 1 subject and 41 days in Cycle 3. In 1 patient who was not able to achieve CR, Cycle 1 was 49 days and Cycle 2 was 48 days.

In Study 059, adverse events occurring at a higher incidence in patients with extension of treatment cycle than in patients without extension of treatment cycle by ≥20% were AST increased and lymphocyte count decreased,[43] both of which were non-serious and manageable. In Study ALL-1, adverse events occurring at a higher incidence in patients with extension of treatment cycle than in patients without extension of treatment cycle by ≥2 subjects were AST increased, ALT increased, skin infection, haematoma, headache, and stomatitis,[44] all of which resolved without dose reduction or interruption, and were manageable.

On the basis of the above findings, in Studies 059 and ALL-1, the efficacy and safety of inotuzumab ozogamicin in patients whose treatment cycle was extended did not tend to differ significantly from the efficacy and safety in patients whose treatment cycle was not extended; therefore, depending on the patient's condition, allowing the treatment cycle to be extended should not be a problem. The specific extension duration should

42) In Study 059, a treatment cycle of 22 days in Cycle 1 and a treatment cycle of 28 days in subsequent cycles were defined as the standard duration. In Study ALL-1, a treatment cycle of 21 days in Cycle 1 and a treatment cycle of 28 days in subsequent cycles were defined as the standard duration. If the duration exceeded the standard number of days in each cycle, it is regarded as "extension of treatment cycle." If the duration exceeded at least once during the treatment period of inotuzumab ozogamicin, the patient are included in those with extension of treatment cycle.

43) The incidence of adverse events in patients with extension of treatment cycle and those without, respectively, were as follows: AST increased, 40.0% (6 of 15 subjects) and 15.4% (4 of 26 subjects); lymphocyte count decreased 26.7% (4 of 15 subjects) and 3.8% (1 of 26 subjects). Among these cases, a causal relationship to inotuzumab ozogamicin could not be ruled out for Grade 3 AST increased (3 subjects) and Grade 3 or 4 lymphocyte count decreased (2 subjects).

44) The incidence of adverse events in patients with extension of treatment cycle and those without, respectively, were as follows: skin infection, 100% (3 of 3 subjects) and 0%; AST increased, 100% (3 of 3 subjects) and 33.3% (1 of 3 subjects); ALT increased, 100% (3 of 3 subjects) and 33.3% (1 of 3 subjects); haematoma, 66.7% (2 of 3 subjects) and 0%; headache, 66.7% (2 of 3 subjects) and 0%; stomatitis, 66.7% (2 of 3 subjects) and 0%. Among these cases, Grade 3 adverse events were skin infection, AST increased, and ALT increased (1 subject each).

be based on Study 059, which allowed an extension of up to 42 days in any cycle, taking into account the possibility that inotuzumab ozogamicin could be administered to patients in whom recovery of hematopoietic function may be delayed due to their prior HSCT.

Furthermore, based on the findings shown below, a statement concerning the number of treatment cycles, the same as that for adult patients, was included in the "Precautions Concerning Dosage and Administration" section, i.e., "a maximum of 3 cycles (for patients proceeding to HSCT) and a maximum of 6 cycles (for patients not proceeding to HSCT; patients who do not have a response to inotuzumab ozogamicin by the end of Cycle 3 should discontinue treatment)."

- In Studies ALL-1 and 059, which were conducted in accordance with the protocol "up to a maximum of 3 cycles (for patients proceeding to HSCT) and a maximum of 6 cycles (for patients not proceeding to HSCT)," in all of the patients who achieved remission, remission had been achieved by Cycle 3.
- Although no patients received ≥5 cycles in Studies ALL-1 and 059, achieving and maintaining remission as a result of inotuzumab ozogamicin treatment is clinically significant; therefore, for patients not proceeding to HSCT, it is clinically significant to provide the opportunity for treatment up to 6 cycles, equivalent to the number of cycles established for adult patients, provided that a response has been achieved by the end of Cycle 3.

PMDA's discussion:
PMDA generally accepted the applicant's explanation. It is acceptable to select the duration of treatment cycle (days) for pediatric patients based on Study 059, given that, in addition to the applicant's explanation above, the majority of patients in Studies 059 and ALL-1 whose basic treatment cycle was extended started the next cycle within 42 days, and that appropriate treatment duration is determined by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

PMDA concluded that the proposed dosage and administration and the "Precautions Concerning Dosage and Administration" section as shown below are appropriate.

Dosage and Administration

The usual dosage is inotuzumab ozogamicin (genetical recombination) 0.8 mg/m^2 (body surface area) on Day 1, 0.5 mg/m^2 (body surface area) on Day 8, and 0.5 mg/m^2 (body surface area) on Day 15, administered as an intravenous infusion over at least 1 hour, followed by a rest period. For adults, the duration of treatment cycle is 21 to 28 days in Cycle 1 and 28 days in subsequent cycles. Treatment should be repeated in cycles. For pediatric patients, the duration of treatment cycle is 21 to 42 days in Cycle 1 and 28 to 42 days in subsequent cycles. Treatment should be repeated in cycles. The number of cycles should be determined depending on whether the patient proceeds to hematopoietic stem cell transplantation. The dose should be decreased according to the patient's condition.

Precautions Concerning Dosage and Administration

- In adults, the duration of treatment cycle is, in principle, 21 days in Cycle 1, and can be extended up to 28 days if remission is achieved (regardless of blood count recovery). For pediatric patients, the duration of treatment cycle is, in principle, 21 days in Cycle 1, and 28 days in subsequent cycles. However, if remission is achieved (regardless of blood count recovery), the treatment cycle may be extended up to 42 days. If remission is achieved (regardless of blood count recovery), the dose on Day 1 of each subsequent cycle should be inotuzumab ozogamicin (genetical recombination) 0.5 mg/m^2 (body surface area). If <5% blasts in the bone marrow, the absence of peripheral blood leukemic blasts, and resolution of any extramedullary disease are achieved, it should be considered that the patient is in remission (regardless of blood count recovery).
- Number of treatment cycles of inotuzumab ozogamicin should be as follows:
  - For patients proceeding to HSCT: due to an increased risk of post-HSCT VOD/SOS with increase in the number of treatment cycles, it is recommended that patients be treated with the fewest number of cycles needed to elicit a response to inotuzumab ozogamicin. Treatment should be discontinued by the end of Cycle 3 unless there is no choice but to continue the treatment.
  - For patients not proceeding to HSCT: up to a maximum of 6 cycles may be administered. However, any patients who do not have a response to inotuzumab ozogamicin by the end of Cycle 3 should discontinue treatment.
- The efficacy and safety of inotuzumab ozogamicin administered ≥7 cycles have not been established.
- The efficacy and safety of inotuzumab ozogamicin in combination with other antineoplastic agents have not been established.
- Premedication with corticosteroids, antipyretic, or antihistamines should be considered to reduce infusion reaction.

7.R.5.2 Dose modifications of inotuzumab ozogamicin

The applicant's explanation about dose modifications of inotuzumab ozogamicin in pediatric patients with relapsed or refractory CD22-positive ALL:

At the time of previous approval (for adults), the dose modifications of inotuzumab ozogamicin specifically for (1) hematological toxicities, (2) non-hematological toxicities, and (3) the dose modification depending on duration of dose interruption due to adverse reactions have been established.

The dose modification criteria used in Studies 059 and ALL-1 were similar[45)] to those established at the time of previous approval (for adults); therefore, it was decided that the same criteria for the previous approval (for adults) should be used for pediatric patients. Since the dose modification criteria for hematological toxicities used in Study ALL-1 are identical to those established for the previous approval (for adults), which focus on

[45)] For hematological toxicities (1): the criteria at the start of the treatment cycle in Study 059 were ANC ≥500/μL and platelet count ≥50,000/μL in Cycle 2, Stratum 1A; ANC ≥500/μL and platelet count ≥30,000/μL in Cycle 3 or subsequent cycles, Stratum 1A and in Cycle 2 or subsequent cycles in the phase II part; while in the previously approved criteria (for adults) at the start of the treatment cycle they were ANC ≥1,000/μL and platelet count ≥50,000/μL, which were the same as those in Study ALL-1. For duration of dose interruption due to adverse reactions in (3): the protocol of Study ALL-1 did not specify that next dose should be omitted within the same cycle for a dose interruption duration ≥7 days within the same cycle; conversely, these criteria are included in the criteria for dose interruption for the approved indication. In Study 059, only 1 dose reduction was allowed after the occurrence of adverse events, while dose reduction was allowed up to 2 times in the criteria for dose interruption for the approved indication. The protocol of Study 059 specified the criteria considering that the study was the first clinical study in pediatric patients, and that the study was expected to enroll patients whose hematopoietic function recovery may be delayed due to prior HSCT.

safety aspects, it is considered that hematological toxicities can be managed in an appropriate manner in pediatric patients.

PMDA's discussion:
PMDA accepted the applicant's explanation and concluded that the criteria for dose interruption, dose reduction, and treatment discontinuation in the event of adverse reactions included in the "Precautions Concerning Dosage and Administration" section in the present partial change application do not need to be changed from those in the previous approval (for adults). Therefore, the proposed dose modification guidelines (shown below) for inotuzumab ozogamicin are appropriate to be followed if adverse reactions occur.

Precautions Concerning Dosage and Administration

- The guidelines below should be taken into account for dose interruption, dose reduction, or treatment discontinuation due to adverse reactions. If the dose is reduced, the dose must not be re-escalated.

Hematological toxicities

Levels prior to inotuzumab ozogamicin treatment	Action(s) taken
Absolute neutrophil count (ANC) was ≥1,000/μL	If ANC decreases at the start of Cycle 2 or subsequent cycles, interrupt administration until ANC recovers to ≥1,000/μL.
Platelet count was ≥50,000/μL*	If platelet count decreases at the start of Cycle 2 or subsequent cycles, interrupt administration until platelet count recovers to ≥50,000/μL.
ANC was <1,000/μL or platelet count was <50,000/μL*	If ANC or platelet count decreases at the start of Cycle 2 or subsequent cycles, interrupt administration until at least one of the below occurs. Stable or improved disease based on the most recent bone marrow test, and the ANC and platelet count decrease are considered to be due to the underlying disease rather than being inotuzumab ozogamicin-related adverse reactions; administration may be resumed. • ANC and platelet count recover to at least pre-inotuzumab ozogamicin treatment levels • ANC recovers to ≥1,000/μL and platelet count recovers to ≥50,000/μL

*, Platelet count used for the assessment for the start of the next cycle must be independent of blood transfusion.

Non-hematological toxicities

Adverse reaction	Action(s) taken
VOD/SOS or other severe liver toxicities	Permanently discontinue treatment.
Total bilirubin elevation >1.5 × institutional ULN or AST/ALT elevation >2.5 × institutional ULN*1	Interrupt administration until recovery of total bilirubin to ≤1.5 × institutional ULN or AST/ALT to ≤2.5 × institutional ULN prior to each dose.
Infusion reaction	Interrupt the infusion and provide appropriate medical treatment such as administration of corticosteroids, antihistamines. Depending on the severity of the infusion reaction, administration may be resumed. For severe infusion reactions, permanently discontinue treatment.
Grade ≥2*2 non-hematological toxicity	Interrupt administration until recovery to Grade 1 or pre-treatment grade levels prior to each dose.

*1, Not applicable if adverse reactions are attributed to Gilbert's disease or hemolysis.
*2, Severity grade is determined in accordance with the CTCAE version 3.0.

Dose modification criteria

Duration of dose interruption due to adverse reaction	Dose modification
<7 days	Delay the next dose within the cycle. (maintain a minimum of 6 days between doses)
≥7 days	Do not administer doses within the cycle.
≥14 days	First occurrence: decrease the dose in the next cycle by 25%. Occurrence after decreasing each dose in the next cycle by 25%: administer 2 doses in the next cycle. Occurrence after modifying to 2 doses in 1 cycle: permanently discontinue treatment.
>28 days	Consider permanent treatment discontinuation.

7.R.6 Post-marketing investigations

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

Although no new safety concerns were identified in the present application for partial change [see Section 7.R.3], given the limited availability of safety data in Japanese pediatric patients with relapsed or refractory CD22-positive ALL who received inotuzumab ozogamicin, the applicant plans to conduct a post-marketing surveillance to investigate the safety and other aspects of inotuzumab ozogamicin in clinical practice in post-marketing settings.

The proposed safety specification for the survey are liver disorder, including VOD/SOS, myelosuppression, infections, haemorrhage, TLS, infusion reaction, pancreatitis, QTc interval prolongation, inflammatory gastrointestinal events, ILD, and reproductive and developmental toxicity, which are the same as those in the ongoing post-marketing surveillance in adult patients with relapsed or refractory CD22-positive ALL. In addition, in the proposed survey, the applicant plans to monitor the incidence of the safety specification, and investigate the risk factors for VOD/SOS.

A planned sample size of 29 patients was selected for the survey based on feasibility and taking into account the number of Japanese pediatric patients with relapsed or refractory CD22-positive ALL, survey period, and other factors.

A follow-up period from the start of treatment up to 28 days after the last dose of inotuzumab ozogamicin was proposed for the survey, taking into account the onset time of the events included in the safety specification reported in Studies 059 and ALL-1. However, a follow-up period of 52 weeks from the start of inotuzumab ozogamicin treatment was selected for VOD/SOS events. These are serious events and were shown to be related to inotuzumab ozogamicin treatment. A period of 52 weeks was set taking into account the reported onset time in Study 1022.

PMDA's discussion:

Due to the limited availability of safety data in Japanese pediatric patients with relapsed or refractory CD22-positive ALL who received inotuzumab ozogamicin, the applicant should conduct a post-marketing surveillance in the patient population to collect the safety data of inotuzumab ozogamicin in clinical practice.

The safety specification and the follow-up period for the survey proposed by the applicant are acceptable. However, while the planned sample size of 29 patients may be acceptable based on the feasibility of the target sample size given that the patients with the condition are rare, it is not sufficient to explore the risk factors for VOD/SOS. Therefore, PMDA concluded that the applicant should revise the plan to register as many patients as possible during the enrollment period to allow a larger sample size to be evaluated.

7.2 Adverse events and other findings observed in clinical studies

The following section discusses clinical study data submitted for the safety evaluation, except for those that resulted in death, which are discussed in Section "7.1 Evaluation data."

7.2.1 Japanese phase I study (Study ALL-1)

Adverse events occurred in 6 of 6 subjects (100%). Adverse events for which a causal relationship to inotuzumab ozogamicin could not be ruled out occurred in all 6 subjects. Adverse events occurring in ≥20% of subjects were ALT increased (4 subjects, 66.7%), AST increased (4 subjects, 66.7%), vomiting (3 subjects, 50.0%), skin infection (3 subjects, 50.0%), stomatitis (2 subjects, 33.3%), pyrexia (2 subjects, 33.3%), hypokalaemia (2 subjects, 33.3%), headache (2 subjects, 33.3%), and haematoma (2 subjects, 33.3%).

Serious adverse events occurred in 3 of 6 subjects (50.0%). These were pyrexia, veno-occlusive liver disease, and ALL in 1 subject each (16.7%). A causal relationship to inotuzumab ozogamicin could not be ruled out for veno-occlusive liver disease (1 subject).

There was 1 adverse event (ALL) leading to treatment discontinuation of inotuzumab ozogamicin (1 subject, 16.7%), and a causal relationship to inotuzumab ozogamicin was denied for the event.

Adverse events leading to dose interruption of inotuzumab ozogamicin occurred in 3 of 6 subjects (50.0%). These were ALT increased (2 subjects, 33.3%), AST increased (2 subjects, 33.3%), blood bilirubin increased (1 subject, 16.7%), and blood ALP increased (1 subject, 16.7%). A causal relationship to inotuzumab ozogamicin could not be ruled out for any of these events.

7.2.2 Foreign phase I/II study (Study ITCC-059)

Adverse events occurred in 12 of 12 subjects (100%) in the 1.4 mg/m^2/cycle group in Stratum 1A of the phase I part (hereinafter referred to as the 1.4 mg/m^2/cycle group), 13 of 13 subjects (100%) in the 1.8 mg/m^2/cycle group in Stratum 1A of the phase I part (hereinafter referred to as the 1.8 mg/m^2/cycle group), and 28 of 28 subjects (100%) in the phase II part. Adverse events for which a causal relationship to inotuzumab ozogamicin could not be ruled out occurred in 8 of 12 subjects (66.7%) in the 1.4 mg/m^2/cycle group, all subjects in the 1.8 mg/m^2/cycle group, and 25 of 28 subjects (89.3%) in the phase II part. Table 19 shows adverse events occurring in ≥20% of subjects.

Table 19. Adverse events occurring in ≥20% of subjects in any group

SOC PT (MedDRA ver.25.1)	n (%)					
	Stratum 1A				Phase II part N = 28	
	1.4 mg/m^2/cycle N = 12		1.8 mg/m^2/cycle N = 13			
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	12 (100)	11 (91.7)	13 (100)	13 (100)	28 (100)	26 (92.9)
Blood and lymphatic system disorders						
Anaemia	6 (50.0)	5 (41.7)	6 (46.2)	6 (46.2)	12 (42.9)	9 (32.1)
FN	3 (25.0)	3 (25.0)	5 (38.5)	5 (38.5)	7 (25.0)	7 (25.0)
Eye disorders						
Periorbital oedema	3 (25.0)	0	0	0	0	0
Gastrointestinal disorders						
Abdominal pain	3 (25.0)	0	3 (23.1)	1 (7.7)	2 (7.1)	0
Constipation	2 (16.7)	0	5 (38.5)	0	3 (10.7)	1 (3.6)
Diarrhoea	1 (8.3)	0	4 (30.8)	0	1 (3.6)	0
Mouth haemorrhage	3 (25.0)	0	2 (15.4)	0	1 (3.6)	0
Nausea	3 (25.0)	0	5 (38.5)	0	9 (32.1)	0
Oral pain	3 (25.0)	0	0	0	0	0
Vomiting	5 (41.7)	0	7 (53.8)	0	12 (42.9)	1 (3.6)
General disorders and administration site conditions						
Face oedema	0	0	4 (30.8)	0	0	0
Fatigue	2 (16.7)	0	4 (30.8)	0	2 (7.1)	0
Oedema peripheral	2 (16.7)	0	3 (23.1)	0	0	0
Pain	1 (8.3)	0	3 (23.1)	0	4 (14.3)	1 (3.6)
Pyrexia	7 (58.3)	0	6 (46.2)	1 (7.7)	13 (46.4)	1 (3.6)
Investigations						
ALT increased	2 (16.7)	2 (16.7)	1 (7.7)	1 (7.7)	7 (25.0)	5 (17.9)
AST increased	2 (16.7)	2 (16.7)	2 (15.4)	1 (7.7)	8 (28.6)	6 (21.4)
GGT increased	2 (16.7)	2 (16.7)	4 (30.8)	3 (23.1)	3 (10.7)	1 (3.6)
Neutrophil count decreased	6 (50.0)	6 (50.0)	5 (38.5)	5 (38.5)	10 (35.7)	10 (35.7)
Platelet count decreased	7 (58.3)	7 (58.3)	8 (61.5)	6 (46.2)	12 (42.9)	11 (39.3)
White blood cell count decreased	3 (25.0)	3 (25.0)	4 (30.8)	4 (30.8)	10 (35.7)	8 (28.6)
Metabolism and nutrition disorders						
Hypokalaemia	2 (16.7)	1 (8.3)	4 (30.8)	3 (23.1)	3 (10.7)	2 (7.1)
Decreased appetite	2 (16.7)	1 (8.3)	3 (23.1)	1 (7.7)	1 (3.6)	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	5 (41.7)	1 (8.3)	3 (23.1)	0	2 (7.1)	0
Nervous system disorders						
Headache	4 (33.3)	0	2 (15.4)	0	5 (17.9)	0
Respiratory, thoracic and mediastinal disorders						
Cough	3 (25.0)	0	4 (30.8)	0	2 (7.1)	0

Serious adverse events occurred in 8 of 12 subjects (66.7%) in the 1.4 mg/m^2/cycle group, 8 of 13 subjects (61.5%) in the 1.8 mg/m^2/cycle group, and 17 of 28 subjects (60.7%) in the phase II part. The reported serious adverse events were pyrexia (3 subjects, 25.0%), FN (2 subjects, 16.7%), disease progression (1 subject, 8.3%), veno-occlusive liver disease (1 subject, 8.3%), encephalitis (1 subject, 8.3%), sepsis (1 subject, 8.3%), sinusitis (1 subject, 8.3%), and fracture (1 subject, 8.3%) in the 1.4 mg/m^2/cycle group; FN (2 subjects, 15.4%), diarrhoea (1 subject, 7.7%), veno-occlusive liver disease (1 subject, 7.7%), graft versus host disease in gastrointestinal tract (1 subject, 7.7%), sepsis (1 subject, 7.7%), pneumonia fungal (1 subject, 7.7%), respiratory tract infection (1 subject, 7.7%), device related infection (1 subject, 7.7%), device related sepsis (1 subject, 7.7%), blood bilirubin increased (1 subject, 7.7%), neutrophil count decreased (1 subject, 7.7%), and haemorrhage intracranial (1 subject, 7.7%) in the 1.8 mg/m^2/cycle group; and FN (5 subjects, 17.9%), veno-

occlusive liver disease (3 subjects, 10.7%), venoocclusive disease (3 subjects, 10.7%), sepsis (2 subjects, 7.1%), pain (1 subject, 3.6%), multiple organ dysfunction syndrome (1 subject, 3.6%), upper respiratory tract infection (1 subject, 3.6%), device related infection (1 subject, 3.6%), neoplasm progression (1 subject, 3.6%), encephalopathy (1 subject, 3.6%), haematuria (1 subject, 3.6%), and rash maculo-papular (1 subject, 3.6%) in the phase II part. Among these serious adverse events, a causal relationship to inotuzumab ozogamicin could not be ruled out for the following: FN, veno-occlusive liver disease, and sinusitis (1 subject each) in the 1.4 mg/m^2/cycle group; FN, veno-occlusive liver disease, sepsis, pneumonia fungal, blood bilirubin increased, neutrophil count decreased, and haemorrhage intracranial (1 subject each) in the 1.8 mg/m^2/cycle group; and FN (3 subjects), venoocclusive disease (3 subjects), veno-occlusive liver disease (2 subjects), and pain (1 subject) in the phase II part.

Adverse events leading to treatment discontinuation of inotuzumab ozogamicin occurred in 2 of 12 subjects (16.7%) in the 1.4 mg/m^2/cycle group, 6 of 13 subjects (46.2%) in the 1.8 mg/m^2/cycle group, and 4 of 28 subjects (14.3%) in the phase II part. The reported adverse events leading to treatment discontinuation of inotuzumab ozogamicin were encephalitis (1 subject, 8.3%) and ALT increased (1 subject, 8.3%) in the 1.4 mg/m^2/cycle group; platelet count decreased (2 subjects, 15.4%), sinus tachycardia (1 subject, 7.7%), hepatomegaly (1 subject, 7.7%), fungal infection (1 subject, 7.7%), sepsis (1 subject, 7.7%), ALT increased (1 subject, 7.7%), blood bilirubin increased (1 subject, 7.7%), GGT increased (1 subject, 7.7%), weight increased (1 subject, 7.7%), haemorrhage intracranial (1 subject, 7.7%), and pulmonary oedema (1 subject, 7.7%) in the 1.8 mg/m^2/cycle group; and disease progression (1 subject, 3.6%), multiple organ dysfunction syndrome (1 subject, 3.6%), ALT increased (1 subject, 3.6%), AST increased (1 subject, 3.6%), and venoocclusive disease (1 subject, 3.6%) in the phase II part. Among these events, a causal relationship to inotuzumab ozogamicin could not be ruled out for the following: ALT increased (1 subject) in the 1.4 mg/m^2/cycle group; platelet count decreased (2 subjects), sinus tachycardia, hepatomegaly, fungal infection, sepsis, ALT increased, blood bilirubin increased, GGT increased, weight increased, haemorrhage intracranial, and pulmonary oedema (1 subject each) in the 1.8 mg/m^2/cycle group; and ALT increased, AST increased, and veno-occlusive liver disease (1 subject each) in the phase II part.

Adverse events leading to dose interruption of inotuzumab ozogamicin occurred in 1 of 12 subjects (8.3%) in the 1.4 mg/m^2/cycle group; 0 of 13 subjects (0.0%) in the 1.8 mg/m^2/cycle group; and 5 of 28 subjects (17.9%) in the phase II part. The reported adverse events leading to dose interruption were headache (1 subject, 8.3%) in the 1.4 mg/m^2/cycle group; ALT increased (4 subjects, 14.3%), AST increased (2 subjects, 7.1%), and FN (1 subject, 3.6%) in the phase II part. Among these events, a causal relationship to inotuzumab ozogamicin could not be ruled out for ALT increased (4 subjects), AST increased (2 subjects), and FN (1 subject) in the phase II part.

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

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

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

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

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

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

On the basis of the data submitted, PMDA has concluded that inotuzumab ozogamicin has a certain level of efficacy in the treatment of pediatric patients with relapsed or refractory CD22-positive ALL, and that inotuzumab ozogamicin has acceptable safety in view of its benefit. Inotuzumab ozogamicin is considered to be a clinically significant treatment option for pediatric patients with relapsed or refractory CD22-positive ALL. PMDA considers that the dosage and administration, and post-marketing investigations require further discussion.

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

Review Report (2)

February 5, 2024

Product Submitted for Approval

Brand Name	Besponsa Injection 1 mg
Non-proprietary Name	Inotuzumab Ozogamicin (Genetical Recombination)
Applicant	Pfizer Japan Inc.
Date of Application	July 27, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy

In view of the discussions presented in Section "7.R.2 Efficacy" in the Review Report (1), in the phase II part of the foreign phase I/II study (Study 059) in pediatric patients with relapsed or refractory CD22-positive ALL, the remission rate for the overall treatment period as assessed by the investigator with the 90% confidence interval, the primary efficacy endpoint, was 78.6% [62.0%, 90.2%] (22 of 28 subjects), indicating that the lower limit of the 90% confidence interval exceeded the prespecified threshold (30%). PMDA concluded that the data including the above results demonstrated a certain level of efficacy of inotuzumab ozogamicin in pediatric patients with relapsed or refractory CD22-positiveALL.

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

1.2 Safety

In view of the discussions in Section "7.R.3 Safety" in Review Report (1), PMDA concluded that adverse events requiring particular caution when administering inotuzumab ozogamicin corresponded to the adverse events of special interest in the previous review of the application for the approved indication (for adults): liver disorder, including VOD/SOS, myelosuppression, infections, haemorrhage, TLS, infusion reaction, pancreatitis, QTc interval prolongation, inflammatory gastrointestinal events, and ILD.

Although the use of inotuzumab ozogamicin requires particular caution for the adverse events mentioned above, PMDA concluded that inotuzumab ozogamicin should be tolerable provided that appropriate steps including monitoring and control of adverse events are taken by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

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

1.3 Clinical positioning and indication

In view of the discussions in Section "7.R.4 Clinical positioning and indication" of Review Report (1), PMDA concluded that the indication for inotuzumab ozogamicin requires no revision from the previously approved indication, given that inotuzumab ozogamicin can be positioned as a treatment option for pediatric patients with relapsed or refractory CD22-positive ALL. Taking into account the risk of developing post-HSCT VOD/SOS, the use of inotuzumab ozogamicin in pediatric patients proceeding to HSCT should be determined carefully, after a thorough consideration of other treatment options, and the cautionary statement shown below should be included in the "Precautions Concerning Indication" section, equivalent to those implemented for adult patients in the previous approval.

Precautions Concerning Indication

- Inotuzumab ozogamicin should be used in patients whose presence of CD22 antigen expression was confirmed by examinations such as flow cytometry.
- Whether a patient is appropriate to receive treatment with inotuzumab ozogamicin should be decided after becoming completely familiar with the details of the "Clinical Studies" section regarding prior treatment and other data on patients enrolled in clinical studies, and gaining a thorough understanding of the efficacy and safety of inotuzumab ozogamicin.
- For patients proceeding to hematopoietic stem cell transplantation, the use of inotuzumab ozogamicin should be determined carefully after thoroughly considering treatment options other than inotuzumab ozogamicin. In adults, data have suggested that the magnitude of impact of inotuzumab ozogamicin on post-hematopoietic stem cell transplantation overall survival may not be similar to that obtained with existing chemotherapies.

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

1.4 Dosage and administration

In view of the discussions in Section "7.R.5 Dosage and administration" in Review Report (1), PMDA concluded that the dosage and administration and the "Precautions Concerning Dosage and Administration" section should be as follows, as proposed by the applicant:

Dosage and Administration

The usual dosage is inotuzumab ozogamicin (genetical recombination) 0.8 mg/m^2 (body surface area) on Day 1, 0.5 mg/m^2 (body surface area) on Day 8, and 0.5 mg/m^2 (body surface area) on Day 15, administered as an

intravenous infusion over at least 1 hour, followed by a rest period. For adults, the duration of treatment cycle is 21 to 28 days in Cycle 1 and 28 days in subsequent cycles. Treatment should be repeated in cycles. For pediatric patients, the duration of treatment cycle is 21 to 42 days in Cycle 1 and 28 to 42 days in subsequent cycles. Treatment should be repeated in cycles. The number of cycles should be determined depending on whether the patient proceeds to hematopoietic stem cell transplantation. The dose should be decreased according to the patient's condition.

Precautions Concerning Dosage and Administration

- In adults, the duration of treatment cycle is, in principle, 21 days in Cycle 1, and can be extended up to 28 days if remission is achieved (regardless of blood count recovery). For pediatric patients, the duration of treatment cycle is, in principle, 21 days in Cycle 1, and 28 days in subsequent cycles. However, if remission is achieved (regardless of blood count recovery), the treatment cycle may be extended up to 42 days. If remission is achieved (regardless of blood count recovery), the dose on Day 1 of each subsequent cycle should be inotuzumab ozogamicin (genetical recombination) 0.5 mg/m^2 (body surface area). If <5% blasts in the bone marrow, the absence of peripheral blood leukemic blasts, and resolution of any extramedullary disease are achieved, it should be considered that the patient is in remission (regardless of blood count recovery).
- Number of treatment cycles of inotuzumab ozogamicin should be as follows:
  - For patients proceeding to HSCT: due to an increased risk of post-HSCT VOD/SOS with increase in the number of treatment cycles, it is recommended that patients be treated with the fewest number of cycles needed to elicit a response to inotuzumab ozogamicin. Treatment should be discontinued by the end of Cycle 3 unless there is no choice but to continue the treatment.
  - For patients not proceeding to HSCT: up to a maximum of 6 cycles may be administered. However, any patients who do not have a response to inotuzumab ozogamicin by the end of Cycle 3 should discontinue treatment.
- The efficacy and safety of inotuzumab ozogamicin administered ≥7 cycles have not been established.
- The guidelines below should be used for dose interruption, dose reduction, or treatment discontinuation due to adverse reactions. If the dose is reduced, the dose must not be re-escalated.

Hematological toxicities

Levels prior to inotuzumab ozogamicin treatment	Action(s) taken
Absolute neutrophil count (ANC) was ≥1,000/μL	If ANC decreases at the start of Cycle 2 or subsequent cycles, interrupt administration until ANC recovers to ≥1,000/μL.
Platelet count was ≥50,000/μL*	If platelet count decreases at the start of Cycle 2 or subsequent cycles, interrupt administration until platelet count recovers to ≥50,000/μL.
ANC was <1,000/μL or platelet count was <50,000/μL*	If ANC or platelet count decreases at the start of Cycle 2 or subsequent cycles, interrupt administration until at least one of the below occurs. Stable or improved disease based on the most recent bone marrow test, and the ANC and platelet count decrease are considered to be due to the underlying disease rather than being inotuzumab ozogamicin-related adverse reactions; administration may be resumed. • ANC and platelet count recover to at least pre-inotuzumab ozogamicin treatment levels • ANC recovers to ≥1,000/μL and platelet count recovers to ≥50,000/μL

*, Platelet count used for the assessment for the start of the next cycle must be independent of blood transfusion.

Non-hematological toxicities

Adverse reaction	Action(s) taken
VOD/SOS or other severe liver toxicities	Permanently discontinue treatment.
Total bilirubin elevation >1.5 × institutional ULN or AST/ALT elevation >2.5 × institutional ULN[*1]	Interrupt administration until recovery of total bilirubin to ≤1.5 × institutional ULN or AST/ALT to ≤2.5 × institutional ULN prior to each dose.
Infusion reaction	Interrupt the infusion and provide appropriate medical treatment such as administration of corticosteroids, antihistamines. Depending on the severity of the infusion reaction, administration may be resumed. For severe infusion reactions, permanently discontinue treatment.
Grade ≥2[*2] non-hematological toxicity	Interrupt administration until recovery to Grade 1 or pre-treatment grade levels prior to each dose.

*1, Not applicable if adverse reactions are attributed to Gilbert's disease or hemolysis.
*2, Severity grade is determined in accordance with the CTCAE version 3.0.

Dose modification criteria

Duration of dose interruption due to adverse reaction	Dose modification
<7 days	Delay the next dose within the cycle. (maintain a minimum of 6 days between doses)
≥7 days	Do not administer doses within the cycle.
≥14 days	First occurrence: decrease the dose in the next cycle by 25%. Occurrence after decreasing each dose in the next cycle by 25%: administer 2 doses in the next cycle. Occurrence after modifying to 2 doses in 1 cycle: permanently discontinue treatment.
>28 days	Consider permanent treatment discontinuation.

- Premedication with corticosteroids, antipyretic, or antihistamines should be considered to reduce infusion reaction.
- The efficacy and safety of inotuzumab ozogamicin in combination with other antineoplastic agents have not been established.

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

1.5 Risk management plan (draft)

The applicant has planned to conduct post-marketing surveillance in pediatric patients with relapsed or refractory CD22-positive ALL who will have received inotuzumab ozogamicin. The objective is to investigate the safety and other aspects of inotuzumab ozogamicin in clinical practice in post-marketing settings. The planned sample size is 29 patients, with a follow-up period for VOD/SOS of 52 weeks from the start of inotuzumab ozogamicin treatment, and a follow-up period from the start of treatment up to 28 days after the last dose for other adverse events included in the safety specification.

In view of the discussions in Section "7.R.6 Post-marketing investigations" in Review Report (1), PMDA concluded that a post-marketing surveillance should be conducted in Japanese pediatric patients with relapsed or refractory CD22-positive ALL, and information including the safety data so obtained should be provided to healthcare professionals in an appropriate manner. However, while the planned sample size of 29 patients is acceptable given that the patients with the condition are rare, it is not sufficient to explore the risk factors for VOD/SOS. Therefore, PMDA concluded that the applicant should revise the plan to register as many patients as possible during the enrollment period to allow a larger sample size to be evaluated.

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

On the basis of the above discussion, PMDA instructed the applicant to re-examine the post-marketing surveillance plan. The applicant's response:

- After the target sample size is achieved, registration of patients will be continued throughout the enrollment period in order to enroll as many participants as possible.

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for inotuzumab ozogamicin should include the safety specification presented in Table 20, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities presented in Tables 21 and 22, respectively.

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

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Liver disorder, including VOD/SOS • Myelosuppression • Infections • Haemorrhage • TLS • Infusion reaction • Pancreatitis	• QTc interval prolongation • Inflammatory gastrointestinal events • ILD • Reproductive and developmental toxicity	None
Efficacy specification		
None		

No changes in the present partial change application

Table 21. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Use-results survey (all-case surveillance) in adult patients with relapsed or refractory CD22-positive ALL • Use-results survey in pediatric patients with relapsed or refractory CD22-positive ALL	None	• Organize and disseminate information materials for healthcare professionals

Underlined activities are to be implemented for the new dosage and administration

Table 22. Outline of use-results survey (draft)

Objective	To evaluate the safety and other aspects in clinical practice in post-marketing settings
Survey method	Central registration
Population	Japanese pediatric patients with relapsed or refractory CD22-positive ALL
Observation period	VOD/SOS: for 52 weeks after the start of inotuzumab ozogamicin treatment Other events: from the start of treatment up to 28 days after the end of treatment
Planned sample size	29 patients
Main survey items	Safety specification: liver disorder, including VOD/SOS, myelosuppression, infections, haemorrhage, TLS, infusion reaction, pancreatitis, QTc interval prolongation, inflammatory gastrointestinal events, ILD, and reproductive and developmental toxicity Other main survey items: patient characteristics (e.g., sex, age, comorbidities, medical history, prior treatment), inotuzumab ozogamicin treatment status, HSCT after inotuzumab ozogamicin treatment, adverse events

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

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

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

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

The new drug application data (CTD 5.3.5.2.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, it was confirmed that the study was generally conducted in compliance with GCP, and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following issues at some study sites. Although the issues had no significant impact on the overall assessment of the studies, the heads of the relevant medical institutions were notified of these issues as findings requiring improvement:

Findings requiring corrective action

Study sites

- The heads of the relevant medical institutions had received the monitoring reports stipulated in the provisions of Article 26-8, paragraph 2 of the Ministerial Ordinance on Good Clinical Practice (GCP) for Drugs, or audit reports stipulated in the provisions of Article 26-9, paragraph 3 of the Ministerial Ordinance on GCP; however, they did not seek the Institutional Review Board for its opinion as to whether the trial had been or was being conducted in an appropriate manner at the sites.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that product may be approved after modifying the proposed dosage and administration as shown below, with the following approval conditions, provided that cautionary statements are included in the package insert and information on the proper use of the product is provided in an appropriate manner after the product launch, and that inotuzumab ozogamicin is used in

compliance with the proper use guidelines under the supervision of a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies at a medical institution capable of providing adequate emergency medical care. While the product has been designated as an orphan drug for the intended indication of "relapsed or refractory acute lymphoblastic leukemia," the product has been used in Japan since its approval in January 2018 in the treatment of relapsed or refractory CD22-positive ALL in adult patients, and therefore a 10-year use-results survey is not necessary. Accordingly, the re-examination period for the product should be 6 years and 1 day, in accordance with "at least 6 years and not exceeding 10 years from the date of the approval" in the provisions of Article 14-4, paragraph (1), item (i), (a) of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.

Indication (no change)
Relapsed or refractory CD22-positive acute lymphoblastic leukemia

Dosage and Administration (Underline denotes additions. Strikethrough denotes deletions.)
The usual ~~adult~~ dosage is inotuzumab ozogamicin (genetical recombination) 0.8 mg/m^2 (body surface area) on Day 1, 0.5 mg/m^2 (body surface area) on Day 8, and 0.5 mg/m^2 (body surface area) on Day 15, administered as an intravenous infusion over at least 1 hour, followed by a rest period. For adults, the duration of treatment cycle is 21 to 28 days in Cycle 1 and 28 days in subsequent cycles. Treatment should be repeated in cycles. For pediatric patients, the duration of treatment cycle is 21 to 42 days in Cycle 1 and 28 to 42 days in subsequent cycles. Treatment should be repeated in cycles. The number of cycles should be determined depending on whether the patient proceeds to hematopoietic stem cell transplantation. The dose should be decreased according to the patient's condition.

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

Warning (No change)
1. Inotuzumab ozogamicin should be administered only to patients assessed appropriate to receive treatment under the supervision of a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies at a medical institution capable of providing adequate emergency medical care. Prior to the start of treatment, the efficacy and risk must be thoroughly explained to the patients and their families, and treatment can be started after informed consent is obtained.
2. Liver disorder, including veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) may occur, and fatal cases have been reported. Perform liver function tests on a regular basis and monitor the patient's condition closely for any signs and symptoms of liver disorder, including VOD/SOS.

Contraindication (no change)
Patients with history of hypersensitivity to any components of Besponsa

Precautions Concerning Indications (Underline denotes additions. Strikethrough denotes deletions.)

1. Inotuzumab ozogamicin should be used in patients whose presence of CD22 antigen expression was confirmed by examinations such as flow cytometry.
2. Whether a patient is appropriate to receive treatment with inotuzumab ozogamicin should be decided after becoming completely familiar with the details of the "17. Clinical Studies" section regarding prior treatment and other data on patients enrolled in clinical studies, and gaining a thorough understanding of the efficacy and safety of inotuzumab ozogamicin.
3. ~~Data have suggested that the magnitude of impact of inotuzumab ozogamicin on post-hematopoietic stem cell transplantation (HSCT) overall survival may not be similar to that obtained with existing chemotherapies.~~ For patients proceeding to hematopoietic stem cell transplantation (HSCT), the use of inotuzumab ozogamicin should be determined carefully after thoroughly considering treatment options other than inotuzumab ozogamicin. In adults, data have suggested that the magnitude of impact of inotuzumab ozogamicin on post-HSCT overall survival may not be similar to that obtained with existing chemotherapies.

Precautions Concerning Dosage and Administration (Underline denotes additions.)

1. In adults, the duration of treatment cycle is, in principle, 21 days in Cycle 1, and can be extended up to 28 days if remission is achieved (regardless of blood count recovery). For pediatric patients, the duration of treatment cycle is, in principle, 21 days in Cycle 1, and 28 days in subsequent cycles. However, if remission is achieved (regardless of blood count recovery), the treatment cycle may be extended up to 42 days. If remission is achieved (regardless of blood count recovery), the dose on Day 1 of each subsequent cycle should be inotuzumab ozogamicin (genetical recombination) 0.5 mg/m^2 (body surface area). If <5% blasts in the bone marrow, the absence of peripheral blood leukemic blasts, and resolution of any extramedullary disease are achieved, it should be considered that the patient is in remission (regardless of blood count recovery).
2. Number of treatment cycles of inotuzumab ozogamicin should be as follows:
   - For patients proceeding to HSCT: due to an increased risk of post-HSCT VOD/SOS with increase in the number of treatment cycles, it is recommended that patients be treated with the fewest number of cycles needed to elicit a response to inotuzumab ozogamicin. Treatment should be discontinued by the end of Cycle 3 unless there is no choice but to continue the treatment.
   - For patients not proceeding to HSCT: up to a maximum of 6 cycles may be administered. However, any patients who do not have a response to inotuzumab ozogamicin by the end of Cycle 3 should discontinue treatment.
3. The efficacy and safety of inotuzumab ozogamicin administered ≥7 cycles have not been established.
4. The guidelines below should be used for dose interruption, dose reduction, or treatment discontinuation due to adverse reactions. If the dose is reduced, the dose must not be re-escalated.

Hematological toxicities

Levels prior to inotuzumab ozogamicin treatment	Action(s) taken
Absolute neutrophil count (ANC) was ≥1,000/μL	If ANC decreases at the start of Cycle 2 or subsequent cycles, interrupt administration until ANC recovers to ≥1,000/μL.
Platelet count was ≥50,000/μL*	If platelet count decreases at the start of Cycle 2 or subsequent cycles, interrupt administration until platelet count recovers to ≥50,000/μL.
ANC was <1,000/μL or platelet count was <50,000/μL*	If ANC or platelet count decreases at the start of Cycle 2 or subsequent cycles, interrupt administration until at least one of the below occurs. Stable or improved disease based on the most recent bone marrow test, and the ANC and platelet count decrease are considered to be due to the underlying disease rather than being inotuzumab ozogamicin-related adverse reactions; administration may be resumed. • ANC and platelet count recover to at least pre-inotuzumab ozogamicin treatment levels • ANC recovers to ≥1,000/μL and platelet count recovers to ≥50,000/μL

*, Platelet count used for the assessment for the start of the next cycle must be independent of blood transfusion.

Non-hematological toxicities

Adverse reaction	Action(s) taken
VOD/SOS or other severe liver toxicities	Permanently discontinue treatment.
Total bilirubin elevation >1.5 × institutional ULN or AST/ALT elevation >2.5 × institutional ULN*1	Interrupt administration until recovery of total bilirubin to ≤1.5 × institutional ULN or AST/ALT to ≤2.5 × institutional ULN prior to each dose.
Infusion reaction	Interrupt the infusion and provide appropriate medical treatment such as administration of corticosteroids, antihistamines. Depending on the severity of the infusion reaction, administration may be resumed. For severe infusion reactions, permanently discontinue treatment.
Grade ≥2*2 non-hematological toxicity	Interrupt administration until recovery to Grade 1 or pre-treatment grade levels prior to each dose.

*1, Not applicable if adverse reactions are attributed to Gilbert's disease or hemolysis.
*2, Severity grade is determined in accordance with the CTCAE version 3.0.

Dose modification criteria

Duration of dose interruption due to adverse reaction	Dose modification
<7 days	Delay the next dose within the cycle. (maintain a minimum of 6 days between doses)
≥7 days	Do not administer doses within the cycle.
≥14 days	First occurrence: decrease the dose in the next cycle by 25%. Occurrence after decreasing each dose in the next cycle by 25%: administer 2 doses in the next cycle. Occurrence after modifying to 2 doses in 1 cycle: permanently discontinue treatment.
>28 days	Consider permanent treatment discontinuation.

5. Premedication with corticosteroids, antipyretic, or antihistamines should be considered to reduce infusion reaction.
6. The efficacy and safety of inotuzumab ozogamicin in combination with other antineoplastic agents have not been established.

Appendix

List of Abbreviations

ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
Application	application for marketing approval
AST	aspartate aminotransferase
Blinatumomab	Blinatumomab (genetical recombination)
CAR-T cell	Chimeric antigen receptor T-cell
CD	cluster of differentiation
CI	confidence interval
CR	complete remission
CRi	complete remission without hematologic recovery
CRp	complete remission without platelet recovery
DLT	dose limiting toxicity
FN	febrile neutropenia
GGT	γ-glutamyl transferase
GVHD	graft versus host disease
HSCT	Allogeneic hematopoietic stem cell transplantation
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH E11 Guidelines	Clinical Investigation of Medicinal Products in the Pediatric Population (PMSB/ELD Notification No. 1334 of the Evaluating and Licensing Division, Pharmaceutical and Medical Safety Bureau, Ministry of Health and Welfare, dated December 15, 2000)
ILD	interstitial lung disease
Imatinib	Imatinib mesilate
Inotuzumab ozogamicin	Inotuzumab ozogamicin (genetical recombination)
k_{des}	decay coefficient associated with time-dependent clearance
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCCN	National Comprehensive Cancer Network
NCCN Guidelines (pediatric ALL)	NCCN Clinical Practice Guidelines in Oncology, Pediatric Acute Lymphoblastic Leukemia
NHL	non-Hodgkin's lymphoma
OS	overall survival
Partial change application	Application for partial change
PD	progressive disease
Ph	Philadelphia chromosome
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial remission
Proportion of responders CR + CRi	proportion of patients achieving CR or CRi
Proportion of responders CR + CRp + CRi	proportion of patients achieving CR, CRp, or CRi
PT	preferred term
QTc	QT interval corrected
RQ-PCR	real-time quantitative reverse transcription polymerase chain reaction
SD	stable disease

SMQ	standardised MedDRA queries
SOC	system organ class
Study 059	Study ITCC-059
Study 1022	Study B1931022
Study ALL-1	Study INO-Ped-ALL-1
TBI	total body irradiation
TKI	tyrosine kinase inhibitor
TLS	tumor lysis syndrome
ULN	upper limit of normal
VOD/SOS	veno-occlusive disease/sinusoidal obstruction syndrome