Review Report

August 5, 2019
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	Benlysta for I.V. Infusion 120 mg Benlysta for I.V. Infusion 400 mg
Non-proprietary Name	Belimumab (Genetical Recombination) (JAN*)
Applicant	GlaxoSmithKline K.K.
Date of Application	November 29, 2018
Dosage Form/Strength	Powder for solution for infusion in a vial: Each vial contains 136 mg[1)] or 432 mg[2)] of Belimumab (Genetical Recombination).
Application Classification	Prescription drug, (6) Drug with new dosages
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of pediatric patients with systemic lupus erythematosus who have inadequately responded to conventional treatments, 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.

Indication

Treatment of patients with systemic lupus erythematosus who have inadequately responded to conventional treatments

(No change)

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1) Each vial is overfilled to compensate for loss during preparation. The 120 mg vial is reconstituted with 1.5 mL of Water for Injection, Japanese Pharmacopoeia (JP), to make a total volume of approximately 1.7 mL. The excess volume allows withdrawal of 1.5 mL of the reconstituted solution containing 120 mg of belimumab (genetical recombination).

2) Each vial is overfilled to compensate for loss during preparation. The 400 mg vial is reconstituted with 4.8 mL of Water for Injection, JP, to make a total volume of approximately 5.4 mL. The excess volume allows withdrawal of the reconstituted solution containing 400 mg of belimumab (genetical recombination).

Dosage and Administration

The usual dosage for adults and children aged ≥5 years is 10 mg/kg of belimumab (genetical recombination) administered as an intravenous infusion on Days 0, 14, and 28, and at 4-week intervals thereafter.

(Underline denotes addition.)

Conditions of Approval

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

2. The applicant is required to conduct a drug use-results survey covering all patients treated with the product in the post-marketing setting until data from a certain number of patients have been gathered in order to collect data on the safety and efficacy of the product as early as possible, and thereby to take appropriate measures for the proper use of the product.

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

July 19, 2019

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

Product Submitted for Approval

Brand Name	Benlysta for I.V. Infusion 120 mg Benlysta for I.V. Infusion 400 mg
Non-proprietary Name	Belimumab (Genetical Recombination)
Applicant	GlaxoSmithKline K.K.
Date of Application	November 29, 2018
Dosage Form/Strength	Powder for solution for infusion in a vial: Each vial contains 136 mg[3)] or 432 mg[4)] of Belimumab (Genetical Recombination).

Proposed Indication

Treatment of patients with systemic lupus erythematosus who have inadequately responded to conventional treatments

(No change)

Proposed Dosage and Administration

The usual dosage for adults and children aged ≥5 years is 10 mg/kg of belimumab (genetical recombination) as an intravenous infusion on Days 0, 14, and 28, and at 4-week intervals thereafter.

(Underline denotes addition.)

3) Each vial is overfilled to compensate for loss during preparation. The 120 mg vial is reconstituted with 1.5 mL of Water for Injection, Japanese Pharmacopoeia (JP), to make a total volume of approximately 1.7 mL. The excess volume allows withdrawal of 1.5 mL of the reconstituted solution containing 120 mg of belimumab (genetical recombination).

4) Each vial is overfilled to compensate for loss during preparation. The 400 mg vial is reconstituted with 4.8 mL of Water for Injection, JP, to make a total volume of approximately 5.4 mL. The excess volume allows withdrawal of the reconstituted solution containing 400 mg of belimumab (genetical recombination).

Table of Contents

List of Abbreviations

See Appendix.

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

Belimumab (genetical recombination), the active ingredient of "Benlysta for I.V. Infusion 120 mg and Benlysta for I.V. Infusion 400 mg" (hereinafter referred to as "belimumab"), is a monoclonal antibody that binds to soluble B lymphocyte stimulator (BLyS). The antibody was developed by Human Genome Science (currently known as GlaxoSmithKline). In Japan, belimumab was approved in September 2017 for the treatment of patients with systemic lupus erythematosus (SLE) who have inadequately responded to conventional treatments.

SLE is a chronic autoimmune disease characterized by a variety of systemic inflammatory lesions including tissue injury caused by deposition of immune complexes in tissues (the Japan Intractable Diseases Research Foundation/Japan Intractable Diseases Information Center; http://www.nanbyou.or.jp/entry/215 [last accessed on July 19, 2019], *Harrison's internal medicine*: 18th ed. The McGraw-Hill Companies, Inc.; 2012.2724-35, etc.). The peak age of onset of SLE is 15 to 40 years, with approximately 10% to 20% of patients developing the disease before the age of 20 years (*Int J Rheum Dis.* 2015;18:182-91, etc.). In Japan, the prevalence of pediatric SLE is estimated to be 3.9 to 5.6 per 100,000 children (*Japanese journal of pediatrics.* 2009;62:1959-71, *Kidney and dialysis.* 2014;76:60-4).

The mainstay for the treatment of pediatric SLE is steroid therapy as is the case with adult patients. In patients with steroid resistance or those having serious adverse reactions to steroids, the use of an immunosuppressant is considered. Pediatric patients with SLE generally have a higher disease activity than adults, and an increase in the cumulative dose of steroids or immunosuppressants may possibly lead to an early onset and increased incidence of organ damage. There are thus expectations of a new therapeutic option for pediatric patients with SLE that cannot be adequately controlled by the standard therapy

In Japan, the clinical development program of belimumab for the treatment of pediatric SLE was initiated in [redacted] 20[redacted]. Recently, a partial change application was submitted for the change to the dosage and administration, based on the results of a global clinical study.

As of July 2019, belimumab is approved for use in adults in not less than 70 countries or regions including the US and Europe, as a therapeutic agent for patients with active SLE receiving standard therapy. For use in children aged ≥5 years, belimumab is under review in Europe as of July 2019 and was approved in the US in April 2019.

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

Since the present application is intended for addition of a new dosage, no data relating to quality of belimumab were submitted.

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

Although the present application is intended for addition of a new dosage, no new study data on non-clinical pharmacology were submitted because the non-clinical pharmacology of belimumab was evaluated during the review process for the initial approval.

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

The present application is intended for addition of a new dosage, and no new study data on non-clinical pharmacokinetics were submitted because the non-clinical pharmacokinetics of belimumab was evaluated during the review process for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

The applicant' explanation about the safety of belimumab in pediatric patients with SLE aged ≥5 years, based on the following toxicology data that had been submitted for approval for adult SLE:

- In the repeated intravenous dose toxicity study up to 6 months in mature cynomolgus monkeys, no belimumab-related findings were observed except decreased B cell count and smaller lymphatic tissues, both of which are related to the pharmacological action of belimumab.

- In a study of effects on pre- and postnatal development, including maternal function in cynomolgus monkeys, exposure to belimumab at a level exceeding the exposure in pediatric patients with SLE was observed in the offspring for a certain period of time. However, no findings related to belimumab were observed except a reversible decrease in blood B cell count and decrease in serum immunoglobulin (Ig) M level.

No new toxicity study using juvenile animals was conducted. However, the offspring was exposed to belimumab in the study of effects on pre- and postnatal development, including maternal function in cynomolgus monkeys. The applicant considered that the safety of belimumab in pediatric patients with SLE could be evaluated based on the data of this study. In addition, the data suggest that there is no significant difference in the toxicity profile between mature animals and juvenile animals and that pediatric patients with SLE are unlikely to experience unexpected serious adverse drug reactions.

PMDA accepted the explanation of the applicant.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

Belimumab concentration, anti-drug antibody (ADA), and neutralizing antibodies in serum were measured by immunological electrochemiluminescence assay (lower limit of quantitation: 100 ng/mL, 0.1 μg/mL, and 0.39 μg/mL, respectively).

6.2 Clinical pharmacology

The applicant submitted the results of the multi-regional phase II study (Study BEL114055 [CTD 5.3.5.1]) in pediatric patients with SLE as the evaluation data and the results of the population pharmacokinetic analysis as the reference data. The dose of Benlysta is expressed as that of belimumab (genetical recombination), and pharmacokinetic parameter values are expressed in mean ± standard deviation (SD).

6.2.1 Study in patients

6.2.1.1 Multi-regional phase II study (CTD 5.3.5.1, Study BEL114055 [Part A] [September 2012 to January 2018])

A multi-regional phase II study was conducted in pediatric patients with SLE (10 patients aged 5 to 11 years and 43 patients aged 12 to 17 years evaluated for pharmacokinetics [including 1 Japanese patient aged 1[redacted] years and 1 Japanese patient aged 1[redacted] years, respectively]) [see Section 7.1]. In the study, subjects received belimumab (10 mg/kg) as an intravenous infusion at Week 0, 2, 4, and then at 4-week intervals for a total of 52 weeks. Table 1 shows changes in the trough serum belimumab concentration over time. No ADA was detected in any of the patients.

Table 1. Trough serum belimumab concentration (μg/mL) following multiple intravenous administration of belimumab (10 mg/kg)

Patients (N)	Week 2	Week 4	Week 8	Week 52
5-11 years of age (10)	79.14 ± 61.001 (9)	83.37 ± 43.352 (10)	55.71 ± 30.730 (10)	53.40 ± 32.846 (9)
12-17 years of age (43)	77.37 ± 34.525 (41)	121.63 ± 63. 371 (43)	65.89 ± 39.256 (40)	72.16 ± 41.348 (33)
Japanese aged 1[redacted] years	93.65	131.77	94.40	76.78
Japanese aged 1[redacted] years	54.99	110.89	76.12	46.98

6.2.2 Population pharmacokinetic analysis (CTD 5.3.3.5)

Using the serum belimumab concentration data (560 sampling points in 53 patients) obtained in the multi-regional phase II study (Study BEL114055) in pediatric patients with SLE, a population pharmacokinetic analysis (NONMEM version 7.3) was conducted with a nonlinear mixed-effects model.

A linear 2-compartment model with first-order elimination process was used as the basic model. Baseline white blood cell count and baseline IgG were identified as the covariates for the distribution volume of the central compartment, and estimated glomerular filtration rate (eGFR) was identified as the covariate for urine protein and CL (clearance). The final model was developed by retaining these covariates.

The population pharmacokinetic parameters (relative standard error [%]) of belimumab estimated from the final model were 158 (3.62) mL/day for CL; 1927 (3.97) mL for central volume of distribution (V1); 701 (18.6) mL/day for clearance between compartments (Q); and 1622 (15.2) mL for peripheral volume of distribution (V2). Table 2 shows the steady-state pharmacokinetic parameters of belimumab estimated from the final model.

Table 2. Steady-state pharmacokinetic parameters following intravenous administration of belimumab (10 mg/kg) (estimated values)

Patients (N)	C_{max} (μg/mL)	C_{min} (μg/mL)	$AUC_{0-\tau}$ (day▪μg/mL)	$t_{1/2\beta}$ (day)	CL (mL/day)	V_{ss} (mL)
5-11 years of age (10)	305 [267, 350]	42 [30, 60]	2569 [1992, 3314]	16.1 [13.4, 19.3]	119 [97, 145]	2542 [1921, 3365]
12-17 years of age (43)	317 [288, 350]	52 [43, 63]	3126 [2765, 3533]	16.4 [14.7, 18.3]	169 [151, 190]	3798 [3425, 4212]

Geometric mean [95% confidence interval (CI)]

6.R Outline of the review conducted by PMDA

6.R.1 Dosage and administration in children

The applicant's explanation about the pharmacokinetics in pediatric patients with SLE:

Table 3 shows the steady-state pharmacokinetic parameters of belimumab in patients with SLE, estimated from the final model of the population pharmacokinetic analysis for children and adults.

Table 3. Steady-state pharmacokinetic parameters following intravenous administration of belimumab 10 mg/kg (estimated values)

Patients (N)	C_{max} (μg/mL)	C_{min} (μg/mL)	$AUC_{0-\tau}$ (day▪μg/mL)	$t_{1/2\beta}$ (day)	CL (mL/day)	V_{ss} (mL)
5-11 years of age (10)[a),d)]	305 [267, 350]	42 [30, 60]	2569 [1992, 3314]	16.1 [13.4, 19.3]	119 [97, 145]	2542 [1921, 3365]
12-17 years of age (43)[a),d)]	317 [288, 350]	52 [43, 63]	3126 [2765, 3533]	16.4 [14.7, 18.3]	169 [151, 190]	3798 [3425, 4212]
Japanese aged 1[redacted] years[a)]	312	70	3576	18.8	108	2823
Japanese aged 1[redacted] years[a)]	279	56	2921	18.6	141	3569
Non-Japanese adults (563)[b)]	308 [303, 314]	46.2 [44.2, 48.3]	2809 [2731, 2888]	18.1 [17.7, 18.5]	232 [226.3, 238.8]	5241 [5186, 5296]
Japanese adults (39)[c)]	275 [265, 285]	48.2 [43.3, 53.6]	2660 [2495, 2835]	20.3 [19.0, 21.7]	201 [186, 218]	5138 [5022, 5258]

Geometric mean [95% CI]

a) Study BEL114055, b) Studies BEL110751 and BEL110752, c) Study BEL113750

d) Includes the Japanese patient.

Study BEL114055 did not show any significant difference in pharmacokinetic parameters between the overall pediatric population and individual Japanese pediatric patients with SLE, nor were there clear ethnic differences in the pharmacokinetics between Japanese and non-Japanese adult patients with SLE (see Review Report on the initial application, dated August 30, 2017). In light of these findings, dose adjustment based on ethnicity was considered to be unnecessary in Japanese children.

The 95% confidence intervals (CIs) of steady-state exposure parameters (C_{max}, C_{min}, and $AUC_{0-\tau}$) overlapped among the pediatric age groups, the overall pediatric population, and the adult patient population. In addition, age was not identified as a covariate in the population pharmacokinetic analysis for pediatric patients with SLE. These findings suggest that age does not significantly affect the pharmacokinetics of belimumab as far as it is administered on a body weight basis. Belimumab should be administered intravenously to pediatric patients with SLE according to the same dosage regimen as that for adults.

PMDA accepted the applicant's explanation and considers that the above dosage regimen does not suggest any particular problems from the point of view of pharmacokinetics.

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

The applicant submitted efficacy and safety evaluation data from the clinical study shown in Table 4.

Table 4. Evaluation data submitted

Region	Study identifier	Phase	Subjects	Number of patients enrolled	Outline of dosage regimen	Main endpoints
Multi-regional	Study BEL114055 (Part A)	II	Pediatric patients with SLE who have inadequately responded to conventional treatments	(a) Belimumab 10 mg/kg: 53 (b) Placebo: 40	Intravenous infusion once every 2 weeks until Week 4, and then at 4-week intervals	Efficacy Safety

7.1 Multi-regional phase II study (CTD 5.3.5.1, Study BEL114055 [Part A] [September 2012 to January 2018])

A randomized, parallel-group, placebo-controlled, double-blind study was conducted in 10 countries or regions including Spain, Peru, the US, and Japan to investigate the efficacy and safety of belimumab in pediatric patients[5] aged 5 to 17 years with SLE with disease activity despite standard therapy for SLE (target sample size, 100 subjects[6] [58 in the belimumab group, 42 in the placebo group]).

The study consisted of a 52-week double-blind period (Part A), an open-label extension period involving patients who had completed Part A (Part B), and a follow-up period involving patients who discontinued Part A or Part B (Part C). Part A consisted of the following 3 cohorts[7]:

- Cohort 1: patients aged 12 to 17 years (higher age bracket; N = 12) randomized to the belimumab group and the placebo group at a ratio of 5:1
- Cohort 2: patients aged 5 to 11 years (lower age bracket; N ≥10) randomized to the belimumab group and the placebo group at a ratio of 5:1
- Cohort 3: patients aged 5 to 17 years (N ≥48) randomized to the belimumab group and the placebo group at a ratio of 1:1[8]

Subjects received belimumab in combination with an SLE drug. In Part A, belimumab (10 mg/kg) or placebo was administered intravenously at Week 0, 2, 4, and then at 4-week intervals for a total of 52 weeks. In Part B, belimumab (10 mg/kg) was administered intravenously in an open-label manner for

5) Key inclusion criteria:
(a) Have a Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index (SELENA SLEDAI) score ≥6 points at screening.
(b) Had positive autoantibody test results at 2 time points (an antinuclear antibody titer ≥ 1:80 or an anti-double stranded DNA [dsDNA] antibody ≥30 IU/mL).
(c) Are on SLE treatment regimen consisting of the following medications (alone or in combination) at a fixed dose for a period of ≥30 days prior to Day 0: steroid (0.1 to 0.5 mg/kg/day of prednisone or equivalent alone, ≤0.5 mg/kg/day of prednisone or equivalent in combination therapy), antimalarial drugs, non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressants or immunomodulators (methotrexate [MTX], azathioprine, leflunomide, mycophenolate mofetil [MMF], calcineurin inhibitors, sirolimus, oral cyclophosphamide, 6-mercaptopurine, thalidomide, etc.).
(d) Have no complications such as nephritis requiring renal replacement therapy, severe or acute lupus nephritis necessitating acute phase treatment including nephritis with eGFR <30 mL/min, or central nervous system lupus (CNS lupus) requiring treatment.
(e) Have SLE meeting at least 4 of 11 items of the American College of Rheumatology (ACR) classification criteria of SLE (1997).

6) During the course of the study, it turned out that the enrollment of the planned number of patients was infeasible. Therefore, the target sample size was changed to ≥70, taking account of the enrollment record as of January 2017.

7) The study was designed to allocate patients to the higher age bracket of Cohort 2 or 3 after the end of the pharmacokinetic analysis of Cohort 1, and to the lower age bracket of Cohort 3 after the end of the pharmacokinetic analysis of Cohort 2.

8) Patients were stratified by a SELENA SLEDAI score at screening (≤12 points vs. ≥13 points) and by age (5-11 years vs. 12-17 years). However, since the target number of patients enrolled in the entire study was achieved before the start of the allocation of patients aged 5 to 11 years to Cohort 3, patients in this age bracket were not allocated to Cohort 3.

up to 10 years. In Part A, standard therapy which subjects had received prior to Day 0 was allowed to be added, discontinued, or changed in dose, according to the pre-specified criteria.[9)]

All of the 93 randomized patients received at least 1 dose of study drug (53 in the belimumab group, 40 in the placebo group). All of them were included in the intent-to-treat (ITT) population. The ITT population was used for the efficacy and safety analyses. In Part A, study treatment was discontinued in 15.1% (8 of 53) of patients in the belimumab group and in 22.5% (9 of 40) of patients in the placebo group. The main reasons for the discontinuation included adverse events (5.7% [3 of 53] of patients in the belimumab group, 12.5% [5 of 40] of patients in the placebo group).

The ITT population included a 6 Japanese subpopulation (2 in the belimumab group, 4 in the placebo group), all of whom completed Part A and entered Part B.

Table 5 shows the result of the efficacy endpoint. i.e., SLE responder index (SRI) response rate at Week 52 (see Section "10. Other" for definition). Table 6 shows the results in the Japanese subpopulation.

Table 5. SRI response rate at Week 52
(ITT population, Dropout/Treatment Failure = nonresponder [DO/TF = NR[10)]])

		Belimumab (N = 53)	Placebo (N = 40)	Odds ratio to placebo[b)] [95% CI]
SRI response rate		52.8 (28/53)	43.6 (17/39)[a)]	1.49 [0.64, 3.46]
Component index	≥4-point reduction in SELENA SLEDAI score	54.7 (29/53)	43.6 (17/39)[a)]	1.62 [0.69, 3.78]
	No worsening in PGA	75.5 (40/53)	66.7 (26/39)[a)]	1.70 [0.66, 4.39]
	No new BILAG 1A/2B organ domain scores	73.6 (39/53)	61.5 (24/39)[a)]	1.96 [0.77, 4.97]

% (n/N)

a) One patient in the placebo group was not subjected to analysis because baseline the Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index (SELENA SLEDAI) had not been assessed.

b) Logistic regression model with treatment, baseline SELENA SLEDAI score (≤12 points vs. ≥13 points), age (5-11 years of age vs. 12-17 years of age) as covariates. Baseline Physician's Global Assessment (PGA) score was added to the covariates for "No worsening in PGA." Baseline British Isles Lupus Assessment Group (BILAG) organ domain involvement (1A/2B vs. ≤1B) was added to the covariates for "No new BILAG 1A/2B organ domain scores."

Table 6. SRI response rate at Week 52
(Japanese subpopulation, ITT population, DO/TF=NR)

		Belimumab (N = 2)	Placebo (N = 4)
SRI response rate		0	25.0 (1/4)
Component index	≥4-point reduction in SELENA SLEDAI score	0	25.0 (1/4)
	No worsening in PGA	100 (2/2)	75.0 (3/4)
	No new BILAG 1A/2B organ domain scores	100 (2/2)	75.0 (3/4)

% (n/N)

9) Steroid (total systemic dose [mean daily dose]): Dose modification was allowed up to Week 24. The dose was increased by ≤25% from baseline or by ≤5 mg/day (whichever was higher) by Week 24 and dose increase by >25% from baseline or by >5 mg/day (whichever was higher) was prohibited after Week 24 (a short-term high dose administration for a purpose other than SLE treatment was permitted). From Week 44 to Week 52, additional dose increase exceeding the baseline level or the dose at Week 44 (whichever was higher) was prohibited. In patients who showed improvement in the disease activity of SLE for ≥4 weeks, the dose was decreased to the target level of ≤7.5 mg/day after Week 24 at the discretion of the investigator.
Antimalarial drugs: Starting treatment with this type of agents or dose increase (exceeding the baseline dose level or the dose at Week 16, whichever was higher) was prohibit at or after Week 16.
Immunosuppressants/immunomodulators: Starting new treatment with these types of agents after the start of study drug or dose increase (exceeding the baseline dose level or the dose at Week 16, whichever was higher) was prohibited at or after Week 16.
NSAIDs and aspirin: Starting treatment with these types of agents at or after Week 44, or newly starting the use of the agents for ≥7 days (only for the dose of aspirin exceeding 1000 mg/day) was prohibited.
Others: Use of concomitant (intravenous) immunoglobulin and other biopharmaceuticals, (intravenous) cyclophosphamide, and plasmapheresis was prohibited.

10) Patients who discontinued the study and patients with treatment failure were defined as nonresponders.

In Part A, adverse events were observed in 79.2% (42 of 53) of patients in the belimumab group and 82.5% (33 of 40) of patients in the placebo group. Table 7 shows main events observed.

Death occurred in 1 patient in the placebo group (pancreatitis acute). Its causal relationship to the study drug was ruled out. Serious adverse events were observed in 17.0% (9 of 53) of patients in the belimumab group (lupus nephritis, lupus nephritis/rash, systemic lupus erythematosus/skin lesion, hypertransaminasaemia, gastroenteritis/vasculitis gastrointestinal, herpes zoster, post herpetic neuralgia, abscess limb, and vulval abscess/idiopathic intracranial hypertension/pericardial effusion [1 patient each]), and in 35.0% (14 of 40) of patients in the placebo group (lupus nephritis [2 patients], glomerulonephritis/herpes zoster, anaemia/thrombocytopenia, retinal vasculitis/headache/pyrexia/fluid overload, epiglottitis/eye swelling/vomiting/headache/suicidal ideation, ligament sprain/major depression, chest pain/SLE arthritis/suicide attempt, pleural effusion, pneumonia, hepatitis A, influenza, pancreatitis acute, and osteochondrosis [1 patient each]). A causal relationship to the study drug could not be ruled out in 1 patient in the belimumab group (abscess limb) and in 4 patients in the placebo group (epiglottitis/suicidal ideation, chest pain/SLE arthritis, pneumonia, and influenza [1 patient each]). Adverse events led to treatment discontinuation in 5.7% (3 of 53) of patients in the belimumab group (lupus nephritis, hypertransaminasaemia, and post herpetic neuralgia [1 patient each]) and in 12.5% (5 of 40) of patients in the placebo group (lupus nephritis [2 patients], and retinal vasculitis, hepatitis A, and pancreatitis acute [1 patient each]).

Adverse drug reactions were observed in 35.8% (19 of 53) of patients in the belimumab group and in 37.5% (15 of 40) of patients in the placebo group.

Table 7. Adverse events reported by ≥5% of patients in either group (Part A, safety analysis set)

Event	Belimumab (N = 53)	Placebo (N = 40)	Event	Belimumab (N = 53)	Placebo (N = 40)
Nasopharyngitis	9 (17.0)	8 (20.0)	Gastroenteritis	3 (5.7)	3 (7.5)
Headache	7 (13.2)	11 (27.5)	Oropharyngeal pain	3 (5.7)	2 (5.0)
Diarrhoea	7 (13.2)	3 (7.5)	Neutropenia	3 (5.7)	1 (2.5)
Upper respiratory tract infection	6 (11.3)	8 (20.0)	Transaminases increased	3 (5.7)	1 (2.5)
Herpes zoster	5 (9.4)	3 (7.5)	Vomiting	2 (3.8)	4 (10.0)
Nausea	5 (9.4)	3 (7.5)	Back pain	2 (3.8)	3 (7.5)
Chest pain	4 (7.5)	4 (10.0)	Leukopenia	2 (3.8)	3 (7.5)
Epistaxis	4 (7.5)	3 (7.5)	Pyrexia	2 (3.8)	3 (7.5)
Rash	4 (7.5)	1 (2.5)	Urinary tract infection	1 (1.9)	4 (10.0)
Arthralgia	3 (5.7)	4 (10.0)	Dyspepsia	1 (1.9)	3 (7.5)
Lupus nephritis	3 (5.7)	4 (10.0)	Anaemia	0	3 (7.5)
Cough	3 (5.7)	3 (7.5)	Influenza	0	3 (7.5)
Pharyngitis	3 (5.7)	3 (7.5)	Insomnia	0	3 (7.5)
Abdominal pain	3 (5.7)	3 (7.5)	Suicidal ideation	0	3 (7.5)

% (n)

Analysis of the Japanese subpopulation data in Part A revealed adverse events occurring in 100% (2 of 2) of patients in the belimumab group and in 75.0% (3 of 4) of patients in the placebo group. The adverse event reported by ≥2 patients in either group was nasopharyngitis (100% [2 of 2] of patients in the belimumab group, 50.0% [2 of 4] of patients in the placebo group). No death occurred. A serious adverse event was observed in 1 patient in the belimumab group (herpes zoster), but its causal relationship to the study drug was ruled out. There were no adverse events leading to treatment discontinuation or adverse drug reactions.

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan of belimumab:

SLE is characterized by chronic systemic inflammation that affects multiple organ systems. Treatment policy is determined based on the global assessment of the disease activity and organ damage. Compared with patients with adult-onset SLE, pediatric patients with SLE have a higher disease activity with more frequent complications with hypocomplementaemia and lupus nephritis, resulting in a tendency toward higher cumulative doses of corticosteroid and immunosuppressants. However, there is no difference in the immunogenetic or serologic pathology between pediatric and adult-onset SLE, and the diagnosis and treatment of SLE do not significantly vary among patients with different ages of onset. The standard diagnosis and treatment of pediatric SLE are the same as those of adult-onset SLE. Thus, physicians are advised to diagnose pediatric SLE by referring to the SLE classification criteria recommended by the American College of Rheumatology (ACR) and to treat SLE mainly with corticosteroid, antimalarial drugs and immunosuppressants, taking into account the organ system lesions and their severity. In Japan, pediatric SLE is diagnosed and treated in line with the Guide Book for the Diagnosis and Treatment of Pediatric Systemic Lupus Erythematosus (*Guide Book for the Diagnosis and Treatment of Pediatric Systemic Lupus Erythematosus*. 2018 edition. Yodosha Co., Ltd.; 2018). There are no significant differences in the diagnosis and treatment policy including treatment algorithm between Japan and foreign countries. In addition, clinical studies of belimumab in adult patients with SLE did not show any clear ethnic difference in the pharmacokinetics of belimumab between Japanese and non-Japanese patients. No clear difference was observed in the efficacy or safety of belimumab between Japanese and non-Japanese patients with SLE (see Review Report on Benlysta [the initial application], dated August 30, 2017).

On the basis of the above discussion, the applicant decided to prepare the clinical data package by conducting a multi-regional clinical study including Japan, and to evaluate the efficacy and safety of belimumab in Japanese pediatric patients with SLE.

Because of the extremely limited number of pediatric patients with SLE who have inadequately responded to conventional treatments, it was considered infeasible to conduct a confirmatory study involving a certain number of pediatric patients with SLE. The applicant therefore conducted a multi-regional study (Study BEL114055) in pediatric patients with SLE using the same dosage regimen, the same efficacy assessment method, and the same patient eligibility criteria, except for age, as those used in the phase III studies (Studies BEL113750, BEL110751, and BEL110752) of Benlysta for intravenous infusion in adult patients with SLE. The efficacy and safety of belimumab in Japanese pediatric patients with SLE were evaluated, taking account of the comparison with the efficacy, safety, and pharmacokinetics in adult patients with SLE.

PMDA's view:

Because of the extremely limited number of pediatric patients with SLE, the applicant considered that it was infeasible to conduct a confirmatory study involving a certain level of pediatric patients with SLE and to evaluate the efficacy of belimumab in the intended patient population. The applicant's decision

is understandable. The efficacy and safety of belimumab in Japanese pediatric patients with SLE can be evaluated based on the data from Study BEL114055 which was conducted according to the similar design as those of the multi-regional phase III studies (Studies BEL113750, BEL110751, and BEL110752) in adult patients with SLE and other studies.

7.R.2 Efficacy

The applicant's explanation about the efficacy of belimumab in pediatric patients with SLE:
The primary endpoint for Study BEL114055 was the same as that used in the phase III studies (Studies BEL113750, BEL110751, and BEL110752) in adult patients with SLE. The primary endpoint was the SRI response rate, whereby SRI is a composite endpoint consisting of (1) safety of estrogens in lupus erythematosus national assessment SLE disease activity index (SELENA SLEDAI) score which evaluates general disease activity, (2) British Isles Lupus Assessment Group (BILAG) which evaluates the specific worsening of each organ domain, and (3) Physician's Global Assessment (PGA) which is a comprehensive evaluation of unscorable systemic conditions by the physician. The criteria for the assessment of each component index are the same as those in Studies BEL113750, BEL110751, and BEL110752. Patients who met all of the following 3 criteria were defined as SRI responders: (1) ≥4-point reduction in SELENA SLEDAI score, (2) no new BILAG category A (severe) organ domain score or 2 new BILAG category B (moderate) organ domain scores, and (3) increase of <0.3 points in PGA (from baseline).

Table 5 shows the SRI response rate at Week 52, the primary endpoint, in Study BEL114055. Table 8 shows the SRI response rate at Week 52 and each component index in Studies BEL114055, BEL113750, BEL110751, and BEL110752. Results of the SRI response rate and each component index in Study BEL114055 showed a tendency similar to those observed in the clinical studies in adult patients with SLE.

Table 8. Between-study comparison of SRI response rate Week 52 (DO/TF = NR)

		Pediatrics (ITT population)				Adults (mITT population)					
		BEL114055				BEL113750				BEL110751/110752	
Population		Overall study population		Japanese subpopulation		Overall study population		Japanese subpopulation		Overall non-Japanese population	
		Belimumab	Placebo	Belimumab	Placebo	Belimumab[a)]	Placebo	Belimumab[a)]	Placebo	Belimumab[a)]	Placebo
N		53	39[b)]	2	4	446	217	39	20	563	562
SRI response rate		52.8 (28)	43.6 (17)	0	25.0 (1)	53.8 (240)	40.1 (87)	46.2 (18)	25.0 (5)	50.6 (285)	38.8 (218)
Odds ratio [95% CI] *P* value		1.49[c)] [0.64, 3.46] NA		NA		1.99[d)] [1.40, 2.82] *P* = 0.0001		2.57[d)] [0.78, 8.47] *P* = 0.1204		1.68[e)] [1.32, 2.15] *P* < 0.0001	
Component index	≤4-point reduction in SELENA SLEDAI	54.7 (29)	43.6 (17)	0	25.0 (1)	55.8 (249)	41.9 (91)	48.7 (19)	25.0 (5)	52.8 (297)	40.9 (230)
	No worsening in PGA	75.5 (40)	66.7 (26)	100 (2)	75.0 (3)	77.4 (345)	68.7 (149)	84.6 (33)	60.0 (12)	74.6 (420)	66.2 (372)
	No new BILAG 1A/2B organ domain scores	73.6 (39)	61.5 (24)	100 (2)	75.0 (3)	80.3 (358)	68.2 (148)	84.6 (33)	60.0 (12)	75.5 (425)	69.2 (389)

% (n)

a) Belimumab 10 mg/kg

b) One patient in the placebo group was not subjected to analysis because baseline SELENA SLEDAI had not been assessed.

c) Logistic regression model comparing the belimumab group and the placebo group using baseline SELENA SLEDAI score (≤12 points vs. ≥13 points), age (5-11 years old vs. 12-17 years old) as covariates

d) Logistic regression model comparing the 10 mg/kg group and the placebo group using dose, baseline SELENA SLEDAI score (≤9 points vs. ≥10 points), complement (low C3 or C4 vs. other), and country as covariates (only treatment identified as covariate for the Japanese subpopulation).

e) Logistic regression model comparing each belimumab group and the placebo group using baseline SELENA SLEDAI score (≤9 points vs. ≥10 points), urine protein (<2 g/day vs. ≥2 g/day), race (African descent or indigenous-American descent vs. other), and study as covariates

The percentage of patients who achieved SRI response at all timepoints of Weeks 44, 48, and 52 was 43.4% (23 of 53 patients) in the belimumab group and 41.0% (16 of 39 patients) in the placebo group. The percentage of patients who achieved SRI-6, the index with the threshold SELENA SLEDAI score specified at 6 points (which is one of the definitions of SRI responders), was 41.2% (21 of 51 patients) in the belimumab group and 34.2% (13 of 38 patients) in the placebo group, showing a tendency toward a higher efficacy in the belimumab group than in the placebo group.

Table 9 shows the results of assessment of pediatric patients according to the Pediatric Rheumatology International Trials Organisation (PRINTO)/ACR Pediatric Response Criteria that consists of Parent's Global Assessment (Parent GA), Pediatric Quality of Life Inventory (PedsQL), which is the outcome reported by the child, urine protein, and other indices [see Section 10 for the definition of each term]. The PRINTO/ACR responder rate tended to be higher in the belimumab group than in the placebo group regardless of the definition.[11)] Also, the efficacy of the treatment tended to be higher in the belimumab group than in the placebo group, as analyzed by component, except PedsQL physical domain score.

[11)] Definition 1: ≥50% improvement in ≥2 of 5 components and ≥30% worsening in ≤1 of the remaining 3 components
Definition 2: ≥30% improvement in ≥3 of 5 components and ≥30% worsening in ≤1 of the remaining 2 components

Table 9. PRINTO/ACR response rate at Week 52 and percent change from baseline in each component (ITT population, DO/TF = NR)

	Belimumab (N = 53)	Placebo (N = 40)	Difference from placebo	Odds ratio to placebo [95% CI]
PRINTO/ACR response rate (definition 1)	60.4 (32/53)	35.0 (14/40)	25.38	2.74 [1.15, 6.54][c)]
PRINTO/ACR response rate (definition 2)	52.8 (28/53)	27.5 (11/40)	25.33	2.92 [1.19, 7.17][c)]
Percent change from baseline in each PRINTO/ACR component (LOCF)				
SELENA SLEDAI[a)]	−43.3 ± 6.01 (53)	−38.0 ± 6.33 (39)		
PGA[a)]	−56.5 ± 6.02 (53)	−48.8 ± 6.65 (40)		
Parent GA[a)]	−19.4 ± 21.56 (47)	2.9 ± 19.02 (38)		
PedsQL physical function domain score[b)]	10.5 (53) [−100, 280]	12.5 (40) [−53, 575]		
Urine protein[b)]	−2.13 (53) [−85.1, 1681.9]	7.09 (40) [−90.6, 570.1]		

% (n/N)
a) Mean ± SD (n)
b) Median (n) [maximum, minimum]
c) Logistic regression model comparing the belimumab group and the placebo group using baseline SELENA SLEDAI score (≤12 points vs. ≥13 points) and age (5 -11 years old vs. 12-17 years old) as covariates

- Reduction in risk for SLE flare

The percentage of patients with severe SLE flare was 42.5% (17 of 40 of patients) in the placebo group and 22.6% (12 of 53patients) in the belimumab group, with the hazard ratio [95% CI] of belimumab to placebo being 0.38 [0.18, 0.82]. Figure 1 shows the Kaplan-Meier estimate for time to first severe SLE flare, suggesting that belimumab tended to reduce a risk for SLE flare compared with placebo, as was observed in Study BEL113750 in adult patients with SLE.

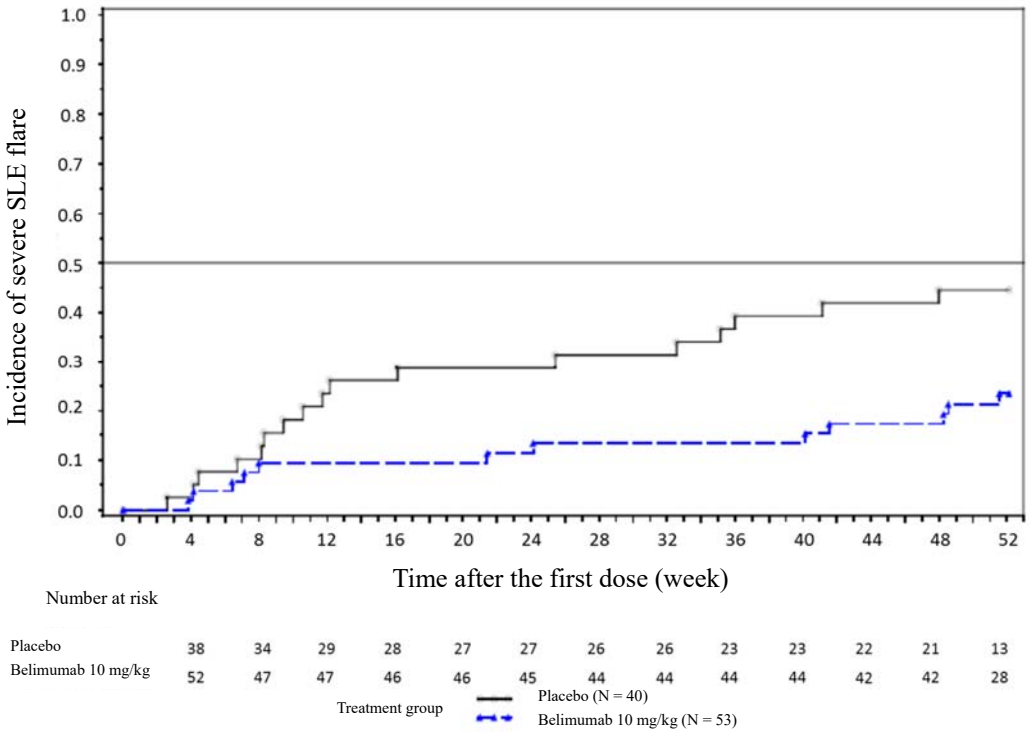

Figure 1. Kaplan-Meier curves for time to first severe flare (Part A) (ITT population)

- Steroid sparing effect

Table 10 shows the percentage of patients who achieved a reduction in the mean daily dose of steroid to ≤7.5 mg/day at Week 52 in Studies BEL114055, BEL113750, and BEL110751/110752. Although the results should be carefully interpreted because of the limited number of patients enrolled in Study BEL114055 and of the difference in baseline steroid dose between the groups, the data suggested a tendency toward a decrease in the dose of steroid in the belimumab group compared with the placebo group. The findings were generally consistent with the results of the phase III studies in adult patients with SLE.

Table 10. Percentage of patients who achieved reduction in mean daily steroid dose to ≤7.5 mg/day at Week 52

	Study BEL114055 (ITT)		Study BEL113750 (mITT)		Pooled data of Studies BEL110751 and BEL110752 (mITT)	
	Belimumab (N = 53)	Placebo (N = 40)	Belimumab[a)] (N = 451)	Placebo (N = 226)	Belimumab[a)] (N = 563)	Placebo (N = 562)
Baseline steroid dose (mg/day; mean ± SD)	9.1 ± 5.6	12.2 ± 8.7	16.0 ± 10.7	17.2 ± 10.8	10.9 ± 9.1	10.7 ± 8.5
Percentage of patients on steroid therapy at a dose of >7.5 mg/day at baseline (n/N)	49.1 (26/53)	55.0 (22/40)	78.0 (352/451)	81.4 (184/226)	57.5 (324/563)	56.6 (318/562)
Percentage of patients on steroid therapy at a dose of ≤7.5 mg/day at Week 52 (n/N)	23.1 (6/26)	13.6 (3/22)	19.3 (68/352)	15.2 (28/184)	21.9 (71/324)	14.5 (46/318)

a) Belimumab 10 mg/kg group

- Efficacy by organ system involved

Table 11 shows the improvement rate for the SELENA SLEDAI score classified by organ system in clinical studies in pediatric and adult patients with SLE. In Study BEL114055, belimumab tended to generally improve various organ system manifestations in SLE patients, particularly mucocutaneous and musculoskeletal manifestations that are common clinical symptoms in patients with SLE, although the study excluded patients who had active central nervous system lupus or unstable severe lupus nephritis. Belimumab's effect to improve immunologic manifestations (increase in anti-DNA antibody and hypocomplementaemia) was not as clear in Study BEL114055 as in the phase III study in adult patients with SLE. However, in patients who were positive for anti-double stranded DNA (dsDNA) (≥30 IU/mL) or had low complement levels (C3 <90 mg/dL and C4 <10 mg/dL), the median percent change from baseline [minimum, maximum] in each parameter at Week 52 was 2.2% [−94.1, 662.2] in anti-dsDNA titer, 6.0% [−25.0, 22.9] in C3 level, and 18.1% [−14.3, 200.0] in C4 level in the placebo group; and −44.9% [−90.0, 279.2] in anti-dsDNA titer, 17.3% [−40.3, 90.4] in C3 level, and 50.0% [−42.9, 650.0] in C4 level in the belimumab group, showing that there were a tendency toward an improvement in all parameters in the belimumab group compared with the placebo group.

Based on the above, the applicant considers that belimumab has a certain level of efficacy in all organ system manifestations including immunological biomarkers in pediatric patients with SLE as is the case in adult patients with SLE.

Table 11. Improvement rate for SELENA SLEDAI score at Week 52, classified by organ system

	Study BEL114055 (ITT)		Study BEL113750 (mITT)		Pooled data of Studies BEL110751 and BEL110752 (mITT)	
	Belimumab (N = 53)	Placebo (N = 40)	Belimumab[a)] (N = 451)	Placebo (N = 226)	Belimumab[a)] (N = 563)	Placebo (N = 562)
Central nervous system	50.0 (1/2)	0 (0/1)	100 (1/1)	0 (0/2)	63.2 (12/19)	9.1 (1/11)
Vascular system	50.0 (1/2)	100 (1/1)	66.7 (42/63)	57.6 (19/33)	73.7 (28/38)	40.5 (15/37)
Musculoskeletal system	71.4 (25/35)	51.5 (17/33)	74.1 (103/139)	54.7 (41/75)	56.5 (208/368)	49.2 (183/372)
Renal system	40.0 (4/10)	12.5 (1/8)	61.8 (84/136)	41.0 (32/78)	49.4 (42/85)	42.4 (39/92)
Mucocutaneous system	64.0 (32/50)	54.3 (19/35)	61.9 (229/370)	53.0 (97/183)	54.8 (249/454)	45.0 (211/469)
Immunologic system	19.5 (8/41)	21.4 (6/28)	27.8 (114/410)	12.9 (26/202)	27.3 (124/455)	10.0 (44/439)
Hematology (including pyrexia)	100 (3/3)	0 (0/2)	38.5 (15/39)	37.0 (10/27)	33.3 (18/54)	45.8 (22/48)
Cardiovascular and respiratory system	75.0 (3/4)	50.0 (1/2)	50.0 (1/2)	66.7 (2/3)	54.1 (20/37)	56.3 (18/32)

Upper row, %
Lower row, "number of patients with 'less-than-baseline' score"/"number of patients with baseline score of >0"
a) Belimumab 10 mg/kg group

- Efficacy by subgroup

Table 12 shows the SRI response rate in subgroups classified by key patient characteristics in Study BEL114055. No subgroups showed a tendency toward a significantly lower SRI response rate in the belimumab group than in the placebo group.

Table 12. SRI response rate at Week 52 in Study BEL114055, by patient characteristics

Patient characteristics		Belimumab (N = 53)	Placebo (N = 39)
Age	5-11 years of age	50.0 (5/10)	33.3 (1/3)
	12-17 years of age	53.5 (23/43)	44.4 (16/36)
Body weight (by quartile)	<43 kg	52.9 (9/17)	50.0 (3/6)
	≥43 kg and <52.5 kg	60.0 (6/10)	53.8 (7/13)
	≥52.5 kg and <60.4 kg	66.7 (8/12)	30.0 (3/10)
	≥60.4 kg	35.7 (5/14)	40.0 (4/10)
Race	White	59.3 (16/27)	52.4 (11/21)
	Asian	25.0 (2/8)	16.7 (1/6)
	Black—African American	66.7 (2/3)	0 (0/1)
	Indigenous Alaskan or American	53.3 (8/15)	45.5 (5/11)
SELENA SLEDAI score	≤9	45.5 (10/22)	35.7 (5/14)
	≥10	58.1 (18/31)	48.0 (12/25)
Anti-dsDNA antibody titer	Low (<30 IU/mL)	66.7 (10/15)	46.2 (6/13)
	High (≥30 IU/mL)	47.4 (18/38)	42.3 (11/26)
C3 level	Normal to high (≥90 mg/dL)	63.6 (21/33)	50.0 (14/28)
	Low (<90 mg/dL)	35.0 (7/20)	27.3 (3/11)
C4 level	Normal to high (≥10 mg/dL)	62.5 (20/32)	48.0 (12/25)
	Low (<10 mg/dL)	38.1 (8/21)	35.7 (5/14)
Steroid dose	0 mg/day	0 (0/3)	0 (0/2)
	>0 mg/day and ≤7.5 mg/day	58.3 (14/24)	68.8 (11/16)
	>7.5 mg/day	53.8 (14/26)	28.6 (6/21)
Antimalarial drug	Not administered	44.4 (4/9)	22.2 (2/9)
	Administered	54.5 (24/44)	50.0 (15/30)
Immunosuppressant	Not administered	60.0 (12/20)	38.5 (5/13)
	Administered	48.5 (16/33)	46.2 (12/26)

% (n/N)

● Efficacy of belimumab in Japanese pediatric patients with SLE

The baseline SELENA SLEDAI score in 6 Japanese pediatric patients with SLE who participated in Study BEL114055 was lower in the belimumab group (4 and 6 points) than in the placebo group (6, 8, 10, and 14 points). Also, disease activity in Japanese pediatric patients with SLE receiving belimumab tended to be lower than the mean disease activity in the overall study population (10.4 points in the placebo group, 10.3 points in the belimumab group).

Tables 6 and 8 show the SRI response rate at Week 52, the primary endpoint, in the Japanese subpopulation of Study BEL114055. Of 6 Japanese pediatric patients with SLE, only 1 (placebo group) achieved SRI response at Week 52. Of the remaining 5 patients who failed to achieve SRI response (2 patients in the belimumab group, 3 patients in the placebo group), 1 patient in the placebo group experienced mild to moderate flare at Week 4 and received an antimalarial drug as an add-on treatment at Week 16. This patient was therefore deemed as a non-responder (Treatment Failure). All of the remaining 4 patients failed to achieve ≥4-point reduction in SELENA SLEDAI score among the parameters of SRI components, and were deemed as non-responders (<4-point reduction [improvement] in SELENA SLEDAI score in 1 patient in the belimumab group, no change in SELENA SLEDAI in 1 patient each in the placebo group and the belimumab group, worsening in SELENA SLEDAI in 1 patient in the placebo group). In the patient who showed improvement in SELENA SLEDAI score (1 patient in the belimumab group), the SELENA SLEDAI score was 4 points at baseline and 2 points at Week 52. The patients may have had a difficulty in achieving ≥4-point reduction because of the low baseline SELENA SLEDAI score. Nevertheless, results suggest a certain level of the efficacy of belimumab because (1) PRINTO/ACR response (definition 1) was achieved, (2) steroid dose was reduced (from 20 mg/day to 4 mg/day), (3) anti-dsDNA antibody titer decreased, (4) complement levels increased, and (5) urine protein decreased.

As described above, the results of Study BEL114055, albeit investigated in an extremely limited number of patients, suggested that belimumab tended to reduce disease activity as assessed by the composite endpoint for efficacy, in Japanese pediatric patients with SLE as in the case of adult patients with SLE. The results of the efficacy endpoints included improvement in SRI response and in clinical manifestations in organ systems, reduction in risk for SLE flare, and steroid dose reduction. In addition, the multi-regional study involving adult patients with SLE also demonstrated that the efficacy of belimumab in the overall population is comparable to that in the Japanese subpopulation (see Review Report on Benlysta (the initial application), dated August 30, 2017). Furthermore, there is no significant difference in exposure to belimumab regardless of age or ethnicity [see Section 6.R.1]. These findings suggest that belimumab is effective in Japanese pediatric patients with SLE as well.

PMDA's view:

The goal of the treatment of SLE is to maintain remission or low disease activity and to prevent flare-up of the disease, thereby to avoid serious and irreversible organ damage. For this purpose, SLE is treated according to the following steps: (1) Administer remission induction therapy with a high-dose steroid and immunosuppressants for suppression of disease activity, and then (2) reduce steroid dose to the lowest possible level (*Ann Rheum Dis*. 2019;78:736-745). Study BEL114055 was conducted using the same target patient population (except the age at enrollment) and the same efficacy endpoint as those

employed in the phase III studies in adult patients with SLE (Studies BEL113750, BEL110751, and BEL110752). SRI response rate, the primary endpoint of Study BEL114055 in the pediatric patients with SLE, tended to be higher in the belimumab group than in the placebo group. This result was consistent with those of the studies in adult patients with SLE. Patients treated with belimumab showed a generally improving tendency in various organ system lesions, mucocutaneous and musculoskeletal manifestations, among others. Also, the risk of serious SLE flare possibly leading to serious and irreversible organ damage and fatal outcome tended to be lower in the belimumab group than in the placebo group. The percentage of patients who achieved a reduction in steroid dose to ≤7.5 mg/day also tended to be higher in the belimumab group than in the placebo group. Study BEL114055 demonstrated a tendency toward belimumab-induced improvement in disease activity, as assessed by the composite endpoint, in Japanese pediatric patients with SLE, albeit a limited number investigated. In addition, the pathology of SLE is generally similar in adults and children and the previously submitted data has demonstrated the efficacy of belimumab in Japanese adult patients with SLE. Based on the above findings, the efficacy of belimumab is promising in Japanese pediatric patients with SLE. The efficacy of belimumab in the reduction of disease activity in Japanese pediatric patients with SLE should be further investigated in the post-marketing surveillance, etc.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.3 Safety

The applicant's explained the safety of belimumab in pediatric patients with SLE, based on the safety data from Study BEL114055, the pooled data of Japanese and foreign comparative studies of Benlysta (belimumab) for intravenous infusion in adult patients with SLE (Studies BEL113750, BEL110751, BEL110752, and LBSL02) (hereinafter referred to as the "pooled analysis of adult IV data"), and the pooled data of Japanese and foreign comparative studies of Benlysta (belimumab) for intravenous infusion and subcutaneous injection in adult patients with SLE (Studies BEL113750, BEL110751, BEL110752, LBSL02, and BEL112341) (hereinafter referred to as the "pooled analysis of adult IV/SC data"). The applicant's explanation is as follows:

Table 13 shows the outline of safety in Study BEL114055, the pooled analysis of adult IV data, and the pooled analysis of adult IV/SC data. Results suggested no clear difference in the safety profile of belimumab between pediatric and adult patients with SLE. The safety data of pediatric patients with SLE were compared with the post-marketing safety profile in adult patients with SLE based on the Periodic Benefit-Risk Evaluation Report (PBRER; March 9, 2017 to March 8, 2018). The results did not show any new safety concerns in pediatric patients with SLE. In addition, available data do not suggest any clear difference in the safety profile between Japanese and non-Japanese pediatric patients with SLE.

Table 13. Outline of safety in pediatric and adult patients with SLE (Studies BEL114055, BEL110751, BEL110752, LBSL02, and BEL112341: ITT population; Study BEL113750: Safety analysis set)

	Study BEL114055		Pooled analysis of adult IV data[a)]			Pooled analysis of adult IV/SC data[b)]	
	Belimumab	Placebo	Belimumab 10 mg/kg	All belimumab combined[c)]	Placebo	All belimumab combined[d)]	Placebo
N	53	40	1144	1928	910	2484	1190
Total duration of exposure (patient-years)	49.1	34.7	1055	1781	829	2293	1078
Summary of adverse events							
All adverse events	42 (79.2)	33 (82.5)	977 (85.4)	1706 (88.5)	801 (88.0)	2155 (86.8)	1037 (87.1)
Serious adverse events	9 (17.0)	14 (35.0)	171 (14.9)	306 (15.9)	146 (16.0)	366 (14.7)	190 (16.0)
Death	0	1 (2.5)	6 (0.5)	11 (0.6)	4 (0.4)	14 (0.6)	6 (0.5)
Adverse events leading to treatment discontinuation	3 (5.7)	5 (12.5)	71 (6.2)	117 (6.0)	70 (7.7)	157 (6.3)	95 (8.0)
Adverse drug reactions	19 (35.8)	15 (37.5)	404 (35.3)	722 (37.4)	337 (37.0)	895 (36.0)	410 (34.5)
Adverse events of special interest							
Infection[e)]	7 (13.2) 18.3	3 (7.5) 8.6	68 (5.9) 7.7	112 (5.8) 7.9	57 (6.3) 7.4	142 (5.7) 7.6	78 (6.6) 7.6
Tuberculosis[e)]	1 (1.9) 2.0	0 0	2 (0.2) 0.3	2 (0.1) 0.2	2 (0.2) 0.4	4 (0.2) 0.2	4 (0.3) 0.5
Opportunistic infection[f)]	1 (1.9) 4.1	0 0	22 (1.9) 2.4	28 (1.5) 1.8	13 (1.4) 1.8	30 (1.2) 1.5	14 (1.2) 1.5
Herpes zoster[e)]	5 (9.4) 14.3	3 (7.5) 8.6	50 (4.4) 4.9	75 (3.9) 4.4	37 (4.1) 4.5	93 (3.7) 4.3	50 (4.2) 4.6
Sepsis[e)]	0 0	0 0	7 (0.6) 0.7	13 (0.7) 0.7	5 (0.5) 0.6	19 (0.8) 0.9	8 (0.7) 0.7
Serious infection	1 (1.9) 2.0	1 (2.5) 2.9	20 (1.7) 2.3	30 (1.6) 1.9	12 (1.3) 1.6	38 (1.5) 1.9	15 (1.3) 1.5
PML	0 0	0 0	0 0	0 0	0 0	0 0	0 0
HBV reactivation	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Post-injection generalised reaction[e)]	4 (7.5) 8.1	3 (7.5) 11.5	144 (12.6) 18.7	262 (13.6) 20.9	97 (10.7) 17.4	300 (12.1) 18.3	122 (10.3) 15.8
Immunogenicity[h)]	0 0	0 0	6 (0.5) 0.6	77 (4.0) 4.3	25 (2.7) 3.0	77 (3.1) 3.4	25 (2.1) 2.3
Malignant tumor[e)]	0 0	0 0	4 (0.3) 0.4	6 (0.3) 0.3	2 (0.2) 0.2	8 (0.3) 0.3	3 (0.3) 0.3
Malignant tumor other than NMSC[e)]	0 0	0 0	1 (0.1) 0.1	3 (0.2) 0.2	1 (0.1) 0.1	5 (0.2) 0.2	2 (0.2) 0.2
Depression and suicide/self-injury[e)]	1 (1.9) 2.0	4 (10.0) 20.2	69 (6.0) 7.9	156 (8.1) 11.2	62 (6.8) 8.9	173 (7.0) 9.5	72 (6.1) 7.9
Interstitial lung disease[e)g)]	0 0	0 0	3 (0.3) 0.3	3 (0.2) 0.2	3 (0.3) 0.4	4 (0.2) 0.2	4 (0.3) 0.4

Upper row, n (%); Lower row, incidence rate per 100 patient-years adjusted for total duration of exposure

a) Combining of pooled data of Studies BEL110751, BEL110752, and LBSL02 (Medical Dictionary for Regulatory Activities [MedDRA] version 17.1) and data of Study BEL113750 (MedDRA version 18.1) (except interstitial pneumonia)
b) Combining of pooled data of Studies BEL110751, BEL110752, LBSL02, and BEL112341 (MedDRA version 17.1) and data of Study BEL113750 (MedDRA version 18.1) (except interstitial pneumonia)
c) Pooled data of the belimumab 1, 4, and 10 mg/kg-iv groups
d) Pooled data of the belimumab 1, 4, and 10 mg/kg-iv groups and 200 mg-sc group
e) Partially modified MedDRA SMQ was used.
f) Sponsor's assessment
g) MedDRA (Studies BEL110751 and BEL110752, Ver. 12.0; Study BEL113750, Ver. 18.1; Study BEL112341, Ver. 17.1)
h) Patients who became ADA-positive until Week 52 after the first dose of study drug were tabulated.

The incidence of adverse events was analyzed for subgroups classified by patient characteristics including age, body weight, race, and concomitant drugs. Results did not show any significant difference in the incidence among subgroups. In the subgroup without immunosuppressant combination therapy, the incidence of infections and infestations (SOC) was 35.0% (7 of 20) of patients in the belimumab group and 76.9% (10 of 13) of patients in the placebo group, whereas the incidence in the subgroup with immunosuppressant combination therapy was 69.7% (23 of 33) of patients in the belimumab group and 66.7% (18 of 27) of patients in the placebo group, showing a tendency toward an increase in infection among patients receiving immunosuppressant combination therapy in the belimumab group. However,

the incidence did not differ between the belimumab group and the placebo group, suggesting that the increased incidence was due to the effect of the concomitant immunosuppressant.

Based on the above, there are currently no clear concerns about the safety of belimumab in pediatric patients with SLE, compared with the safety profile in adult patients with SLE, the approved patient population for belimumab. The applicant therefore considers that the safety risk during the use of belimumab in pediatric patients with SLE is manageable by taking safety measures similar to those currently taken for adult patients with SLE.

PMDA's view:
There are currently no data suggesting any new concerns about the safety of belimumab in pediatric patients with SLE, compared with the safety profile of belimumab in adult patients with SLE, the approved patient population for belimumab. However, patients on belimumab should be monitored for the occurrence of known adverse drug reactions reported in adult patients with SLE, such as serious infection. Also, physicians should be advised to take safety measures similar to those taken during the use of belimumab in adult patients with SLE. Because of the extremely limited number of Japanese pediatric patients with SLE investigated in clinical studies, information on the safety of belimumab in pediatric patients with SLE should be collected continuously in the post-marketing surveillance, etc., and the information thus obtained should be communicated appropriately to healthcare professionals.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning of belimumab in the treatment of pediatric SLE:
Standard therapy for pediatric SLE is steroid therapy as in the case of the treatment of adult SLE. Immunosuppressants and antimalarial drugs are also used, depending on the clinical conditions of individual patients, after the global assessment of disease activity and organ damage, and the severity thereof. Study BEL114055 investigated the efficacy and safety of belimumab used as an add-on therapy in patients with SLE who have inadequately responded to the conventional treatments such as steroid and immunosuppressant, as was the case with the phase III studies in adult patients (Studies BEL113750, BEL110751, and BEL110752). Conventional drugs used at baseline in participants in Study BEL114055 were similar to those in the phase III studies in adult patients (see Table 12 and the Review Report on Benlysta, dated August 30, 2017 [the initial application]). Based on the above, belimumab should be added to ongoing treatment in pediatric patients with SLE with active disease activity despite standard therapy for SLE, such as steroid and immunosuppressants, after careful consideration of the use of these anti-SLE drugs, as is the case with adult patients with SLE.

In addition, the applicant intends to provide the following information similar to that provided for the use of belimumab in adult patients with SLE: Patients with severe lupus nephritis or severe central nervous system lupus were investigated neither in Study BEL114055 nor in the phase III studies in adult patients, while autoantibody-positive patients with SLE were enrolled in these studies.

PMDA's view:
Belimumab can be positioned as one of the options for the treatment of pediatric patients with SLE with a high disease activity despite treatment with steroid and immunosuppressants, as is the case with the positioning of belimumab in the treatment of adult SLE. The applicant should inform healthcare professionals that Study BEL114055 did not investigate severe lupus nephritis or severe central nervous system lupus, as was not the case with adult patients with SLE. Whether a patient is eligible for treatment with belimumab should be carefully determined by physicians with sufficient knowledge and experience in the diagnosis and treatment of SLE, upon careful judgment of benefits expected from the clinical conditions of each patient, based on the thorough understanding of efficacy and safety data, including the eligibility criteria, patient characteristics, and concomitant drugs.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.5 Dosage and administration

The applicant's explanation about the proposed dosage and administration:
In Cohort 1 (children aged 12-17 years) of Study BEL114055, the same dosage as that in adults (10 mg/kg) was administered for the following reasons: (1) The belimumab dose of 10 mg/kg was selected as the dose for pediatrics based on the results of phase III studies (Studies BEL113750, BEL110751, and BEL110752) in adult patients with SLE, and (2) the population pharmacokinetic analysis of Studies BEL113750, BEL110751, and BEL110752 suggested that dose adjustment for body weight could avoid the effect of age on the exposure. Allocation of patients to Cohort 2 (children aged 5-11 years) was started after the decision was made on the necessity of dose adjustment in Cohort 1, and children aged 12-17 years and children aged 5-11 years were to be allocated to Cohort 3 after the interim analysis of Cohort 2 data and the decision on the necessity of dose adjustment. Results of the interim analysis of Cohort 1 data showed that the exposure in children aged 12-17 years with SLE was similar to that in adult patients with SLE, indicating no safety concerns. Also, results of the interim analysis of Cohort 2 data showed that the exposure in children aged 5-11 years with SLE was similar to that in children aged 12-17 years with SLE and to that in adult patients with SLE, indicating no safety concerns. In Study BEL114055, therefore, the dosage of 10 mg/kg was to be used regardless of age, and the study was continued.

The SRI response rate, the primary endpoint of Study BEL114055, tended to be higher in the belimumab 10 mg/kg group than in the placebo group. The results of other efficacy endpoints also showed a tendency toward improvement in the 10 mg/kg group [see Section 7.R.2]. In addition, the safety profile of belimumab does not raise any new concerns currently [see Section 7.R.3]. Furthermore, the population pharmacokinetic analysis of the final data from Study BEL114055 showed that the estimated exposure parameters were almost similar among the pediatric age groups, the overall pediatric population, the adult SLE patient population, with a largely overlapping distribution [see Section 6.R.1].

On the basis of the above findings, the applicant proposed the dosage regimen of belimumab at 10 mg/kg at Weeks 0, 2, and 4 (i.e., Days 0, 14, and 28), and thereafter at 4-week intervals, as is the case with the regimen for adults.

Based on the applicant's explanation, submitted data, and reviews in Sections 7.R.2 and 7.R.3, PMDA has concluded that the proposed dosage and administration for pediatric patients with SLE ("administer belimumab 10 mg/kg at Weeks 0, 2, and 4 [Days 0, 14, and 28], and thereafter at 4-week intervals") is appropriate.

The above conclusion by PMDA will be discussed at the Expert Discussion.

7.R.6 Post-marketing investigations

The applicant's explanation:
As described in Section 7.R.3, the safety profile of belimumab in pediatric patients with SLE does not raise any new particular concerns compared with that in adult patients with SLE, the approved patient population group for belimumab. However, because of the limited number of Japanese pediatric patients with SLE investigated, the applicant plans to conduct a post-marketing surveillance covering all pediatric patients with SLE treated with belimumab to investigate clinical safety and efficacy such as the long-term safety and efficacy of belimumab in the post-marketing setting, and also to continue the current safety measures taken for adult patients with SLE.

PMDA's view:
As discussed in Section 7.R.3, there are currently no new safety concerns outweighing the safety risk in adult patients with SLE, the approved patient population for belimumab. Therefore, the safety of belimumab in pediatric patients with SLE is acceptable. However, the safety and efficacy of belimumab should be investigated continuously in the post-marketing surveillance covering all patients treated with belimumab because (1) only a limited number of Japanese pediatric patients with SLE were investigated in clinical studies, and (2) SLE is often more severe in pediatric patients than in adult patients and, it is likely that in routine clinical practice, belimumab is used in pediatric patients with SLE that is more severe than the disease encountered in the clinical studies.

As is the case with adult patients, the use of belimumab in pediatric patients with SLE should be decided by physicians with thorough knowledge of belimumab and with sufficient experience in the treatment of SLE, upon careful assessment of risks and benefits of the drug in individual pediatric patients with SLE. Further, belimumab should be properly used by such physicians. The same safety measures should be taken as those taken for adult patients with SLE, the approved patient population for belimumab.

The above conclusion by PMDA and the necessity of further safety measures will be discussed in the Expert Discussion.

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

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

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

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

The inspection is currently ongoing. Its results and the conclusion of 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 belimumab has efficacy in the treatment of SLE in children, and that the belimumab has acceptable safety in view of its benefits. Benlysta (belimumab) has clinical significance because it offers a new treatment option for pediatric patients with SLE. The safety and efficacy of belimumab in Japanese pediatric patients with SLE should be further investigated in the post-marketing surveillance, etc.

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

10. Other

The main efficacy endpoints used in the multi-regional phase III study (BEL114055) are as shown below.

Endpoint	Definition
SRI response	Clinical response defined as achieving all of the following 3 measures at the time of assessment compared to baseline: • ≥4-point improvement (reduction) in SELENA-SLEDAI score • No worsening in PGA (increase of <0.3 points in PGA score) • No new BILAG A organ domain scores or <2 new BILAG B organ domain scores
SRI response rate	Percentage of patients showing SRI response
SELENA SLEDAI score	This index is a modified version of the SLEDAI developed for a US National Institute of Health-sponsored multi-center study on the use of estrogen/progesterone in female patients with SLE (*Ann Intern Med.* 2005;21:953-62, *N Engl J Med.* 2005;15:2550-8). The disease activity was assessed based on the sum (0-105 points) of the scores for each of the following items corresponding to the disease conditions of the patients in 10 days prior to the visit. • Central nervous system items (8 points for each item): Seizure, psychiatric symptom, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache • Vascular items (8 points for each item): Cerebrovascular disorder, vasculitis • Musculoskeletal items (4 points for each item): Arthritis, myositis • Renal item (4 points for each item): Urinary casts, haematuria, proteinurine, pyuria • Mucocutaneous items (2 points for each item): New rash, alopecia, mucosal ulcer • Cardiovascular and respiratory items (2 points for each item): Pleurisy, pericarditis • Immunologic items (2 points for each item): Hypocomplementaemia, increased anti-DNA antibody • Hematologic items (including pyrexia) (1 point for each symptom): Pyrexia, platelet count decreased, white blood cell count decreased A ≥3-point increase in the SELENA SLEDAI score is regarded as worsening of disease activity, and ≥4-point reduction defined as improvement.
PGA	The physician's global assessment of disease activity on a 10-cm visual analogue scale (VAS), anchored at a score of 0 to 3 (1 [mild], 2 [moderate], and 3 [severe]). Increase in PGA score is correlated with worsening of disease activity. At final assessment, increase of ≥1 point and ≤2.5 points is assessed as mild to moderate worsening, and increase of >2.5 points as severe worsening (*Arthritis Rheum.* 1992;35:630-40, *Arthritis Rheum.* 1991;34:937-44, *Lupus.* 1999;8:685-91)

Endpoint	Definition
BILAG	BILAG is intended to evaluate changes in disease activity, thereby assessing the necessity of alterations of therapy based on the patient's clinical signs and symptoms. A score is calculated for each organ system, depending on clinical symptoms associated with the SLE activity in the past 28 days (according to whether the symptoms are not present, improving, the same, worse, new) to select the appropriate treatment intensity (category). **Organ system** • General • Mucocutaneous • Neurological • Musculoskeletal • Cardiovascular and respiratory • Vasculitis • Renal • Hematology **Treatment intensity (category)** • Category A: Severe (symptoms require change in therapy) • Category B: Moderate (reversible symptoms manageable by symptomatic therapy) • Category C: Mild (stable symptoms) • Category D: No current symptoms, but the system has previously been involved. • Category E: No current or previous symptoms (the system has never been involved). "Worsening in ≥1 organ system to Category A" represents symptoms requiring steroid or immunosuppressant therapy. "Worsening in ≥2 organ systems to Category B" indicates reversible symptoms manageable with symptomatic therapy (*Q J MED*. 1993;86:447-58, *Lupus*. 2000;9:651-4).
PRINTO/ACR response	The clinical condition that meets each of the following criteria of the PRINTO/ACR, the composite index developed to evaluate the disease activity and health status of pediatric patients with SLE based on the physician's assessment and the parent's assessment (*Arthritis Rheum.* 2005;52:2854-64): Criterion 1: ≥50% improvement from baseline in any 2 of 5 outcome measures and ≥30% worsening in ≤1 of the remaining measures Criterion 2: ≥30% improvement from baseline in any 3 of 5 outcome measures and ≥30% worsening in ≤1 of the remaining measures The 5 outcome measures are as follows: • Parent's global assessment (Parent GA) • PGA • SELENA SLEDAI score • Proteinuria • PedsQL physical function domain score
PRINTO/ACR responder rate	Percentage of patients achieving PRINTO/ACR response
Parent GA	The parent's global assessment of the health condition of his/her child on a visual analogue scale containing 21 points, scored in 0.5 increments from 0 to 10. In the assessment, 0 indicates "excellent" and 10 indicates "very poor."
PedsQL physical domain score	PedsQL is a validated general scale for evaluating the quality of life (QOL) for children, consisting of 23 items, and the scores of the physical function domain (8 items) are transformed to a scale of 0 to 100. The patient (if aged ≥8 years) or the parent (if aged ≤7 years) answers the questions according to the following 5 grades: • 0: Never a problem • 1: Almost never a problem • 2: Sometimes a problem • 3: Often a problem • 4: Almost always a problem
SLE flare	The patient is diagnosed with severe SLE flare if the SELENA SLEDAI score exceeds 12 points and if at least 1 of other severity criteria (new onset or worsening of SLE symptom, prednisone dose increase by >0.5 mg/kg/day, new addition of an immunosuppressant, hospitalization for treatment, increase of >2.5 points in PGA score) is met. The patient is diagnosed with mild-to-moderate SLE flare if at least 1 of the following criteria are met: SELENA SLEDAI ≥3 points (≤12 points), new onset or worsening of SLE symptom, prednisone dose increase by ≤0.5 mg/kg/day, new addition of non-steroidal anti-inflammatory drug (NSAID) or hydroxychloroquine, and increase of ≥1 point (but ≤2.5 point) in PGA score.

Review Report (2)

August 5, 2019

Product Submitted for Approval

Brand Name	Benlysta for I.V. Infusion 120 mg Benlysta for I.V. Infusion 400 mg
Non-proprietary Name	Belimumab (Genetical Recombination)
Applicant	GlaxoSmithKline K.K.
Date of Application	November 29, 2018

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, safety, dosage and administration, post-marketing safety measures, and risk management plan (draft)

The expert advisors of the Expert Discussion supported PMDA's decision on the efficacy, safety, dosage and administration, and post-marketing safety measures of belimumab described in Review Report (1). The following comments were raised by the expert advisors: (i) Information on both adult and pediatric patients with SLE should be provided, and (ii) given that only a limited number of Japanese pediatric patients with SLE were investigated in clinical studies and that the disease often become more severe in pediatric patients than in adult patients, information on the long-term safety in Japanese pediatric patients with SLE should be collected continuously in the post-marketing surveillance.

Based on its review presented in Section "7.R.6 Post-marketing investigations" of the Review Report (1) and the comments raised by the expert advisors at the Expert Discussion, PMDA has concluded that the risk management plan (draft) for belimumab should include the safety specifications presented in Table 14, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 15. PMDA instructed the applicant to conduct post-marketing surveillances, etc., that allow investigations of these items.

Table 14. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious hypersensitivity • Serious infection (including tuberculosis, pneumonia, *Pneumocystis* pneumonia, sepsis, and opportunistic infection) • Reactivation of hepatitis virus B • PML	• Interstitial pneumonia • Malignant tumor • Immunogenicity • Effect on vaccination-induced immunoreactivity • Events related to depression and suicide/self-injury	• None
Efficacy specification		
• Efficacy in clinical use		

(No change)

Table 15. 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 (children) • Specified use-results survey (adults) (all-case surveillance) • Specified use-results survey (children) (all-case surveillance) • Post-marketing clinical study[a)]	• Provision of information based on data from the early post-marketing phase vigilance (children) • Preparation and distribution of materials for healthcare professionals. • Preparation and distribution of materials on self-administration (subcutaneous injection only) • Ensuring provision of information on proper use prior to delivery

a) After the approval of the present application for Benlysta, Studies BEL114333, BEL116027, and BEL114055 will be switched to post-marketing clinical studies.

(Underline denote additions.)

The applicant's explanation:

As described in Table 16, a specified use-results survey with a 52-week observation period will be conducted in pediatric patients with SLE who have inadequately responded to conventional treatments to confirm the safety and efficacy of belimumab in clinical use. The survey will cover all patients treated with belimumab until data are collected from a certain number of patients (target sample size, 115 patients) treated with belimumab, as is the case with the ongoing specified use-results survey in adult patients with SLE. In addition, patients will be followed for up to 3 years after the start of the treatment to investigate long-term safety by monitoring the occurrence of serious infection, progressive multifocal leukoencephalopathy (PML), malignant tumor, and adverse events leading to death, to the extent possible.

Table 16. Outline of specified use-results survey (draft)

Objective	To confirm the safety and efficacy of belimumab in clinical use
Survey method	All-case surveillance
Population	Pediatric patients with SLE who have inadequately responded to conventional treatments
Observation period	52 weeks (2-year follow-up will be conducted after the observation period)
Planned sample size	115 patients (for safety analysis)
Main survey items	• Safety specification: Serious hypersensitivity, serious infection (including tuberculosis, pneumonia, *Pneumocystis* pneumonia, sepsis, and opportunistic infection), reactivation of hepatitis virus B, progressive multifocal leukoencephalopathy (PML), interstitial pneumonia, malignant tumor, events related to depression and suicide/self-injury • Patient characteristics (body weight, age, disease duration, disease activity, organ system lesion, concurrent illness/past illness, etc.) • Prior treatment for SLE • Status of belimumab treatment • Concomitant drugs/therapies • Steroid dose • Adverse events • Efficacy evaluation

PMDA accepted these responses. The information obtained through these activities should be communicated appropriately and promptly to healthcare professionals, etc.

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

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

The new application data (CTD 5.3.5.1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below with the following conditions. The present application is intended to add a new dosage. Since the previously specified re-examination period remains more than 4 years, the re-examination period for the present application is the remainder of the ongoing re-examination period for the initial approval of the product (until September 26, 2025).

Indication

Treatment of patients with systemic lupus erythematosus who have inadequately responded to conventional treatments

(No change)

Dosage and Administration

The usual dosage for adults and pediatric patients aged ≥5 years is 10 mg/kg of belimumab (genetical recombination) as an intravenous infusion on Days 0, 14, and 28 and at 4-week intervals thereafter.

(Underline denotes addition.)

Conditions of Approval

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

2. The applicant is required to conduct a drug use-results survey covering all patients treated with the product in the post-marketing setting until data from a specified number of patients have been gathered in order to collect data on the safety and efficacy of the product as early as possible, and thereby to take appropriate measures for the proper use of the product.

Appendix

List of Abbreviations

ACR	American College of Rheumatology
ADA	Anti-drug antibody
$AUC_{0-\tau}$	Area under the concentration-time curve from time zero to τ
Benlysta	Benlysta for I.V. Infusion 120 mg, Benlysta for I.V. Infusion 400 mg
BILAG	British isles lupus assessment group
CI	Confidence interval
CL	Clearance
C_{max}	Maximum observed serum drug concentration
C_{min}	Minimum observed serum drug concentration
CNS lupus	Central nervous system lupus
DO/TF=NR	Dropout/Treatment Failure = Non-responder
dsDNA	Double stranded DNA
Ig	Immunoglobulin
ITT	Intent-to-treat
IV	Intravenous infusion
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMF	Mycophenolate mofetil
MTX	Methotrexate
NSAID	Non-steroidal anti-inflammatory drug
Parent GA	Parent's Global Assessment
PedsQL	Pediatric Quality of Life Inventory
PGA	Physician's Global Assessment
PMDA	Pharmaceuticals and Medical Devices Agency
PML	Progressive multifocal leukoencephalopathy
PRINTO	Pediatric Rheumatology International Trials Organization
Q	Clearance between compartments
SC	Subcutaneous injection
SDI	Systemic lupus International Collaborating Clinics/ACR Damage Index
SELENA SLEDAI	Safety of estrogens in lupus erythematosus national assessment SLE disease activity index
SLE	Systemic lupus erythematosus
SRI	SLE responder index
$t_{1/2,\beta}$	Terminal phase half-life
t_{max}	Time to reach maximum serum concentration
V1	Central volume of distribution
V2	Peripheral volume of distribution
Vss	Volume of distribution at steady state