Report on the Deliberation Results

November 12, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Uplizna for Intravenous Infusion 100 mg
Non-proprietary Name	Inebilizumab (Genetical Recombination) (JAN*)
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	March 19, 2025

Results of Deliberation

In its meeting held on October 30, 2025, the First 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 Council.

The re-examination period is 10 years.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

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

Review Report

October 15, 2025
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	Uplizna for Intravenous Infusion 100 mg
Non-proprietary Name	Inebilizumab (Genetical Recombination)
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	March 19, 2025
Dosage Form/Strength	Injectable solution containing 100 mg of Inebilizumab (Genetical Recombination) per vial (10 mL)
Application Classification	Prescription drug, (4) Drug with a new indication
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 647 of 2024 [*R6 yaku*], PSB/PED Notification No. 1225-6 dated December 25, 2024, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the suppression of recurrence of immunoglobulin (Ig) G4-related diseases, 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 indications and dosage and administration shown below, with the following condition.

Indications

○ Prevention of relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)
○ Suppression of recurrence of IgG4-related disease

(Underline denotes additions.)

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Dosage and Administration

The usual adult dosage is 300 mg of inebilizumab (genetical recombination) administered by intravenous infusion. The initial dose is followed 2 weeks later by the second dose and subsequent doses starting 6 months from the initial dose and thereafter once every 6 months.

(No change)

Approval Condition

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

Attachment

Review Report (1)

September 17, 2025

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	Uplizna for Intravenous Infusion 100 mg
Non-proprietary Name	Inebilizumab (Genetical Recombination)
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	March 19, 2025
Dosage Form/Strength	Injectable solution containing 100 mg of Inebilizumab (Genetical Recombination) per vial (10 mL)

Proposed Indications

○ Prevention of relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)
○ IgG4-related disease

(Underline denotes additions.)

Proposed Dosage and Administration

The usual adult dosage is 300 mg of inebilizumab (genetical recombination) administered by intravenous infusion. The initial dose is followed 2 weeks later by the second dose and subsequent doses starting 6 months from the initial dose and thereafter once every 6 months.

(No change)

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List of Abbreviations

See Appendix.

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

Immunoglobulin G4-related disease (IgG4-RD) is a disease of unknown etiology characterized by elevated serum immunoglobulin (Ig) G4 levels, marked infiltration of lymphocytes and IgG4-positive plasma cells, significant fibrosis, etc., causing to form enlarged, nodulated, or thickened lesions in all organs in the body either synchronously or metachronously. IgG4-RD is generally painless and slowly progressive with repeated cycles of relapses and remissions. Tissue damage and irreversible organ impairment progress even in the absence of symptoms, and approximately 60% of patients are diagnosed with irreversible organ impairment (*Expert Rev Clin Immunol.* 2017;13:867-75; *Arthritis Rheumatol.* 2020;72:7-19). In Japan, IgG4-RD has been designated as an intractable disease (MHLW Public Notice No. 300 dated July 1, 2015). Currently in Japan, there is no drug product approved for the indication of IgG4-RD. Relapses often occur despite the use of steroids as the first-line therapy, for which there is no established treatment.

Inebilizumab (genetical recombination) (hereinafter referred to as inebilizumab) is a humanized IgG1 monoclonal antibody against CD19 in-licensed by Mitsubishi Tanabe Pharma Corporation from Viela Bio, Inc (currently Amgen Inc). It was approved in Japan in March 2021 for the indication of " the prevention of relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)." Inebilizumab specifically binds to CD19 and enhances antibody-dependent cellular cytotoxicity and antibody-dependent cellular phagocytosis against CD19-positive B cells, thereby reducing the number of CD19-positive B cells. Through this mechanism of action, inebilizumab is expected to exsert its therapeutic effect against IgG4-RD.

Based on the results of a global study in patients with IgG4-RD and other data, the applicant submitted a partial change application for marketing approval for the additional indication of IgG4-RD, concluding that the results have demonstrated the efficacy and safety of inebilizumab.

In foreign countries, inebilizumab was first approved in the US in June 2020 for the indication of the prevention of relapse of neuromyelitis optica spectrum disorder (NMOSD). As of June 2025, inebilizumab has been approved in ≥40 countries or regions including Europe and the US. For the indication of IgG4-RD, it has been approved in 2 countries including the US, and [redacted] as of September 2025.

Inebilizumab was designated as an orphan drug for the intended indication of "IgG4-related disease" on December 25, 2024 (Orphan Drug Designation No. 647 of 2024 [*R6 Yaku*]).

2. Quality and Outline of the Review Conducted by PMDA

The present application pertains to a new indication. No quality-related data were submitted.

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

The present application pertains to a new indication. However, the binding affinity of inebilizumab for CD19, decrease in B cells, etc. were evaluated during the review process for the initial approval (Review Report for "Uplizna for Intravenous Infusion 100 mg" [dated February 3, 2021]), and no new data have been submitted.

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

The present application pertains to a new indication. However, non-clinical pharmacokinetic data were evaluated during the review process for the initial approval (Review Report for "Uplizna for Intravenous Infusion 100 mg" [dated February 3, 2021]), and no new data have been submitted.

5. Toxicology and Outline of the Review Conducted by PMDA

The present application pertains to a new indication. No data relating to toxicity have been submitted.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

The global phase III study (Study VIB0551.P3.S2) that provided evaluation data submitted for the present application used a formulation identical to the commercial drug product.

Serum concentrations of inebilizumab in humans were measured using an enzyme-linked immunosorbent assay (ELISA) method, with a lower limit of quantification of 100 or 200 ng/mL. Peripheral blood CD20-positive B-cell counts were measured by flow cytometry. Anti-drug antibodies (ADA) were measured using an electro-chemiluminescence immunoassay (ECLIA) method.

6.2 Clinical pharmacology

6.2.1 Global phase III study (MITIGATE study) (CTD 5.3.5.1-1, Study code VIB0551.P3.S2 ongoing since December 2020 [data cutoff on April 9, 2024 (randomized controlled period), February 9, 2024 (open-label period)])

Pharmacokinetics, pharmacodynamics, etc. following multiple intravenous administration of inebilizumab were investigated in Japanese and non-Japanese patients with IgG4-RD [See Section 7.1 for the study outline and results on efficacy and safety].

Placebo or inebilizumab 300 mg was administered intravenously on Day 1, Day 15, and Week 26 (Day 183).

Table 1 shows the serum pharmacokinetic parameters of inebilizumab during the randomized controlled period.

Table 1. Serum pharmacokinetic parameters of inebilizumab

Time point	C_{max}[a)] (μg/mL)	$AUC_{0\text{-}14day}$[a)] (μg·day/mL)	$AUC_{0\text{-}last}$[a)] (μg·day/mL)	t_{max}[a),b)] (day)	AUC_{cum}[c)] (μg·day/mL)	$t_{1/2}$ (day)
First dose	108 ± 32.9 (63)	820 ± 253 (63)	827 ± 256 (63)	0.08 [0.07, 0.15] (63)	4,620 ± 1,720 (64)	18.4 ± 4.21 (53)
Second dose	133 ± 39.2 (64)	1,150 ± 333 (64)	2,280 ± 897 (64)	0.08 [0.07, 14] (64)		
Third dose	100 ± 21.8 (51)	951 ± 215 (51)	1,920 ± 574 (51)	0.08 [0.07, 0.13] (51)		

Mean ± standard deviation (SD) (number of patients)

a) The calculation of the first dose was based on a total of 3 data points from pre-first dose to pre-second dose, a total of 6 data points from pre-second dose to pre-third dose for the second dose, and a total of 5 data points from pre-third dose to Day 365 for the third dose.

b) Median [minimum, maximum]

c) AUC from time 0 after the initial dose to the last quantifiable time point after the final dose

Table 2 presents pharmacodynamic data of inebilizumab showing the time course of peripheral blood B-cell counts[1)] during the randomized controlled period. The decrease in peripheral blood B-cell counts with inebilizumab was maintained from Day 15 through Day 365, and was lower than that in the placebo group at all evaluation time points.

Table 2. Time course of peripheral blood B-cell counts

Group	Peripheral blood B cell count (cells/μL)							
	Baseline	Day 15	Day 29	Day 85	Day 141	Day 183	Day 267	Day 365
Inebilizumab	428 ± 392 (61)	13.6 ± 15.4 (61)	5.52 ± 7.46 (53)	1.60 ± 1.38 (32)	2.54 ± 3.15 (37)	32.1 ± 55.5 (44)	16.8 ± 59.4 (35)	53.3 ± 96.2 (42)
Placebo	294 ± 221 (57)	371 ± 314 (62)	319 ± 293 (61)	185 ± 139 (58)	226 ± 161 (50)	220 ± 158 (54)	284 ± 293 (57)	198 ± 145 (54)

Mean ± SD (number of patients)

ADAs were detected in 10.4% (7 of 67) of patients in the placebo group and 23.5% (16 of 68) of patients in the inebilizumab group[2)] by Week 52 of the randomized controlled period.

6.R Outline of the review conducted by PMDA

6.R.1 Differences in pharmacokinetics of inebilizumab between Japanese and non-Japanese patients with IgG4-RD

The applicant's explanation about the differences in pharmacokinetics of inebilizumab between Japanese and non-Japanese patients with IgG4-RD:

Table 3 shows the serum pharmacokinetic parameters of inebilizumab in Japanese and non-Japanese patients with IgG4-RD in the global phase III study (MITIGATE study). Exposure in Japanese patients tended to be slightly higher than in non-Japanese patients, and this is attributable to the gap in body size between Japanese and non-Japanese patients (baseline mean body weight in the MITIGATE study, 60.2 kg in Japanese patients and 73.6 kg in non-Japanese patients). Figures 1 and 2 show the correlation between body weight and serum pharmacokinetic parameters (C_{max} or $AUC_{0\text{-}14\ day}$) of inebilizumab on Day 15 and Day 183, respectively. Exposure to inebilizumab tended to be higher in patients with lower body weight, and the serum pharmacokinetic parameters of Japanese patients generally overlapped with those of non-Japanese patients. Taking into account the body weight gap between the two populations, there are no clear differences in pharmacokinetic characteristics between Japanese and non-Japanese patients with IgG4-RD.

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1) Since inebilizumab interferes with detection of B cells based on CD19, B-cell counts were quantified by measuring CD20-positive B-cell counts.

2) ADAs were detected at baseline in 4 of 7 patients in the placebo group and 11 of 16 patients in the inebilizumab group.

Table 3. Serum pharmacokinetic parameters of inebilizumab

Time point	C_{max} (μg/mL)		$AUC_{0\text{-}14day}$ (μg·day/mL)	
	Japanese	Non-Japanese	Japanese	Non-Japanese
Second dose	149 ± 44.9 (19)	126 ± 34.7 (45)	1,300 ± 356 (19)	1,090 ± 305 (45)
Third dose	106 ± 19.5 (19)	97.1 ± 22.6 (32)	1,010 ± 196 (19)	915 ± 220 (32)

Mean ± SD (number of patients)

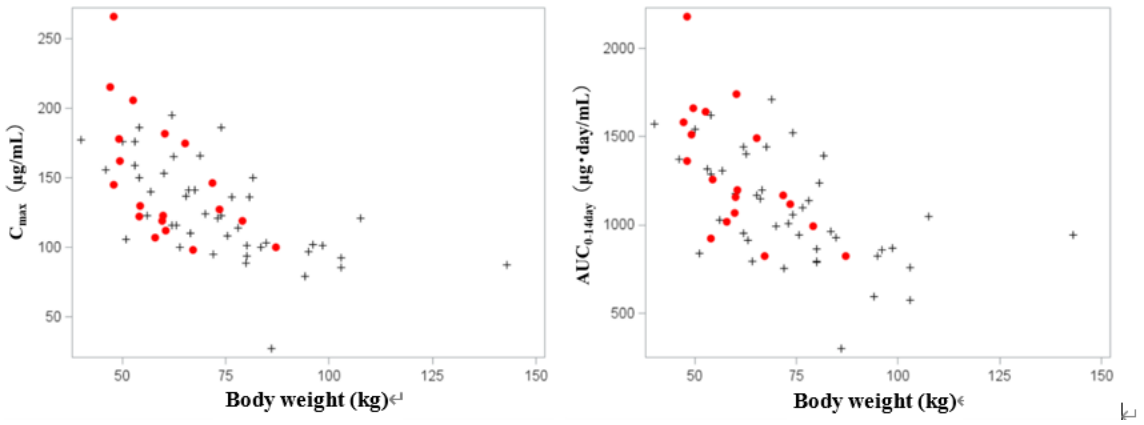


Figure 1. Relationship between serum pharmacokinetic parameters of inebilizumab and body weight (Day 15)

The left panel shows C_{max}, and the right panel shows $AUC_{0\text{-}14day}$. ● indicates the Japanese population, and + indicates the non-Japanese population.

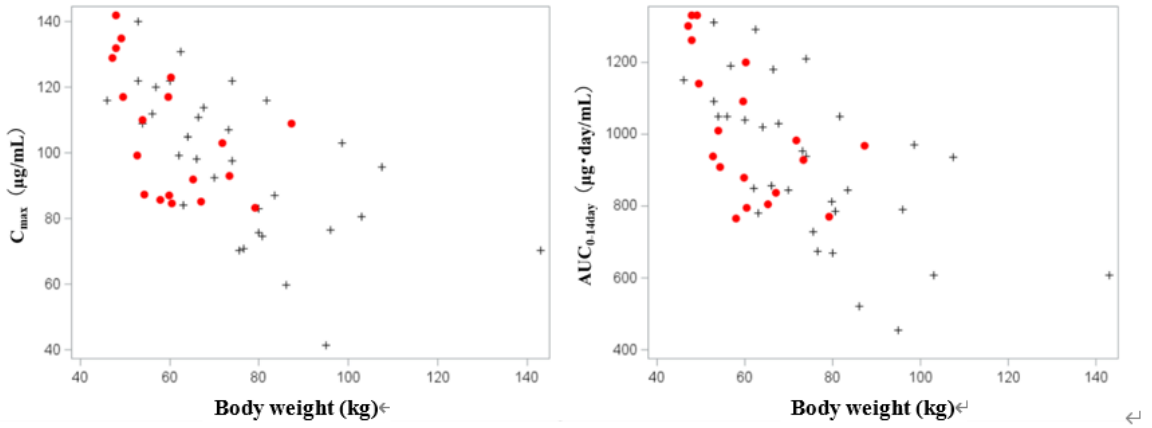


Figure 2. Relationship between serum pharmacokinetic parameters of inebilizumab and body weight (Day 183)

The left panel shows C_{max}, and the right panel shows $AUC_{0\text{-}14day}$. ● indicates the Japanese population, and + indicates the non-Japanese population.

PMDA considers the applicant's explanation appropriate.

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

The applicant submitted results from 1 global phase III study, as efficacy and safety evaluation data (Table 4).

Table 4. Summary of data on efficacy and safety

Region	Phase	Study	Study population	Study design	Number of patients enrolled (Number of Japanese patients)	Dosage regimen	Primary efficacy endpoint
Global	III	VIB0551 .P3.S2	Patients with IgG4-RD	(Randomized, controlled period) Randomized, double-blind, placebo-controlled, parallel-group (Open-label period) Open-label, uncontrolled	(Randomized, controlled period) (1) Placebo: 67 (7) (2) Inebilizumab: 68 (20) (Open-label period)[a)] (3) placebo/ inebilizumab: 49 (6) (4) Inebilizumab/ inebilizumab: 53 (19)	(Randomized controlled period (52 weeks)) (1) Placebo is administered intravenously on Day 1, Day 15, and Week 26. (2) Inebilizumab 300 mg is administered intravenously on Day 1, Day 15, and Week 26. (Open-label period (3 years)) (3) Inebilizumab 300 mg is administered intravenously on Day 1, Day 15, Week 26, and every 6 months thereafter. (4) Inebilizumab 300 mg is administered intravenously on Day 1, followed by placebo on Day 15, and inebilizumab 300 mg on Week 26 and every 6 months thereafter.	Time to first flare

a) After the completion of the randomized controlled period, an optional 3-year open-label period was scheduled. Patients assigned to the placebo group and the inebilizumab group in the randomized controlled period received inebilizumab during the open-label period in (3) the placebo/inebilizumab group and (4) the inebilizumab/inebilizumab group, respectively, while blinding was maintained.

7.1 Global phase III study (MITIGATE study) (CTD 5.3.5.1-1, Study code VIB0551.P3.S2 ongoing since December 2020 [data cutoff on April 9, 2024 (randomized controlled period), February 9, 2024 (open-label period)])

A multicenter, randomized, double-blind, placebo-controlled, parallel-group study (partially open-label, uncontrolled) was conducted to evaluate the efficacy and safety of inebilizumab in patients with IgG4-RD (Table 5) (target sample size, 160 subjects[3)]) at 46 study sites in 16 countries or regions including Japan (10 Japanese sites).

3) The assessment of the primary endpoint (time to first treatment of IgG4-RD flare as judged by the Adjudication Committee [AC] during the randomized controlled period) was based on the following assumptions in view of the lack of experience with inebilizumab in patients with IgG4-RD when the study began: Inebilizumab reduced the risk of attacks by approximately 77% in a global Phase II/III study in adult patients with NMO and NMOSD (N-MOmentum study), based on which the hazard ratio of the inebilizumab group versus the placebo group was assumed as 0.35. Relapse rates at 1 year after steroid tapering in patients with IgG4-RD were reported as 38.5% and 40% (*Rheumatology.* 2019;58:52-60; *Sci Rep.* 2017;7:6195), based on which the event rate in the placebo group was assumed as 0.35. A log-rank test with an allocation ratio of 1:1, a two-sided significance level of 5%, and a power of 90% yielded the required number of events and the required sample size as 39 and of 160 subjects (80 per group), respectively.

Table 5. Main inclusion and exclusion criteria

Main inclusion criteria
- Aged ≥18 years
- Diagnosis of IgG4-RD
- Meeting the 2019 ACR/EULAR IgG4-RD classification criteria (*Arthritis Rheumatol.* 2020;72:7-19) (involvement of at least 1 organ among pancreas, bile ducts/biliary tract, orbit, lungs, kidneys, lacrimal glands, major salivary glands, retroperitoneum, aorta, dura mater, or thyroid; not meeting the exclusion criteria of the classification criteria; and having a classification criteria score of ≥20 points)
- Active disease (new onset or relapse) requiring steroid therapy (maximum 60 mg/day prednisolone-equivalent for up to 4 weeks prior to consent or for 3-8 weeks prior to randomization), with tapering to ≤20 mg/day prednisolone-equivalent by randomization
- History of IgG4-RD involving at least 2 organs/sites (at least 1 of which must be included in the ACR/EULAR classification criteria [pancreas, bile ducts/biliary tract, orbit, lungs, kidneys, lacrimal glands, major salivary glands, retroperitoneum, aorta, dura mater, or thyroid])

Main exclusion criteria
- Prior treatment with B-cell-targeting agents such as rituximab (genetical recombination) within 6 months before screening
- Prior treatment with immunosuppressants other than steroids (e.g., non-biologic disease-modifying antirheumatic drugs or azathioprine) within 4 weeks before screening
- History of or carrier status for hepatitis B virus, hepatitis C virus, or human immunodeficiency virus (patients with hepatitis C virus were eligible if viral load was below the limit of detection ≥24 weeks after antiviral therapy at the study site or the central laboratory)
- History of immunodeficiency
- History of organ transplantation or cell-based transplantation
- Diagnosis of malignancy within the past 10 years (excluding cervical carcinoma in situ that was treated curatively ≥12 months prior to screening; basal cell carcinoma or squamous cell carcinoma of the skin that was treated curatively; prostate cancer that underwent radical prostatectomy or definitive radiation therapy ≥3 years prior to screening with no evidence of recurrence or no ongoing treatment; or thyroid cancer that was surgically resected)

Figure 3 overviews the study. The study consisted of a screening period (28 days), a randomized controlled period (52 weeks), and an optional open-label period (3 years).

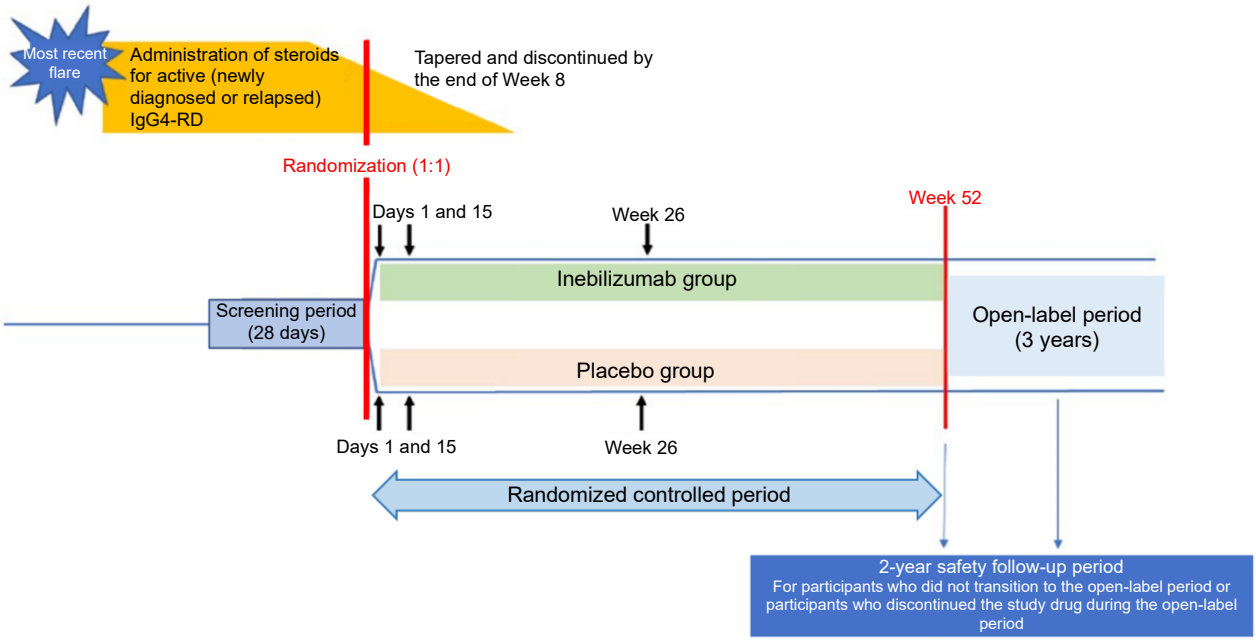


Figure 3. Overview of the MITIGATE study

During the randomized controlled period, placebo or inebilizumab 300 mg was administered intravenously on Day 1, Day 15, and Week 26. During the open-label period, patients in the placebo group in the randomized controlled period received inebilizumab 300 mg intravenously on Day 1, Day 15, Week 26, and every 6 months thereafter (placebo/inebilizumab group), and patients in the

inebilizumab group in the randomized controlled period received inebilizumab 300 mg on Day 1, placebo on Day 15, and inebilizumab 300 mg intravenously on Week 26 and every 6 months thereafter (inebilizumab/inebilizumab group). During the screening period, all patients were required to receive steroid therapy for active IgG4-RD (new onset or relapse) (maximum 60 mg/day prednisolone-equivalent for up to 4 weeks prior to consent or for 3-8 weeks prior to randomization),[4] with tapering to ≤20 mg/day prednisolone-equivalent by the randomization. After the randomization, steroids were discontinued by Week 8 according to the predefined tapering schedule.[5] In cases of adrenal insufficiency or intolerance to steroid tapering, steroid administration of ≤2.5 mg/day prednisolone-equivalent was permitted. Concomitant use of immunosuppressants other than steroids was prohibited, and the administration of prohibited concomitant drugs led to study drug discontinuation.

All 135 randomized patients (67 in the placebo group [7 Japanese], 68 in the inebilizumab group [20 Japanese]) received the study drug, and were included in the full analysis set (FAS) and the safety analysis set for the randomized controlled period. The FAS was the primary efficacy analysis set. A total of 8 patients (4 each in the placebo group and the inebilizumab group) discontinued during the randomized controlled period, due to "other" in 3 patients (2 in the placebo group, 1 in the inebilizumab group), "adverse event" in 2 patients (inebilizumab group), "consent withdrawal" in 2 patients (1 each in the placebo group and the inebilizumab group), and "lost to follow-up" in 1 patient (placebo group). Among Japanese patients, 1 discontinuation due to "other" was reported. Of the 127 patients who completed the randomized controlled period, 102 patients (49 in the placebo/inebilizumab group [6 Japanese], 53 in the inebilizumab/inebilizumab group [19 Japanese]) entered the open-label period, and none of them had completed the open-label period as of the data cutoff. A total of 8 patients (3 in the placebo/inebilizumab group, 5 in the inebilizumab/inebilizumab group) discontinued during the open-label period due to "adverse event" in 5 patients (1 in the placebo/inebilizumab group, 4 in the inebilizumab/inebilizumab group), and "other" in 2 patients (placebo/inebilizumab group), and "lost to follow-up" in 1 patient (inebilizumab/inebilizumab group). A total of 2 Japanese patients discontinued due to "adverse event." Overall, 112 patients (26 Japanese) who received at least 1 dose of inebilizumab (inebilizumab-treated population) were included in the safety analysis set for the combined period of the randomized controlled and open-label periods.

The primary endpoint of the study was "time to first flare." "Time to first flare" was defined as the time from Day 1 to the first treatment of an IgG4-RD flare determined by the Adjudication Committee (AC) during the randomized controlled period. The flare criteria were predefined based on the 2019 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) IgG4-RD classification criteria (*Arthritis Rheumatol.* 2020;72:7-19). Flares were validated against the criteria by the AC, which was established for the purpose of bias minimization (Figure 4).

4) Either starting a new regimen or increasing maintenance dose from ≤10 mg/day prednisolone-equivalent was allowed.
5) Prednisolone-equivalent doses of 20 mg/day for Weeks 1 to 2, 15 mg/day for Weeks 3 to 4, 10 mg/day for Weeks 5 to 6, and 5 mg/day for Weeks 7 to 8

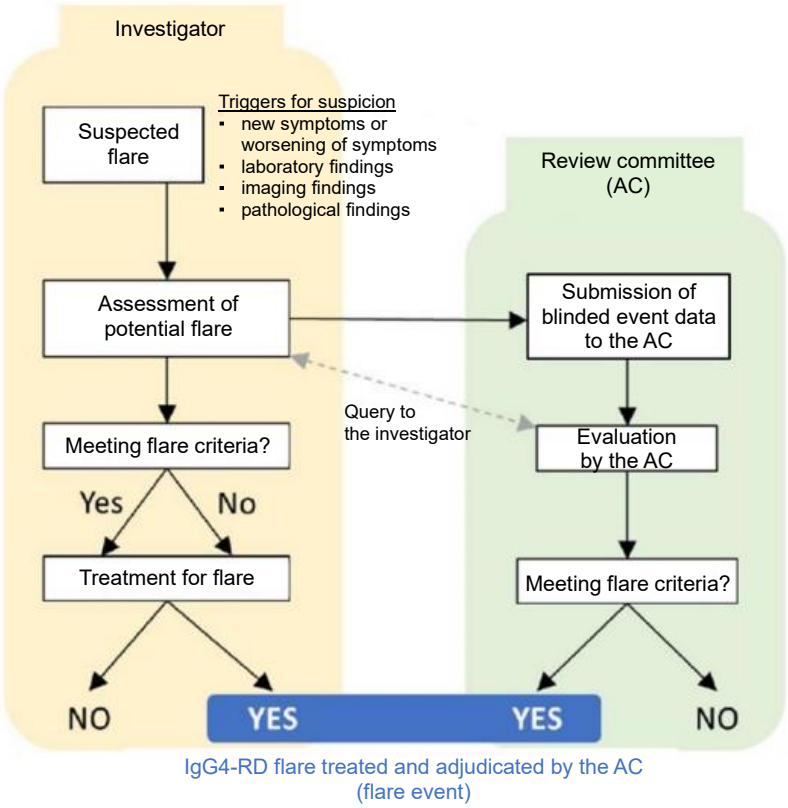


Figure 4. Process for determination of flare events

Table 6 and Figure 5 show the primary efficacy endpoint of "time to first flare," and its Kaplan-Meier curves, respectively, demonstrating the superiority of inebilizumab over placebo.

Table 6. Time to first flare[a] (FAS)

	Placebo	Inebilizumab
Number of patients	67	68
Number of events (%)	40 (59.7)	7 (10.3)
Median [95% CI] (days)	246.0 [191.0, -]	- [371.0, -]
Hazard ratio [95% CI][b]	0.13 [0.06, 0.28]	
P value[b]	<0.0001[c]	

- Not estimable
a) Time from Day 1 in the randomized controlled period to the first treatment of an IgG4-RD flare adjudicated by the AC
b) Cox proportional hazards model with treatment group and disease activity status (new onset, relapse) as explanatory variables
c) Two-sided significance level of 5%

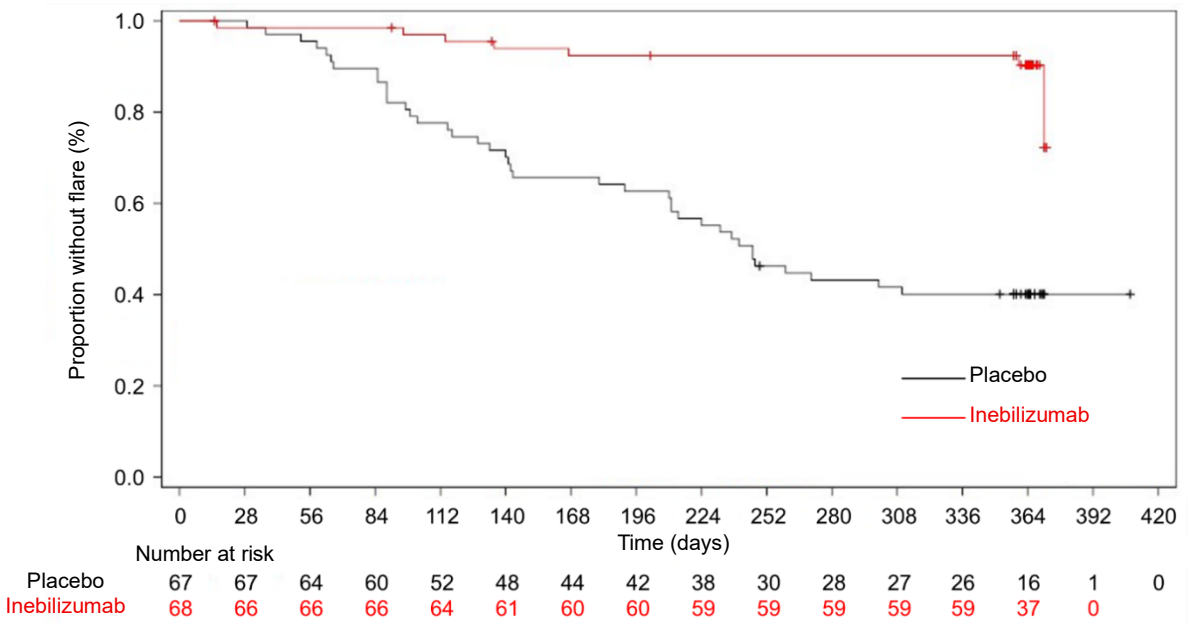


Figure 5. Kaplan-Meier curves for time to first flare (FAS)

The safety data from the randomized controlled period revealed adverse events observed in 98.5% (66 of 67) of patients in the placebo group and 97.1% (66 of 68) of patients in the inebilizumab group, and adverse drug reactions in 23.9% (16 of 67) of patients in the placebo group and 41.2% (28 of 68) of patients in the inebilizumab group. In the Japanese population, adverse events were observed in 100% (7 of 7) of patients in the placebo group and 95.0% (19 of 20) of patients in the inebilizumab group, and adverse drug reactions were observed in 14.3% (1 of 7) of patients in the placebo group and 45.0% (9 of 20) of patients in the inebilizumab group. Table 7 shows adverse events observed in ≥5% of patients in either group in the overall population. The adverse drug reaction observed in ≥5% of patients in the inebilizumab group was lymphopenia (overall population, 4.5% [3 of 67] of patients in the placebo group and 8.8% [6 of 68] of patients in the inebilizumab group; Japanese population, 0% [0 of 7] of patients in the placebo group and 10.0% [2 of 20] of patients in the inebilizumab group).

Table 7. Adverse events observed in ≥5% of patients in either group in the overall population (randomized controlled period, safety analysis set)

	Overall population		Japanese population	
	Placebo (n = 67)	Inebilizumab (n = 68)	Placebo (n = 7)	Inebilizumab (n = 20)
All adverse events	98.5 (66)	97.1 (66)	100 (7)	95.0 (19)
COVID-19	19.4 (13)	23.5 (16)	14.3 (1)	25.0 (5)
Lymphopenia	9.0 (6)	16.2 (11)	0	25.0 (5)
Urinary tract infection	6.0 (4)	11.8 (8)	0	0
Back pain	7.5 (5)	8.8 (6)	0	5.0 (1)
Headache	10.4 (7)	8.8 (6)	0	10.0 (2)
Nasopharyngitis	6.0 (4)	8.8 (6)	0	15.0 (3)
Pyrexia	4.5 (3)	8.8 (6)	0	15.0 (3)
Fatigue	7.5 (5)	7.4 (5)	0	0
Abdominal pain	10.4 (7)	5.9 (4)	0	0
Arthralgia	10.4 (7)	5.9 (4)	14.3 (1)	0
γ-GTP increased	4.5 (3)	5.9 (4)	0	10.0 (2)
Myalgia	0	5.9 (4)	0	10.0 (2)
Neutropenia	4.5 (3)	5.9 (4)	14.3 (1)	10.0 (2)
Palpitations	1.5 (1)	5.9 (4)	0	5.0 (1)
Upper respiratory tract infection	11.9 (8)	5.9 (4)	0	5.0 (1)

Incidence % (number of patients with events), Medical Dictionary for Regulatory Activities (MedDRA) ver.26.1

No deaths occurred in the randomized controlled period. Serious adverse events occurred in 9.0% (6 of 67) of patients (coronary artery stenosis, hepatic function abnormal, diabetes mellitus, acute kidney injury, epistaxis, and sinus disorder [1 patient each]) in the placebo group and 17.6% (12 of 68) of patients (anaphylactic reaction, appendicitis, COVID-19, COVID-19 pneumonia, diverticulitis, femoral neck fracture, gout, hyponatraemia, anal cancer, fibroadenomatoid mastopathy, pulmonary atypical adenomatous hyperplasia, pulmonary embolism, and deep vein thrombosis [1 patient each, some patients had multiple events]) in the inebilizumab group. No serious adverse drug reactions occurred in the placebo group, whereas 2.9% (2 of 68) of patients in the inebilizumab group experienced serious adverse drug reactions (anaphylactic reaction and COVID-19 [1 patient each]). In the Japanese population, while no serious adverse events occurred in the placebo group, 20.0% (4 of 20) of patients in the inebilizumab group experienced serious adverse events (appendicitis, COVID-19, diverticulitis, and pulmonary atypical adenomatous hyperplasia [1 patient each]). COVID-19 in 1 patient in the inebilizumab group was an adverse drug reaction.

In the randomized controlled period, adverse events led to study drug discontinuation in 4.5% (3 of 67) of patients (abdominal pain, swelling, and varicella zoster virus infection [1 patient each]) in the placebo group and 8.8% (6 of 68) of patients (anaphylactic reaction, COVID-19 pneumonia, herpes zoster, anal cancer, malignant melanoma, pulmonary embolism, and deep vein thrombosis [1 patient each, some patients had multiple events]) in the inebilizumab group. Adverse drug reactions led to study drug discontinuation in 3.0% (2 of 67) of patients (swelling and varicella zoster virus infection [1 patient each]) in the placebo group and 2.9% (2 of 68) of patients (anaphylactic reaction and herpes zoster) in the inebilizumab group. In the Japanese population, an adverse event led to study drug discontinuation in 1 patient (varicella zoster virus infection) in the placebo group, and the event was an adverse drug reaction.

The safety data from the combined period of the randomized controlled period and the open-label period (inebilizumab-treated population) revealed adverse events in 95.5% (107 of 112) of patients and adverse

drug reactions in 40.2% (45 of 112) of patients. In the Japanese population, adverse events occurred in 96.2% (25 of 26) of patients and adverse drug reactions in 53.8% (14 of 26) of patients. Table 8 shows adverse events observed in ≥5% of patients in the overall population. The adverse drug reaction observed in ≥5% of patients in the overall population was lymphopenia (6.3% [7 of 112 patients]).

Table 8. Adverse events observed in ≥5% of patients in the overall population (combined period of randomized controlled and open-label periods, inebilizumab-treated population[a])

	Overall population (n = 112)	Japanese population (n = 26)
All adverse events	95.5 (107)	96.2 (25)
COVID-19	28.6 (32)	26.9 (7)
Lymphopenia	10.7 (12)	19.2 (5)
Upper respiratory tract infection	10.7 (12)	3.8 (1)
Nasopharyngitis	9.8 (11)	26.9 (7)
Urinary tract infection	8.9 (10)	0
Back pain	8.0 (9)	7.7 (2)
Fatigue	8.0 (9)	0
Pyrexia	8.0 (9)	11.5 (3)
Headache	7.1 (8)	11.5 (3)
Abdominal pain	6.3 (7)	0
Arthralgia	6.3 (7)	0
Hypertension	6.3 (7)	3.8 (1)
Influenza	6.3 (7)	7.7 (2)
Myalgia	6.3 (7)	19.2 (5)
Cough	5.4 (6)	3.8 (1)
Neutropenia	5.4 (6)	7.7 (2)
Urticaria	5.4 (6)	11.5 (3)

Incidence % (number of patients with events), MedDRA ver.26.1

a) Patients who received at least 1 dose of the study drug during the combined period of the randomized controlled period and the open-label period

No deaths occurred in the combined period of the randomized controlled period and the open-label period (inebilizumab-treated population). Serious adverse events occurred in 22.3% (25 of 112) of patients (COVID-19 pneumonia and pneumonia [2 patients each]; cataract, anaphylactic reaction, appendicitis, COVID-19, dengue fever, diverticulitis, febrile infection, ankle fracture, fall, femoral neck fracture, infusion related reaction, diabetes mellitus, gout, hyponatraemia, anal cancer, benign ovarian tumor, fibroadenomatoid mastopathy, prostate cancer, dizziness, transient ischaemic attack, organising pneumonia, pulmonary atypical adenomatous hyperplasia, pulmonary embolism, lichen sclerosus, and deep vein thrombosis [1 patient each, some patients had multiple events]) and serious adverse drug reactions occurred in 5.4% (6 of 112) of patients (anaphylactic reaction, COVID-19, febrile infection, infusion related reaction, prostate cancer, and organising pneumonia [1 patient each]). In the Japanese population, serious adverse events occurred in 26.9% (7 of 26) of patients (cataract, appendicitis, COVID-19, diverticulitis, prostate cancer, organising pneumonia, and pulmonary atypical adenomatous hyperplasia [1 patient each]) and serious adverse drug reactions in 11.5% (3 of 26) of patients (COVID-19, organising pneumonia, and prostate cancer [1 patient each]).

In the combined period of the randomized controlled period and the open-label period (inebilizumab-treated population), adverse events led to study drug discontinuation in 10.7% (12 of 112) of patients (hypoglobulinaemia, drug-induced liver injury, anaphylactic reaction, COVID-19 pneumonia, dengue fever, herpes zoster, infusion related reaction, anal cancer, malignant melanoma, prostate cancer, organising pneumonia, pulmonary embolism, and deep vein thrombosis [1 patient each, some patients had multiple events]). Adverse drug reactions led to study drug discontinuation in 6.3% (7 of 112) of

patients (hypoglobulinaemia, drug-induced liver injury, anaphylactic reaction, herpes zoster, infusion related reaction, prostate cancer, and organising pneumonia). In the Japanese population, adverse events led to study drug discontinuation in 3 patients (hypoglobulinaemia, prostate cancer, and organising pneumonia [1 patient each]), all of which were adverse drug reactions.

7.R Outline of the review conducted by PMDA

7.R.1 Inclusion of Japanese patients in the global phase III study (MITIGATE study)

The applicant's explanation about the inclusion of Japanese patients in the phase III MITIGATE study, which was conducted as a global study:

Intrinsic ethnic factors:
During the planning of the MITIGATE study, there were no data from patients with IgG4-RD treated with inebilizumab. However, a population pharmacokinetic analysis using pharmacokinetic data from clinical studies in patients with NMOSD revealed no impact of race on inebilizumab's pharmacokinetics (Review Report for "Uplizna for Intravenous Infusion 100 mg" [dated February 3, 2021]). In a global phase II/III study (Study 1155) in patients with NMOSD, pharmacokinetic parameters of Japanese subjects were within the range of variability observed in non-Japanese subjects, and safety data indicated no substantial differences between Japanese and non-Japanese subjects.

Extrinsic ethnic factors:
Outside Japan, the 2019 ACR/EULAR IgG4-RD classification criteria (*Arthritis Rheumatol.* 2020;72:7-19) are internationally recognized diagnostic criteria for IgG4-RD and were also used as the inclusion criteria of the MITIGATE study. In Japan, the 2020 Revised Comprehensive Diagnostic (RCD) Criteria for IgG4-RD (Japanese association of IgG4-related disease: https://igg4.w3.kanazawa-u.ac.jp/reference/ [last accessed on September 17, 2025]) are used. The Japanese diagnostic criteria, however, have been revised in consideration of the 2019 ACR/EULAR IgG4-RD classification criteria, and thus there are no marked differences between the two. The treatment systems of IgG4-RD are steroid-centered both in Japan and Europe/the US, showing no substantial differences.

Based on the above, there were no problem with the inclusion of Japanese patients in the MITIGATE study, and it is appropriate to evaluate the efficacy and safety of inebilizumab in Japanese patients with IgG4-RD based on the results of the MITIGATE study.

PMDA's view:
The applicant's explanation is appropriate. It is possible to evaluate the efficacy and safety of inebilizumab in Japanese patients with IgG4-RD based on the results of the MITIGATE study conducted as a global study.

7.R.2. Efficacy

Based on the reviews in Sections 7.R.2.1 and 7.R.2.2, PMDA has concluded that the efficacy of inebilizumab was demonstrated in patients with IgG4-RD.

7.R.2.1 Results of the primary endpoint and major secondary endpoints

The applicant's explanation about the results of the primary endpoint and major secondary endpoints in the MITIGATE study:

The primary endpoint of the MITIGATE study was "time to first flare." IgG4-RD flares have been reported from 40% to 76% of responders to steroid therapy after the tapering or discontinuation of steroids (*Expert Rev Clin Immunol.* 2017;13:867-75). Flares cause organ inflammation, functional impairment, fibrosis, accumulation of organ damage, and decreased quality of life (QOL), and require treatment with steroids, etc. Flare onset is thus considered the most critical event in patients with IgG4-RD. During the planning phase of the MITIGATE study, no established criteria for IgG4-RD flares were available, and, therefore, flare criteria were defined in accordance with the 2019 ACR/EULAR IgG4-RD classification criteria. Flares were validated against the criteria by the AC, which was established for the purpose of bias minimization (Figure 4).

The superiority of inebilizumab over placebo was demonstrated by the primary endpoint, "time to first flare" [see Section 7.1]. Table 9 and Figure 6 show the results of "time to first flare" and the Kaplan-Meier curves in the Japanese population, respectively, with similar trends to those observed in the overall population.

Table 9. Time to first flare in the Japanese population[a)] (FAS)

	Placebo	Inebilizumab
Number of patients	7	20
Number of events (%)	4 (57.1)	0
Median [95% CI](days)	246.0 [65.0, -]	- [-, -]
Hazard ratio [95% CI][b)]	0.0 [0.0, -]	

- Not estimable
a) Time from Day 1 in the randomized controlled period to the first treatment of an IgG4-RD flare adjudicated by the AC
b) Cox proportional hazards model with treatment group and disease activity status (new onset, relapse) as explanatory variables

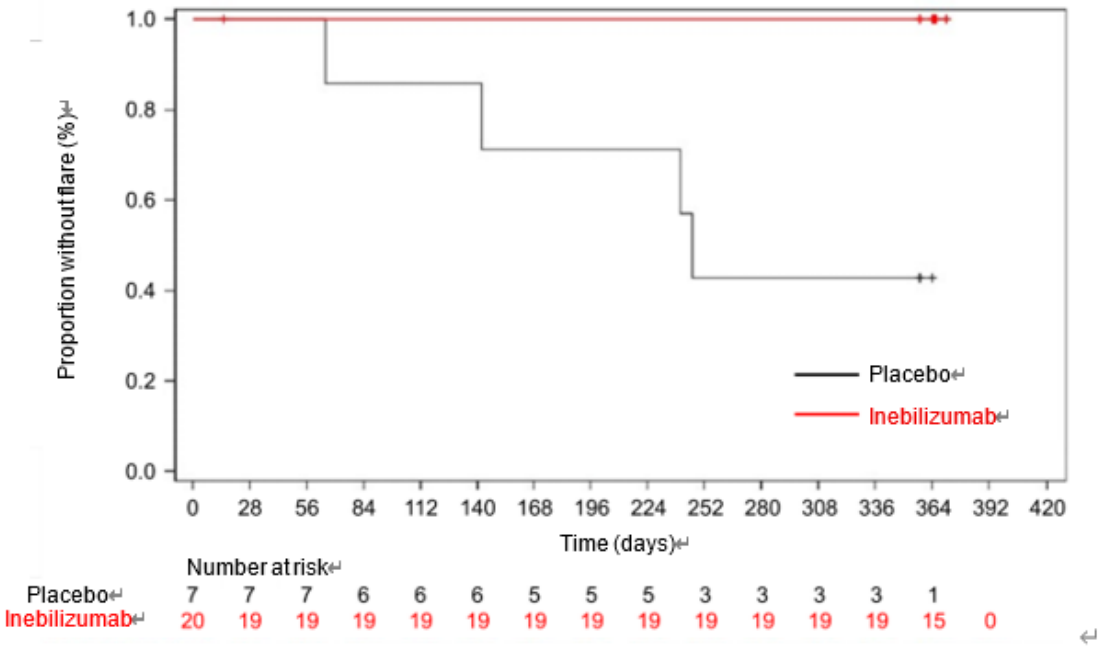


Figure 6. Kaplan-Meier curves for time to first flare in the Japanese population (FAS)

Table 10 shows the results of the major secondary endpoints. All endpoints showed favorable trends in the inebilizumab group compared with the placebo group, and the Japanese population showed similar trends to those observed in the overall population.

Table 10. Results of major secondary endpoints (randomized controlled period, FAS)

	Overall population		Japanese population	
	Placebo (n = 67)	Inebilizumab (n = 68)	Placebo (n = 7)	Inebilizumab (n = 20)
Annual rate of flare requiring treatment and adjudicated by the AC [95% CI][a)]	0.71 [0.53, 0.94]	0.10 [0.05, 0.21]	0.67 [0.22, 2.07]	0.00 [0.00, -]
Proportion of patients who achieved complete remission without flare at Week 52[c)] without receiving treatment for flare during the randomized controlled period[b)]	22.4% (n = 15)	57.4% (n = 39)	14.3% (n = 1)	50.0% (n = 10)
Proportion of patients who achieved complete remission without flare at Week 52[c)] without receiving steroids during the randomized controlled period[b)]	22.4% (n = 15)	58.8% (n = 40)	14.3% (n = 1)	50.0% (n = 10)

- Not estimable
a) Negative binomial model with treatment group and disease activity status (new onset, relapse) as explanatory variables
b) Excluding steroid administration during the predefined 8-week tapering period
c) Defined as either (a) IgG4-RD Responder Index score (*Arthritis Care Res.* 2018;70:1671-8) of 0, or (b) no disease activity of IgG4-RD as determined by the investigator based on physical findings, hematological findings, histopathological findings, etc.

Based on the above, the MITIGATE study demonstrated the efficacy of inebilizumab, and the results of the major secondary endpoints supported the primary endpoint results. The Japanese population and the overall population showed similar trends. Thus, the efficacy of inebilizumab has been demonstrated in patients with IgG4-RD, including Japanese patients.

7.R.2.2 Efficacy by patient characteristics

The applicant's explanation about the efficacy by major patient characteristics in the MITIGATE study:
Table 11 shows the number of events and hazard ratios for "time to first flare" by major patient characteristics in the MITIGATE study. No clear tendency toward attenuated efficacy was observed in any specific subgroups.

Table 11. Number of events and hazard ratios for time to first flare by major patient characteristics (FAS)

		Placebo (n = 67)	Inebilizumab (n = 68)	Hazard ratio [95% CI]
Total		40/67	7/68	0.13 [0.06, 0.28]
Age	< 65	30/46	6/47	0.14 [0.06, 0.33]
	≥ 65	10/21	1/21	0.09 [0.01, 0.69]
Sex	Male	30/49	4/39	0.12 [0.04, 0.33]
	Female	10/18	3/29	0.16 [0.04, 0.58]
Baseline serum IgG4 concentration[a)]	< median[b)]	14/29	3/30	0.18 [0.05, 0.61]
	≥ median[b)]	24/31	3/29	0.08 [0.02, 0.27]
Disease state	New onset	17/31	1/31	0.05 [0.01, 0.34]
	Relapse	23/36	6/37	0.18 [0.07, 0.44]
Number of affected organs	< median[c)]	13/26	4/27	0.26 [0.08, 0.81]
	≥ median[c)]	27/41	3/41	0.07 [0.02, 0.24]

a) Subjects with recorded baseline serum IgG4 levels (60 subjects in the placebo group, 59 subjects in the inebilizumab group)
b) 424.0 mg/dL in the placebo group, 404.0 mg/dL in the inebilizumab group
c) 3 in both the placebo group and inebilizumab group

Table 12 shows the number of events and the hazard ratios for "time to first flare" by affected organ at baseline in the MITIGATE study. Although some organs had limited numbers of patients and events, the results showed no clear tendency toward decreased efficacy in any specific organs affected.

Table 12. Number of events and hazard ratios for time to first flare by major affected organs at baseline (FAS)

	Placebo (n = 67)	Inebilizumab (n = 68)	Hazard ratio [95% CI]
Overall	40/67	7/68	0.13 [0.06, 0.28]
Lymph nodes	18/26	3/26	0.13 [0.04, 0.44]
Submandibular gland	9/20	3/31	0.17 [0.05, 0.63]
Pancreas	17/24	1/27	0.03 [0.00, 0.21]
Lacrimal gland	10/18	2/27	0.10 [0.02, 0.47]
Kidney	12/19	2/21	0.08 [0.02, 0.36]
Bile duct	12/15	0/13	0.00 [0.00, -]
Parotid gland	6/10	2/17	0.16 [0.03, 0.79]
Lung	9/15	0/10	0.00 [0.00, -]
Paranasal sinuses	7/12	2/12	0.39 [0.08, 1.97]

- Not estimable

PMDA's view on the efficacy of inebilizumab based on Sections 7.R.2.1 and 7.R.2.2:
The following outcomes support the efficacy of inebilizumab in patients with IgG4-RD and indicate promising efficacy in Japanese patients with IgG4-RD:

- "Time to first flare," the primary endpoint of the MITIGATE study, demonstrated the superiority of inebilizumab over placebo. Flares rarely occurred in the inebilizumab group, which indicates clinically significant effects of inebilizumab.
- The results of major secondary endpoints, which are considered clinically important, support the primary endpoint results.
- The limited numbers of Japanese subjects and events reported in the MITIGATE study prevented a thorough efficacy evaluation in Japanese patients based solely on data from the Japanese population. However, the results showed similar trends between the Japanese population and the overall population.

Flares tended to occur less frequently in the inebilizumab group compared with the placebo group, regardless of patient characteristics. It is unlikely that any of the patient characteristics examined will significantly affect the efficacy of inebilizumab.

7.R.3 Safety

PMDA's view:
Based on the reviews in Sections 7.R.3.1 to 7.R.3.3 and taking account of the efficacy of inebilizumab demonstrated in the MITIGATE study [see Section 7.R.2], inebilizumab has acceptable safety in patients with IgG4-RD when used under the supervision of physicians with adequate knowledge of inebilizumab and expert knowledge and experience in the treatment of IgG4-RD, with the same cautionary advice as last time for the approved indications.

7.R.3.1 Overview of the incidence of adverse events

The applicant's overview of the occurrence of adverse events in the MITIGATE study:
Table 13 summarizes the occurrence of adverse events in the MITIGATE study. All serious adverse drug reactions and adverse drug reactions leading to the discontinuation of inebilizumab in the inebilizumab group (anaphylactic reaction, COVID-19, and herpes zoster) resolved, and no concerning trends were observed in the Japanese population compared with the overall population. Compared with the

inebilizumab group in the randomized controlled period, there was no evident increase in the incidence of adverse drug reactions, serious adverse events, or adverse events leading to the discontinuation of inebilizumab during the combined period of the randomized controlled and open-label periods [see Section 7.1].

Table 13. Incidence of adverse events in the MITIGATE study (randomized controlled period, safety analysis set)

	Overall population		Japanese population	
	Placebo (n = 67)	Inebilizumab (n = 68)	Placebo (n = 7)	Inebilizumab (n = 20)
All adverse events	98.5 (66)	97.1 (66)	100 (7)	95.0 (19)
All adverse drug reactions	23.9 (16)	41.2 (28)	14.3 (1)	45.0 (9)
Deaths	0	0	0	0
Serious adverse events	9.0 (6)	17.6 (12)	0	20.0 (4)
Serious adverse drug reactions	0	2.9 (2)	0	5.0 (1)
Adverse events leading to discontinuation of the study drug	4.5 (3)	8.8 (6)	14.3 (1)	0
Adverse events leading to interruption of the study drug	1.5 (1)	5.9 (4)	0	0

Incidence, % (number of patients with events)

PMDA's view:

In the MITIGATE study, inebilizumab showed higher incidence of adverse drug reactions than the placebo, but most events were Grade ≤2. The serious adverse drug reactions and adverse drug reactions leading to study drug discontinuation in the inebilizumab group were all known risks, and all events resolved. Although the limited number of subjects in the Japanese population constrained the comparison of safety profiles with the non-Japanese population, the trends in the occurrence of adverse events did not differ from the overall population. Taken together, when inebilizumab is used by physicians with adequate knowledge of inebilizumab and expert knowledge and experience in the treatment of IgG4-RD, the safety of inebilizumab can be well-managed in patients with IgG4-RD including Japanese patients, by offering cautionary advice as last time for the approved indications.

7.R.3.2 Safety by patient characteristics

The applicant's explanation about the safety by major patient characteristics:

Table 14 shows the incidence of adverse events and Grade ≥3 adverse events by major patient characteristics in the MITIGATE study. In the population aged ≥65 years, the incidence of Grade ≥3 adverse events tended to be higher in the inebilizumab group than in the placebo group, and the incidence of serious adverse events was also higher in the inebilizumab group than in the placebo group. However, all 3 events in the inebilizumab group that were serious adverse drug reactions or Grade ≥3 adverse drug reactions (lymphopenia, anaphylactic reaction, and COVID-19 in 1 patient each) resolved. In the other populations, no trends of particular concerns were observed.

Taken together, there were no trends indicating particular safety concerns with inebilizumab in any of the populations.

Table 14. Incidence of adverse events by major patient characteristics in the MITIGATE study (randomized controlled period, safety analysis set)

		Placebo (n = 67)		Inebilizumab (n = 68)	
		All adverse events	Grade ≥3 adverse events	All adverse events	Grade ≥3 adverse events
Overall		98.5 (66/67)	11.9 (8/67)	97.1 (66/68)	17.6 (12/68)
Age	< 65	97.8 (45/46)	13.0 (6/46)	97.9 (46/47)	10.6 (5/47)
	≥ 65	100 (21/21)	9.5 (2/21)	95.2 (20/21)	33.3 (7/21)
Sex	Male	98.0 (48/49)	12.2 (6/49)	97.4 (38/39)	23.1 (9/39)
	Female	100 (18/18)	11.1 (2/18)	96.6 (28/29)	10.3 (3/29)
Baseline serum IgG4 level	< median[a)]	96.6 (28/29)	10.3 (3/29)	96.7 (29/30)	23.3 (7/30)
	≥ median[a)]	100 (31/31)	12.9 (4/31)	96.6 (28/29)	13.8 (4/29)
Disease state	New onset	100 (31/31)	12.9 (4/31)	96.8 (30/31)	12.9 (4/31)
	Relapse	97.2 (35/36)	11.1 (4/36)	97.3 (36/37)	21.6 (8/37)

Incidence % (number of patients with events/number of patients evaluated)
a) Placebo group, 424.0 mg/dL; inebilizumab group, 404.0 mg/dL

PMDA's view:
In the MITIGATE study, Grade ≥3 adverse events and serious adverse events occurred in patients aged ≥65 years at higher incidence in the inebilizumab group than in the placebo group. However, the events found as adverse drug reactions were all known risks and all resolved. These results are not indicative of particular safety concerns of inebilizumab in any of the populations evaluated.

7.R.3.3 Adverse events of special interest

Based on the mechanism of action of inebilizumab and the results of non-clinical and clinical studies, the applicant explains the adverse events of special interest (infusion related reaction, hypersensitivity, cytopenia, serious infections and opportunistic infections, and malignancy) as follows.

7.R.3.3.1 Infusion-related reactions

The applicant's explanation about infusion-related reactions:
The MITIGATE study specified premedication with antihistamines, antipyretic analgesics, and corticosteroids to mitigate infusion-related reactions, as in the global phase II/III study in patients with NMOSD (Study 1155). Infusion-related reactions[6)] occurred during the randomized controlled period of the MITIGATE study in 14.9% (10 of 67) of patients in the placebo group and 7.4% (5 of 68) of patients in the inebilizumab group (Table 15). All events were non-serious, and no events led to study drug discontinuation. During the open-label period, infusion-related reactions occurred in 4.5% (2 of 44) of patients (infusion related reaction in 2 patients) in the placebo/inebilizumab group and 6.5% (3 of 46) of patients (blood pressure increased, infusion related reaction, and tension headache in 1 patient each) in the inebilizumab/inebilizumab group. One of these events was a serious adverse drug reaction that led to the discontinuation of inebilizumab, but it resolved. In the Japanese population, 1 event (infusion related reaction) was observed in the inebilizumab group during the randomized controlled period. In the open-label period, 1 event (infusion related reaction) in the placebo/inebilizumab group and 1 event (infusion related reaction; the same patient as in the randomized controlled period) in the inebilizumab/inebilizumab group occurred. All events were non-serious.

6) The following events defined as infusion-related reactions: (a) All events reported in the electronic Case Report Form (eCRF) as "infusion related reaction" by the principal investigator, or (b) all events occurring on the day of administration of the study drug or the following day, excluding events corresponding to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) "Infections and infestations," "Blood and lymphatic system disorders," "Hepatobiliary disorders," or "Investigations" (excluding events classified under the High Level Group Term [HLGT] "Cardiac and vascular investigations [excl enzyme tests]")

Table 15. Incidence of infusion-related reactions in the MITIGATE study (randomized controlled period, safety analysis set)

	Overall population		Japanese population	
	Placebo (n = 67)	Inebilizumab (n = 68)	Placebo (n = 7)	Inebilizumab (n = 20)
Infusion related reaction	14.9 (10)	7.4 (5)	0	5.0 (1)
Palpitations	1.5 (1)	2.9 (2)	0	0
Dizziness	1.5 (1)	1.5 (1)	0	0
Flatulence	0	1.5 (1)	0	0
Infusion related reaction	0	1.5 (1)	0	5.0 (1)
Vomiting	0	1.5 (1)	0	0

Incidence % (number of patients with events), MedDRA ver.26.1

As described, infusion-related reactions associated with inebilizumab rarely occurred in the MITIGATE study, revealing no new safety concerns of inebilizumab in patients with IgG4-RD. The safety of inebilizumab can be well-managed by conveying appropriate cautionary advice via the package insert, as last time for the existing indications.

PMDA's view:
Although infusion-related reactions rarely occurred in the MITIGATE study, an event for which a causal relationship to inebilizumab could not be ruled out occurred. Therefore, infusion-related reactions warrant special attention. Premedication with antihistamines, antipyretic analgesics, and corticosteroids as well as close monitoring of patient's condition should be requested via the package insert, as last time for the existing indications.

7.R.3.3.2 Hypersensitivity

The applicant's explanation about hypersensitivity:
Anaphylaxis[7)] and serious hypersensitivity reactions[8)] were not observed in the placebo group during the randomized controlled period of the MITIGATE study, whereas 1 event (anaphylactic reaction) occurred in the inebilizumab group. The event, a serious adverse drug reaction, led to the discontinuation of inebilizumab but resolved. During the open-label period, no anaphylaxis or serious hypersensitivity reactions occurred. In the Japanese population, no anaphylaxis or serious hypersensitivity reactions occurred throughout the study period.

Thus, anaphylactic reactions and serious hypersensitivity reactions associated with inebilizumab rarely occurred in the MITIGATE study, suggesting no clinically significant safety concerns in patients with IgG4-RD. However, information about the anaphylactic reaction in the inebilizumab group will be communicated via the package insert.

PMDA's view:
Although anaphylactic reactions and serious hypersensitivity occurred rarely in the MITIGATE study, a causal relationship to inebilizumab could not be ruled out for the anaphylactic reaction reported. It is appropriate to provide information about anaphylactic reactions in the package insert.

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7) Events defined as (a) events reported in the eCRF by the investigator based on the National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis Network (FAAN) criteria specified in the clinical study protocol, or (b) events corresponding to the MedDRA Standardised MedDRA queries (SMQ) "Anaphylactic reaction"

8) Events defined as (a) all serious events reported as hypersensitivity reactions by the principal investigator, or (b) events corresponding to the MedDRA SMQ "Hypersensitivity (narrow)" that were serious and occurred outside the 24-hour allowable window for administration of the study drug

7.R.3.3.3 Cytopenia

The applicant's explanation about cytopenia:

Cytopenia[9)] occurred in 16.4% (11 of 67) of patients in the placebo group and 25.0% (17 of 68) of patients in the inebilizumab group during the randomized controlled period of the MITIGATE study (Table 16). All events were non-serious, and no cytopenia led to study drug discontinuation. During the open-label period, cytopenia was reported from 6.8% (3 of 44) of patients (leukopenia in 2 patients, and lymphopenia, neutropenia, and thrombocytopenia in 1 patient each) in the placebo/inebilizumab group, and from 1 patient (neutropenia) in the inebilizumab/inebilizumab group. All events were non-serious, and no cytopenia led to study drug discontinuation. In the Japanese population, cytopenia was reported from 14.3% (1 of 7) of patients in the placebo group and 40.0% (8 of 20) of patients in the inebilizumab group during the randomized controlled period; all events were non-serious, and no events were observed during the open-label period.

Table 16. Incidence of cytopenias in the MITIGATE study (randomized controlled period, safety analysis set)

	Overall population		Japanese population	
	Placebo (n = 67)	Inebilizumab (n = 68)	Placebo (n = 7)	Inebilizumab (n = 20)
Cytopenia	16.4 (11)	25.0 (17)	14.3 (1)	40.0 (8)
Lymphopenia	9.0 (6)	16.2 (11)	0	25.0 (5)
Neutropenia	4.5 (3)	5.9 (4)	14.3 (1)	10.0 (2)
Anaemia	1.5 (1)	2.9 (2)	0	5.0 (1)
Lymphocyte count decreased	0	2.9 (2)	0	10.0 (2)
Platelet count decreased	3.0 (2)	1.5 (1)	0	0
Leukopenia	1.5 (1)	1.5 (1)	0	0
Cytopenia	0	1.5 (1)	0	0
Iron deficiency anaemia	0	1.5 (1)	0	5.0 (1)

Incidence % (number of patients with events), MedDRA ver.26.1

As described, there are no new safety concerns with the risk of inebilizumab-associated cytopenia in patients with IgG4-RD. The safety of inebilizumab can be well-managed by conveying appropriate cautionary advice via the package insert, as last time for the approved indications.

PMDA's view:

No serious cytopenia was reported in the MITIGATE study. However, the use of inebilizumab, in light of its mechanism of action, warrants careful attention to possible cytopenia. The necessity of regular blood tests should be reminded appropriately via the package insert, as last time for the approved indications.

7.R.3.3.4 Serious infection and opportunistic infection

The applicant's explanation about serious infection and opportunistic infection:

Serious infections[10)] were not observed in the placebo group during the randomized controlled period of the MITIGATE study but occurred in 5.9% (4 of 68) of patients in the inebilizumab group (Table 17), of which 1 event (COVID-19 pneumonia) was an adverse drug reaction. An event (COVID-19

9) Events corresponding to the MedDRA SMQ "Haematopoietic cytopenias affecting more than one type of blood cell (narrow)," "Haematopoietic erythropenia (broad)," "Haematopoietic leukopenia (narrow)," and "Haematopoietic thrombocytopenia (narrow)."

10) Serious events corresponding to the MedDRA SOC "Infections and infestations."

pneumonia) led to study drug discontinuation in 1 patient in the inebilizumab group. During the open-label period, serious infections occurred in 6.8% (3 of 44) of patients (pneumonia in 2 patients and febrile infection in 1 patient) in the placebo/inebilizumab group and 4.3% (2 of 46) of patients (COVID-19 pneumonia and dengue fever in 1 patient each) in the inebilizumab/inebilizumab group. Of these, 1 event (febrile infection) in the placebo/inebilizumab group was found to be an adverse drug reaction. Events leading to study drug discontinuation did not occur in the placebo/inebilizumab group but were reported from 4.3% (2 of 46) of patients (COVID-19 pneumonia and dengue fever in 1 patient each) in the inebilizumab/inebilizumab group. In the Japanese population, no serious infections occurred in the placebo group during the randomized controlled period but occurred in 15.0% (3 of 20) of patients (appendicitis, COVID-19, and diverticulitis in 1 patient each) in the inebilizumab group. Of these, 1 event (COVID-19) was an adverse drug reaction. No events led to study drug discontinuation. No serious infections occurred during the open-label period in the Japanese population.

Opportunistic infections[11)] occurred in 1 patient (herpes zoster) in the placebo group and in 2.9% (2 of 68) of patients (herpes zoster in 2 patients) in the inebilizumab group during the randomized controlled period of the MITIGATE study, which were all non-serious. Events leading to study drug discontinuation did not occur in the placebo group but occurred in 1 patient (herpes zoster) in the inebilizumab group. During the open-label period, no opportunistic infections occurred in the inebilizumab/inebilizumab group while 1 event (herpes zoster) occurred in the placebo/inebilizumab group, but no events led to study drug discontinuation. No opportunistic infections were reported from the Japanese population throughout the randomized controlled and open-label periods.

Table 17. Incidence of serious infections and opportunistic infections in the MITIGATE study (randomized controlled period, safety analysis set)

	Overall population		Japanese population	
	Placebo (n = 67)	Inebilizumab (n = 68)	Placebo (n = 7)	Inebilizumab (n = 20)
Serious infection	0	5.9 (4)	0	15.0 (3)
Appendicitis	0	1.5 (1)	0	5.0 (1)
COVID-19	0	1.5 (1)	0	5.0 (1)
COVID-19 pneumonia	0	1.5 (1)	0	0
Diverticulitis	0	1.5 (1)	0	5.0 (1)
Opportunistic infection	1.5 (1)	2.9 (2)	0	0
Herpes zoster	1.5 (1)	2.9 (2)	0	0

Incidence % (number of patients with events), MedDRA ver.26.1

Accordingly, there are no new safety concerns with the risk of serious infections and opportunistic infections associated with inebilizumab in patients with IgG4-RD. The safety of inebilizumab can be well-managed by conveying appropriate cautionary advice via the package insert, as last time for the approved indications.

PMDA's view:

Although serious infections and opportunistic infections associated with inebilizumab rarely observed in the MITIGATE study, the use of inebilizumab warrants careful attention to possible infections including serious infections and opportunistic infections in light of inebilizumab's mechanism of action

[11)] Events defined as (a) opportunistic infection reported by the principal investigator, or (b) events identified based on preferred term (PT) described in *Ann Rheum Dis.* 2015;74:2107-16 or a combination of the MedDRA SMQ "Opportunistic infections (narrow)" and the MedDRA FDA Medical Query (FMQ) "Opportunistic infections (narrow)."

and reported serious infection and opportunistic infection for which a causal relationship to inebilizumab could not be ruled out. Prior to the enrollment in the MITIGATE study, participants were checked for hepatitis B virus infection, and those who had a history of hepatitis B virus infection or hepatitis B virus carriers were excluded. The necessity of hepatitis B virus screening and proper measures prior to inebilizumab administration should be communicated via the package insert, as last time for the approved indications.

7.R.3.3.5 Malignancy

The applicant's explanation about malignancy:
Malignancies[12)] were detected in 1.5% (1 of 67) of patients (renal cell carcinoma) in the placebo group and 2.9% (2 of 68) of patients (anal cancer and malignant melanoma in 1 patent each) in the inebilizumab group during the randomized controlled period of the MITIGATE study; none were found as adverse drug reactions. No events led to study drug discontinuation in the placebo group, while 2.9% (2 of 68) of patients (anal cancer and malignant melanoma in 1 patient each) in the inebilizumab group discontinued the study drug. During the open-label period, malignancies were reported from 1 patient (squamous cell carcinoma) in the placebo/inebilizumab group and 1 patient (prostate cancer) in the inebilizumab/inebilizumab group, and both were found as adverse drug reactions. There was no event leading to study drug discontinuation in the placebo/inebilizumab group, whereas prostate cancer in 1 patient in the inebilizumab/inebilizumab group led to study drug discontinuation. In the Japanese population, no malignancies were observed in the randomized controlled period or in the placebo/inebilizumab group during the open-label period, whereas prostate cancer was detected in 1 patient in the inebilizumab/inebilizumab group during the open-label period.

Table 18 shows malignancies reported as adverse drug reactions to inebilizumab in all clinical studies of inebilizumab and in domestic and foreign post-marketing safety information.[13)] These data, however, lacked necessary information for evaluation and cases of clear relevance to inebilizumab.

12) Events corresponding to MedDRA SMQ "Malignant tumours."
13) Clinical studies: Global phase III study in patients with IgG4-RD (MITIGATE study), global phase III study in patients with myasthenia gravis, global phase II/III study in patients with NMOSD, Japanese phase IV study in patients with NMOSD, global phase IV study in patients with NMOSD, and global phase II study in patients with NMOSD.
Post-marketing safety information: From June 11, 2020 to data cut-off on [redacted], 20[redacted]; 9,677 person-years.

Table 18. List of patients with malignancies reported as adverse drug reactions to inebilizumab

	Age	Sex	Ethnicity	Primary disease	Adverse events	Date of occurrence	Use of inebilizumab	Outcome
MITIGATE study	7[redacted]	Male	Non-Japanese	IgG4-RD	Squamous cell carcinoma	539	None	Recovered
	6[redacted]	Male	Japanese	IgG4-RD	Prostate cancer	749	Discontinued	Recovered
Post-marketing in Japan	6[redacted]	Male	Japanese	NMOSD	Acute myelomonocytic leukaemia	210	None	Unknown
Post-marketing in foreign countries	4[redacted]	Female	Non-Japanese	Unknown	Thyroidectomy Parathyroidectomy	155	Unknown	Unknown
	2[redacted]	Male	Non-Japanese	Unknown	CD19 lymphocytes decreased	Unknown	Discontinued	Not recovered
	6[redacted]	Female	Non-Japanese	NMOSD	Squamous cell carcinoma of the oral cavity	Unknown	Discontinued	Unknown
	4[redacted]	Female	Non-Japanese	NMOSD	Mastectomy	Unknown	Discontinued	Not recovered
	4[redacted]	Female	Non-Japanese	Unknown	Triple negative breast cancer	Unknown	Unknown	Unknown
	5[redacted]	Female	Non-Japanese	Unknown	Appendix cancer	Unknown	None	Unknown
	5[redacted]	Female	Non-Japanese	Unknown	Thyroid cancer	Unknown	Unknown	Unknown
	6[redacted]	Female	Non-Japanese	Unknown	Spindle cell sarcoma	Unknown	Unknown	Unknown
	5[redacted]	Female	Non-Japanese	NMOSD	Thyroid cancer	Unknown	None	Recovered
	6[redacted]	Female	Non-Japanese	NMOSD	Breast cancer	Unknown	None	Unknown
	Unknown	Female	Non-Japanese	NMOSD	Neoplasm malignant	Unknown	None	Recovered
	Unknown	Female	Non-Japanese	NMOSD	Skin cancer	Unknown	Temporary withdrawal	Unknown
	5[redacted]	Female	Non-Japanese	NMOSD	Bladder transitional cell carcinoma	203	Discontinued	Recovered
	Unknown	Unknown	Non-Japanese	NMOSD	Pancreatic carcinoma	Unknown	Not applicable[a)]	Death

MedDRA ver.26.1

a) Pancreatic carcinoma occurred at an unknown time after the last dose of inebilizumab.

As mentioned, the risks of malignancies associated with the administration of inebilizumab have not been clarified by the MITIGATE study or post-marketing safety information. No cautionary advice is necessary on malignancies in the package insert.

PMDA's view:

Malignancies have been reported as adverse drug reactions to inebilizumab from the MITIGATE study and post-marketing settings. Even so, at present, a definitive conclusion on the risks of malignancies associated with inebilizumab treatment is precluded because of the lack of evaluable data and cases showing a clear association between inebilizumab and malignancies. The applicant should continue to collect data on malignancies from the clinical studies after marketing. Any new findings should be communicated to healthcare professionals appropriately.

7.R.4 Clinical positioning and indication

The applicant's explanation about the clinical positioning and indication of inebilizumab:

IgG4-RD is a systemic immune-mediated chronic disease characterized by fibroinflammatory lesions affecting systemic organs, typically with repeated relapses and remissions. Flare-associated inflammatory fibrotic responses may lead to acute damage or permanent organ failure. Currently in Japan, there are no approved drugs indicated for IgG4-RD. Steroids are used for the induction of remission in active IgG4-RD both in Japan and abroad, and their therapeutic effects are shown in ≥90% of patients. However, flares occur in 40% to 76% of patients after steroid tapering or discontinuation

(*Expert Rev Clin Immunol.* 2017;13:867-75). Steroid therapy also brings concerns about adverse drug reactions such as diabetes mellitus. There is a need for treatment options that prevent flares and lead to the tapering or discontinuation of steroids.

Inebilizumab is a B-cell-depleting antibody targeting CD19 that is expected to be a new treatment option for IgG4-RD, in which B cells, particularly IgG4-positive plasma cells and plasmablasts, act a central role in the pathogenesis. The global phase III study in patients with IgG4-RD (MITIGATE study) demonstrated the efficacy of inebilizumab [see Section 7.R.2] with acceptable safety in light of the observed efficacy [see Section 7.R.3]. Thus, inebilizumab is a promising new treatment option for IgG4-RD. Accordingly, the indication of inebilizumab was proposed as "IgG4-related disease."

The MITIGATE study targeted patients with active (new-onset or relapsing) IgG4-RD receiving steroid therapy. The following explains the view on the administration of inebilizumab in patients with inactive IgG4-RD who were not receiving steroids or were receiving low-dose steroids. Table 19 shows the incidence of flare and steroid use during the randomized controlled period and the open-label period in 27 patients[14)] in the placebo group during the randomized controlled period of the MITIGATE study who had no disease activity prior to transition to the open-label period (at Week 52 of the randomized controlled period). The incidence of flare was low and the dose of steroid tended to decrease during the open-label period after starting inebilizumab, compared with the randomized controlled period during which inebilizumab was not administered. Safety data showed, during the open-label period, adverse events occurring in 88.9% (24 of 27) of patients, adverse drug reactions in 22.2% (6 of 27) of patients, Grade ≥3 adverse events in 7.4% (2 of 27) of patients, serious adverse events in 14.8% (4 of 27) of patients, and adverse events leading to inebilizumab discontinuation in 3.7% (1 of 27) of patients, with no particular safety concerns compared with the inebilizumab group in the randomized controlled period (Table 13). Therefore, the administration of inebilizumab is of clinical significance and recommended even for patients with inactive IgG4-RD who are not on steroids or are on low-dose steroids.

Table 19. Incidence of flare[a)] and steroid use in subjects without disease activity prior to transition to the open-label period in the placebo group during the randomized controlled period of the MITIGATE study (FAS)

	Randomized controlled period (n = 27)	Open-label period (n = 27)
Incidence of flare (%)	44.4 (n = 12)	0.0 (n = 0)
Mean annual flare rate ± SD (%)	0.52 ± 0.70	0.00 ± 0.00
Proportion of patients receiving steroids (%)	51.9 (n = 14)	44.4 (n = 12)
Mean daily steroid dose ± SD (mg, prednisolone equivalent)	3.559 ± 5.124	0.914 ± 2.379

a) IgG4-RD flares treated and adjudicated by AC

PMDA's view:

The efficacy of inebilizumab in patients with IgG4-RD was demonstrated in the MITIGATE study [see Section 7.R.2], and the safety is considered acceptable in light of the observed efficacy [see Section 7.R.3]. These outcomes indicate that inebilizumab may be a new treatment option for IgG4-RD. However, the MITIGATE study was conducted with the primary endpoint of "time to first flare," while

14) Defined as either (a) an IgG4-RD Responder Index score (*Arthritis Care Res*. 2018;70:1671-8) of 0 at Week 52 of the randomized controlled period, or (b) no disease activity determined by the principal investigator based on symptoms, clinical laboratory tests, physical examination, imaging findings, and pathological findings.

the efficacy of inebilizumab was demonstrated in the suppression of flares, i.e., recurrence of IgG4-RD, instead of the treatment of flares per se. Thus, the indication of inebilizumab should be "the suppression of recurrence of IgG4-related disease." In view of a certain levels of efficacy and safety of inebilizumab confirmed in patients who were disease activity-free for a certain period, albeit in limited number, the administration of inebilizumab may be acceptable for patients with inactive IgG4-RD as well. Nevertheless, it is important to highlight in the package insert, in its Clinical Studies section, that the MITIGATE study targeted patients with active (new-onset or relapsing) IgG4-RD receiving steroid therapy.

7.R.5 Dosage and administration

The applicant's explanation about the dosage regimen of inebilizumab:

Based on the following clinical study results, the MITIGATE study was conducted according to the dosing regimen of intravenous inebilizumab 300 mg administered on Day 1, Day 15, and Week 26, and every 6 months thereafter, from the randomized controlled period through the open-label period.

- In foreign phase I studies in patients with multiple sclerosis and scleroderma (Studies CP200 and 1102), B-cell depletion was incomplete and not sustained at doses of inebilizumab <300 mg.
- In a global phase II/III study in patients with NMOSD (Study 1155), intravenous inebilizumab of 300 mg on Day 1, Day 15, and every 6 months thereafter achieved a significant reduction of CD20-positive B-cell counts by Day 8 after the initial dose compared with baseline, and the counts thereafter remained below the lower limit of normal. The superiority of inebilizumab over placebo was demonstrated in the primary endpoint, "time to first AC-adjudicated attack," and the safety profile was considered acceptable based on the observed efficacy (Review Report for "Uplizna for Intravenous Infusion 100 mg" [dated February 3, 2021]).

Taken together, the MITIGATE study demonstrated the efficacy of inebilizumab [see Section 7.R.2], and the study yielded an acceptable safety profile in view of the observed efficacy [see Section 7.R.3]. The proposed dosage and administration remains the same as for the approved indication, i.e., intravenous administration of inebilizumab 300 mg on Day 1, Day 15, and every 6 months thereafter from the initial dose.

PMDA's view:

The MITIGATE study demonstrated the efficacy of inebilizumab in patients with IgG4-RD [see Section 7.R.2]. The safety of inebilizumab can be managed under the supervision of physicians with adequate knowledge of inebilizumab and expert knowledge and experience in the treatment of IgG4-RD [see Section 7.R.3]. Thus the dosage regimen of inebilizumab in accordance with the MITIGATE study, i.e., intravenous inebilizumab 300 mg on Day 1, Day 15, and every 6 months thereafter from the initial dose, is appropriate. In the MITIGATE study, steroids were used concomitantly with inebilizumab at the start of the randomized controlled period and were thereafter discontinued at Week 8, according to the tapering schedule [see Section 7.1]. The rule for steroid administration in the MITIGATE study should be communicated in the Clinical Studies section of the package insert.

7.R.6 Post-marketing investigations

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

In Japan, inebilizumab was approved in March 2021 for the indication of "prevention of relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)." The specified use-results survey is underway in accordance with the risk management plan, in addition to routine pharmacovigilance activities and early post-marketing phase vigilance. The specified use-results survey began in June 2021, and patient registration was completed in November 2023. The interim analysis data were compiled in September 2024 (248 registered cases, 218 fixed cases, observation period [median (interquartile range)] 111.0 [43.0, 366.0] days). The adverse events reported during the early post-marketing phase vigilance and those identified in the interim results of the specified use-results survey were all known events, indicating no new safety concerns. The MITIGATE study in patients with IgG4-RD also revealed no new risks of inebilizumab compared with the approved indication [see Section 7.R.3].

Based on the above, the discussion conducted in accordance with the notification "Procedures for Developing Post-marketing Study Plans for Drugs" (PSEHB/PED Notification No. 0314-4/PSEHB/PSD Notification No. 0304-4 dated March 14, 2019) concluded that there were no additional research questions to be addressed in the present application, and that no additional pharmacovigilance activities would be necessary in addition to the early post-marketing phase vigilance for IgG4-RD.

PMDA's view:

The following observations justifies the applicant's point that no additional pharmacovigilance activities are necessary other than the early post-marketing phase vigilance for IgG4-RD. If any safety concern is suggested during routine pharmacovigilance activities, the need for additional pharmacovigilance activities should be discussed again.

- The MITIGATE study in patients with IgG4-RD showed higher incidence of adverse drug reactions in the inebilizumab group than in the placebo group, but most events were Grade ≤2. Serious adverse drug reactions and adverse drug reactions leading to study drug discontinuation in the inebilizumab group were all known risks and all resolved [see Section 7.R.3.1].
- No safety issues requiring new measures have been identified so far in post-marketing experience with inebilizumab for the approved indication.

7.R.7 Development of inebilizumab for pediatric patients

The applicant's explanation about the development of inebilizumab for pediatric IgG4-RD:

Planning is underway for a global clinical study in pediatric patients aged ≥2 to <18 years with IgG4-RD, and the participation of Japanese patients is scheduled [redacted].

PMDA's view:

In light of the prevalence of IgG4-RD in children and current treatment options for this population, inebilizumab needs to be developed for pediatric use. The development plan for pediatric inebilizumab has been confirmed in accordance with the guidelines "Planning of the Pediatric Drug Development Program during Development of Drugs for Adults" (PSB/PED Notification No. 0112-3 dated January 12, 2024).

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

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

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

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

The new drug application data (CTD 5.3.5.1-1) 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, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that inebilizumab has efficacy in the suppression of recurrence of IgG4-related disease, and that inebilizumab has acceptable safety in view of its benefits. Inebilizumab is clinically meaningful because it offers a new treatment option for patients with IgG4-related disease.

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

Review Report (2)

October 15, 2025

Product Submitted for Approval

Brand Name	Uplizna for Intravenous Infusion 100 mg
Non-proprietary Name	Inebilizumab (Genetical Recombination)
Applicant	Mitsubishi Tanabe Pharma Corporation
Date of Application	March 19, 2025

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 and safety

At the Expert Discussion, the expert advisers supported PMDA's conclusions on issues presented in Sections "7.R.2 Efficacy" and "7.R.3 Safety" in the Review Report (1).

The expert advisors made the following comment on the safety of inebilizumab:

- Unlike NMOSD, IgG4-RD is treated with inebilizumab across various clinical departments, and many physicians are assumed to have only limited experience in B-cell depletion therapy using rituximab (genetical recombination), etc. Thorough safety measures for inebilizumab, including infection control, should be taken.

PMDA requested the applicant to ensure proper communication to healthcare professionals via written materials, etc. about the risks of inebilizumab including infections and to thoroughly implement necessary safety measures. The applicant agreed to take appropriate actions.

1.2 Indications

At the Expert Discussion, the expert advisers supported PMDA's conclusion on the issues mentioned in Section "7.R.4 Clinical positioning and indication" of the Review Report (1).

PMDA concluded that the indications should be defined as follows, and the applicant responded appropriately.

Indications

○ Prevention of relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)

○ Suppression of recurrence of IgG4-related disease

(Underline denotes additions.)

1.3 Dosage and administration

At the Expert Discussion, the expert advisers supported PMDA's conclusion on issues discussed in Section "7.R.5 Dosage and administration" of the Review Report (1).

PMDA has concluded that the dosage and administration should be specified as follows, and the applicant responded appropriately.

Dosage and Administration

The usual adult dosage is 300 mg of inebilizumab (genetical recombination) administered by intravenous infusion. The initial dose is followed 2 weeks later by the second dose and subsequent doses starting 6 months from the initial dose and thereafter once every 6 months.

(No change)

1.4 Post-marketing investigations

At the Expert Discussion, the expert advisers supported PMDA's conclusions on the issues mentioned in Section "7.R.6 Post-marketing investigations" of the Review Report (1).

PMDA has concluded that the risk management plan (draft) for inebilizumab should include the safety specification presented in Table 20, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 21.

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

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infusion reaction • Infections	• Hepatitis B virus reactivation • Progressive multifocal leukoencephalopathy (PML) • Decreased immune response • Malignancy	• None
Efficacy specification		
• None		

(No change from the current RMP)

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

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance (IgG4-RD) • Use-results survey (NMOSD)	• Disseminate data gathered during early post-marketing phase vigilance (IgG4-RD) • Organize and disseminate materials for healthcare professionals (NMOSD, IgG4-RD) • Organize and disseminate materials for patients (NMOSD, IgG4-RD)

(Underlined parts: Additions to the current RMP)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following approval condition. The product has been designated as an orphan drug, and the re-examination period is 10 years.

Indications

○ Prevention of relapse of neuromyelitis optica spectrum disorder (including neuromyelitis optica)
○ Suppression of recurrence of IgG4-related disease

(Underline denotes additions.)

Dosage and Administration

The usual adult dosage is 300 mg of inebilizumab (genetical recombination) administered by intravenous infusion. The initial dose is followed 2 weeks later by the second dose and subsequent doses starting 6 months from the initial dose and thereafter once every 6 months.

(No change)

Approval Condition

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

List of Abbreviations

AC	Adjudication Committee
ACR/EULAR	American College of Rheumatology/European League Against Rheumatism
ADA	Anti-drug antibody
AUC	Area under the concentration versus time curve
CI	Confidence interval
CL	Clearance
C_{max}	Maximum serum concentration
COVID-19	Coronavirus disease 2019
DMARD	Disease-modifying anti-rheumatic drug
ECLIA	Electro-chemiluminescence immunoassay
eCRF	Electronic Case Report Form
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
FMQ	FDA Medical Query
HLGT	High Level Group Term
Ig	Immunoglobulin
IgG4-RD	Immunoglobulin G4 related disease
Inebilizumab	Inebilizumab (Genetical Recombination)
MedDRA	Medical Dictionary for Regulatory Activities
MITIGATE study	Global phase III study in ≥18 years patients with IgG4-RD (CTD 5.3.5.1-1, study code VIB0551.P3.S2)
NMOSD	Neuromyelitis Optica Spectrum Disorder
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred term
QOL	Quality of life
SMQ	Standardised MedDRA queries
SOC	System organ class
$t_{1/2}$	Elimination half life
t_{max}	Time to reach maximum concentration
γ-GTP	Gamma-glutamyltransferase