**Report on the Deliberation Results**

September 12, 2017

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

| | |
|---|---|
| **Brand Name** | Benlysta for I.V. Infusion 120 mg<br>Benlysta for I.V. Infusion 400 mg<br>Benlysta for S.C. Injection 200 mg Autoinjector<br>Benlysta for S.C. Injection 200 mg Syringe |
| **Non-proprietary Name** | Belimumab (Genetical Recombination) (JAN*) |
| **Applicant** | GlaxoSmithKline K.K. |
| **Date of Application** | December 13, 2016 |

**Results of Deliberation**

In its meeting held on September 8, 2017, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

**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.

**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**

August 30, 2017
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.

| | |
|---|---|
| **Brand Name** | (a) Benlysta for I.V. Infusion 120 mg<br>Benlysta for I.V. Infusion 400 mg<br>(b) Benlysta for S.C. Injection 200 mg Autoinjector<br>Benlysta for S.C. Injection 200 mg Syringe |
| **Non-proprietary Name** | Belimumab (Genetical Recombination) |
| **Applicant** | GlaxoSmithKline K.K. |
| **Date of Application** | December 13, 2016 |
| **Dosage Form/Strength** | (a) Powder for solution for infusion in a vial: Each vial contains 136 mg[1)] or 432 mg[2)] of Belimumab (Genetical Recombination).<br>(b) Injection: Each 1-mL pre-filled syringe contains 200 mg of Belimumab (Genetical Recombination). |
| **Application Classification** | Prescription drug, (1) Drug with a new active ingredient |

**Definition**

Belimumab is a recombinant human IgG1 monoclonal antibody against the soluble form of human B cell activating factor belonging to the tumor necrosis factor family (BAFF). Belimumab is produced in mouse myeloma (NS0) cells. Belimumab is a glycoprotein (molecular weight: ca.147,000) composed of 2 H-chain (γ1-chain) molecules consisting of 453 amino acid residues each and 2 L-chain (λ1-chain) molecules consisting of 214 amino acid residues each.

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 5.0 mL of the reconstituted solution containing 400 mg of belimumab (genetical recombination).

*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.*

**Structure**

Amino acid sequence:

L chain

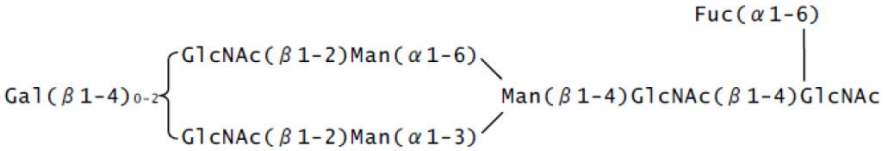
SSELTQDPAV SVALGQTVRV TCQGDSLRSY YASWYQQKPG QAPVLVIYGK
NNRPSGIPDR FSGSSSGNTA SLTITGAQAE DEADYYCSSR DSSGNHWVFG
GGTELTVLGQ PKAAPSVTLF PPSSEELQAN KATLVCLISD FYPGAVTVAW
KADSSPVKAG VETTTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE
GSTVEKTVAP TECS

H chain

QVQLQQSGAE VKKPGSSVRV SCKASGGTFN NNAINWVRQA PGQGLEWMGG
IIPMFGTAKY SQNFQGRVAI TADESTGTAS MELSSLRSED TAVYYCARSR
DLLLFPHHAL SPWGRGTMVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG
TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR
EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS
PGK

C213 in L chain - C226 in H chain, C232 in H chain - C232 in H chain, C235 in H chain - C235 in H chain: disulfide bonds
Q1 in H chain: pyroglutamate
N303 in H chain: glycosylated
K453 in H chain: truncated

Predicted structure of the main carbohydrate chain




Molecular formula: $C_{6358}H_{9868}N_{1728}O_{2008}S_{44}$ (protein moiety composed of 4 chains)
(light chain) $C_{992}H_{1531}N_{271}O_{333}S_5$
(heavy chain) $C_{2187}H_{3407}N_{593}O_{671}S_{17}$

Molecular weight: 144,051.62 (protein moiety composed of 4 chains)
(light chain) 22,741.71
(heavy chain) 49,288.13

**Items Warranting Special Mention** None

**Reviewing Office** Office of New Drug IV

**Results of Review**

On the basis of the data submitted, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the product has efficacy in the treatment of 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. However, the product has been shown to cause adverse events such as serious infection and may also induce serious adverse reactions such as progressive multifocal leukoencephalopathy (PML) and malignant tumor. Therefore, safety measures should be taken, for example, by advising physicians to closely monitor the patient's symptoms, etc. and then assess the risks and benefits of treatment with the product before the start of treatment and to appropriately manage adverse events, if any. An all-case post-marketing surveillance should be conducted until data are collected from a specified number of patients treated with the product, in order to delineate the safety profile of the product, including the occurrence of unknown adverse events, as early as possible. In addition, the surveillance should be designed to allow follow-up of serious infection, PML, malignant tumor, etc., during the long-term treatment.

**Indication**

Benlysta for I.V. Infusion 120 mg
Benlysta for I.V. Infusion 400 mg

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

Benlysta for S.C. Injection 200 mg Autoinjector
Benlysta for S.C. Injection 200 mg Syringe

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

**Dosage and Administration**

Benlysta for I.V. Infusion 120 mg
Benlysta for I.V. Infusion 400 mg

The usual dosage for adults 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.

Benlysta for S.C. Injection 200 mg Autoinjector
Benlysta for S.C. Injection 200 mg Syringe

The usual dosage for adults is 200 mg of belimumab (genetical recombination) once weekly administered subcutaneously.

**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.

**Attachment**

**Review Report (1)**

July 28, 2017

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.

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | (a) Benlysta for I.V. Infusion 120 mg<br>Benlysta for I.V. Infusion 400 mg<br>(b) Benlysta for S.C. Injection 200 mg Autoinjector<br>Benlysta for S.C. Injection 200 mg Syringe |
| **Non-proprietary Name** | Belimumab (Genetical Recombination) |
| **Applicant** | GlaxoSmithKline K.K. |
| **Date of Application** | December 13, 2016 |
| **Dosage Form/Strength** | (a) Powder for solution for infusion in a vial: Each vial contains 136 mg[3)] or 432 mg[4)] of Belimumab (Genetical Recombination).<br>(b) Injection: Each 1-mL pre-filled syringe contains 200 mg of Belimumab (Genetical Recombination). |
| **Proposed Indication** | Treatment of patient with systemic lupus erythematosus |

**Proposed Dosage and Administration**

(a) The usual dosage for adults 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.

(b) The usual dosage for adults is 200 mg of belimumab (genetical recombination) once weekly administered subcutaneously.

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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). In this report, the dose of Benlysta is expressed as that 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 5.0 mL of the reconstituted solution containing 400 mg of belimumab (genetical recombination). In this report, the dose of Benlysta is expressed as that of belimumab (genetical recombination).

**Table of Contents**

**List of Abbreviations**

| | |
|---|---|
| ADA | anti-drug antibody |
| ADCC | antibody-dependent cell cytotoxicity |
| [redacted] | [redacted] |
| AI | auto injector |
| ALT | alanine aminotransferase |
| ANA | antinuclear antibody |
| APRIL | a proliferation-inducing ligand |
| AST | aspartate aminotransferase |
| AUC | area under the serum concentration versus time curve |
| $AUC_{inf}$ | area under the serum concentration versus time curve from time zero to infinity |
| $AUC_{\tau}$ | area under the serum concentration versus time curve during one dosing interval |
| BA | bioavailability |
| BCMA | B cell maturation antigen |
| Belimumab | Belimumab (Genetical Recombination) |
| Belimumab intravenous infusion | Benlysta for I.V. Infusion 120 mg, Benlysta for I.V. Infusion 400 mg |
| Belimumab subcutaneous injection | Benlysta for S.C. injection 200 mg Autoinjector, Benlysta for S.C. Injection 200 mg Syringe |
| Benlysta | Benlysta for I.V. Infusion 120 mg, Benlysta for I.V. Infusion 400 mg, Benlysta for S.C. Injection 200 mg Autoinjector, and Benlysta for S.C. Injection 200 mg Syringe |
| BILAG | British Isles Lupus Assessment Group |
| BLyS | B lymphocyte stimulator |
| BMI | body mass index |
| BR3 | BAFF receptor |
| CAL | cells at the limit of *in vitro* cell age used for production |
| $C_{ave}$ | average serum drug concentration |
| CDC | complement-dependent cytotoxicity |
| [redacted] | [redacted] |
| CGE | capillary gel electrophoresis |
| CI | confidence interval |
| CL | clearance |
| $C_{max}$ | maximum observed serum drug concentration |
| CNS lupus | central nervous system lupus |
| CYP | cytochrome P450 |
| dsDNA | double stranded DNA |
| $EC_{50}$ | 50% effective concentration |
| ECL | immunological electrochemiluminescence |
| ELISA | enzyme-linked immunosorbent assay |
| F | absolute bioavailability |
| Fab | fragment antigen binding |
| Fc | Immunoglobulin constant region (fragment crystallizable) |
| FcRn | neonatal Fc receptor |
| FcγR | Fcγ receptor |
| HPLC | high performance liquid chromatography |
| $IC_{50}$ | half maximal inhibitory concentration |
| ICH | International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use |
| [redacted] | [redacted] |
| Ig | immunoglobulin |

| | |
|---|---|
| IV | intravenous infusion |
| LIGHT | homologous to lymphotoxin, exhibits inducible expression and competes with HSV glycoprotein D for binding to herpesvirus entry mediator, a receptor expressed on T lymphocytes |
| MCB | master cell bank |
| MedDRA/J | medical dictionary for regulatory activities Japanese version |
| mITT | modified intent-to-treat (all subjects receiving at least 1 dose of the study drug after randomization) |
| MMF | mycophenolate mofetil |
| MRT | mean residence time |
| MTX | methotrexate |
| NMSC | nonmelanoma skin cancer |
| NSAID | non-steroidal anti-inflammatory drug |
| PBMC | peripheral blood mononuclear cell |
| PFS | prefilled syringe |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| PML | progressive multifocal leukoencephalopathy |
| Q | clearance between compartments |
| QxW | Administration at x-week intervals. X is omitted if x is 1. |
| SC | subcutaneous injection |
| [redacted] | [redacted] |
| [redacted] | [redacted] |
| SELENA SLEDAI | safety of estrogens in lupus erythematosus national assessment systemic lupus erythematosus disease activity index |
| SLE | systemic lupus erythematosus |
| SLEDAI | systemic lupus erythematosus disease activity index |
| SPR | Surface plasmon resonance |
| SRI | SLE responder index |
| $t_{1/2}$ | elimination half-life |
| TACI | transmembrane activator and calcium-modulator and cyclophilin ligand interactor |
| TL1A | TNF-like ligand 1A |
| $t_{max}$ | time to reach maximum serum concentration |
| TNF | tumor necrosis factor |
| V1 | central volume of distribution |
| V2 | peripheral volume of distribution |
| $V_{ss}$ | volume of distribution at steady state |
| WCB | working cell bank |

## 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, etc., is a monoclonal antibody that binds to soluble B lymphocyte stimulator (BLyS). The antibody was developed by Human Genome Sciences (currently known as GlaxoSmithKline).

Systemic lupus erythematosus (SLE) is an autoimmune disease accompanied by immunologic abnormalities, such as abnormal B lymphocyte response and autoantibody production characterized by the presence of anti-DNA antibodies and anti-nuclear antibodies. SLE is characterized by diverse systemic inflammatory lesions including, among others, tissue injuries caused by tissue deposition of immune complexes (the Japan Intractable Diseases Research Foundation/ the Japan Intractable Diseases Information Center [http://www.nanbyou.or.jp/entry/215], *Harrison's internal medicine.* 18th ed. The McGraw-Hill Companies, Inc.; 2012;2724-35, etc.). Cardinal clinical symptoms of SLE include systemic conditions (fatigue, malaise, pyrexia, inappetence, decreased weight, etc.), dermal and mucosal symptoms (butterfly erythema, discoid rash, etc.), muscular and articular symptoms (myalgia, arthritis, etc.), renal symptoms (glomerulonephritis [lupus nephritis], etc.), neurological symptoms (central nervous system symptoms [CNS lupus], etc.), and hematological symptoms (anaemia, leukopenia, thrombocytopenia, etc.). Symptoms observed in individual patients are diverse depending on the types of affected organs and the severity of the disorders. In a majority of patients, the disease follows a chronic course with repeated remission and relapse. In Japan, SLE is a designated intractable disease (MHLW Ministerial Announcement No. 393 dated October 21, 2014). As of the end of FY 2014., a total of 63,622 patients (7066 men and 56,556 women) hold an "intractable disease medical treatment recipient certificate." In other word, the prevalence of SLE was approximately 50 cases per 100,000 people (Number of "intractable disease medical treatment recipient certificate" holders; Report on Public Health Administration and Services FY2014, 2015, MHLW).

Currently in Japan, the following drugs are approved for the treatment of SLE: methylprednisolone sodium succinate, azathioprine, cyclophosphamide hydrate, hydroxychloroquine sulfate, and alprostadil. Mycophenolate mofetil (MMF) and tacrolimus hydrate are also used, though the two drugs are approved for the treatment of lupus nephritis. Steroid therapy is the standard therapy for SLE. After remission has been achieved, the objective of the treatment is to maintain the disease activity at a low level by administering steroid at the minimum maintenance dose to prevent flare-up. If patients with SLE are steroid-resistant or if steroid therapy leads to any serious adverse reaction, use of an immunosuppressant is considered.

BLyS belongs to tumor necrosis factor (TNF) ligand superfamily and is known to contribute to inhibition of B cell apoptosis and to differentiation of B cells to immunoglobulin-producing cells (*Science*. 1999;285:260-63, *J Exp Med*. 2000;192:953-64). Moreover, there are reports that suggest the relationship of BLyS with the pathogenesis of SLE. For example, the overexpression of BLyS was seen in patients with SLE or other autoimmune diseases (*Arthritis Rheum.* 2001;44:1313-9, *J Immunol*. 2001;166:6-10, etc.) and there were a correlation between serum BLyS concentrations and lupus disease activity (*Arthritis Rheum*. 2008;58:2453-9). Belimumab binds to soluble BLyS, thereby inhibiting its biological activity. The clinical development of belimumab was therefore undertaken as a therapeutic agent for SLE.

Outside Japan, Benlysta for intravenous infusion containing belimumab as the active ingredient was approved in March 2011 in the US and in July 2011 in the EU as a therapeutic agent for treating patients with active, autoantibody-positive SLE who are receiving standard therapy. As of July 2017, belimumab has been approved in not less than 70 counties, including the US and European countries. An application for subcutaneous injection containing belimumab as the active ingredient was submitted in September 2016 in both Europe and the US. It is under review in Europe as of July 2017 and approved in the US in July 2017.

In Japan, the clinical development program of Benlysta (belimumab) for the treatment of SLE was initiated in [redacted] after completion of the foreign phase III study of Benlysta for intravenous infusion. A marketing application has been filed, based on the results of the multi-regional clinical study including Japan and other studies.

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

### 2.1 Drug substance

Descriptions in Sections 2.1.1, 2.1.3, 2.1.5, and 2.1.6 are common between the drug substance of the drug product for intravenous infusion and that of the drug product for subcutaneous injection.

#### 2.1.1 Generation and control of cell substrate

Clones encoding single chain variable region with high affinity to human BLyS protein were selected from a phage display library constructed from mRNAs isolated from B cells of healthy human origin, and these clones were used to prepare double stranded DNA (dsDNA) encoding heavy-chain variable region and that encoding light-chain variable region. They were then inserted into a vector containing the constant region of human immunoglobulin (Ig) G1 gene or the constant region of λ light chain gene to prepare a vector containing the gene encoding full-length heavy chain or light chain. The heavy chain-expressing unit was inserted into the light chain-expressing vector to generate a gene expression construct for belimumab. The expression construct thus obtained was introduced into NS0 cell line, and master cell bank (MCB) and working cell bank (WCB) were prepared using clones suitable for the manufacture of belimumab.

Characterization and purity test of the MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) were performed in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q5A (R1), Q5B, and Q5D guidelines. Results demonstrated their genetic stability during the manufacturing process. Retroviruses and retrovirus-like particles commonly observed in rodent-derived cell lines were detected, whereas no other viral or non-viral adventitious agents were detected within the range tested.

The MCB and WCB are stored in liquid nitrogen. There is no plan to generate new MCB or WCB.

### 2.1.2 Manufacturing process

#### 2.1.2.1 Manufacturing process (intravenous infusion)

The manufacturing process of the drug substance for the intravenous infusion comprises thawing of WCB, expanded culture, production culture, harvesting, [redacted] chromatography, low-pH virus inactivation, [redacted], [redacted], virus filtration, [redacted] chromatography, concentration/ultrafiltration/drug substance preparation, final filtration/filling, and testing. The production culture, [redacted] chromatography, low-pH virus inactivation, [redacted], [redacted], virus filtration, and [redacted] chromatography are defined as critical steps.

The manufacturing process of the drug substance for the intravenous infusion drug product is subjected to process validation on a commercial production scale.

#### 2.1.2.2 Manufacturing process (subcutaneous injection)

The manufacturing process of the drug substance for the subcutaneous injection drug product comprises thawing of WCB, expanded culture, production culture, harvesting, [redacted] chromatography, low-pH virus inactivation, [redacted], [redacted], virus filtration, [redacted] chromatography, concentration/ultrafiltration, concentration by [redacted], final filtration/filling, and testing. The production culture, [redacted] chromatography, low-pH virus inactivation, [redacted], [redacted], virus filtration, and [redacted] chromatography are defined as critical steps.

The manufacturing process of the drug substance for the subcutaneous injection is subjected to process validation on a commercial production scale.

### 2.1.3 Safety evaluation of adventitious agents

In the manufacturing process of the drug substance, the following biological materials are used: NS0 cell line (host cells), bovine milk-derived peptone, bovine milk-derived casein hydrolysate, and porcine pancreas-derived pancreatin. All of these materials have been confirmed to meet the Standards for Biological Ingredient.

MCB, WCB, and CAL have been subjected to purity tests [see Section 2.1.1]. Unpurified bulks obtained before harvest from the commercial-scale culture were subjected to microbial limit test, mycoplasma testing, *in vitro* adventitious virus testing, and test for minute virus of mice. Contamination with viral or non-viral adventitious agents was not observed within the range of the tests performed. These tests are established as in-process control tests for the unpurified bulk before harvesting.

The purification process was subjected to virus clearance studies using model viruses, and results demonstrated a sufficient level of viral clearance (Table 1).

**Table 1. Results of viral clearance studies**

| Manufacturing process | Virus reduction factor ($log_{10}$) | | | |
|---|---|---|---|---|
| | Xenotropic murine leukemia virus | Minute virus of mice | Reovirus | Pseudorabies virus |
| [redacted] chromatography | [redacted] | [redacted] | [redacted] a) | Not tested |
| Virus inactivation at low pH | [redacted] | Not tested | Not tested | [redacted] |
| [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Virus filtration | [redacted] | [redacted] | [redacted] | [redacted] |
| [redacted] chromatography | [redacted] | Not tested | Not tested | Not tested |
| Overall reduction factor | ≥20.61 | 8.56 | ≥9.34 | ≥14.85 |

a) Not used for calculating overall reduction factor

### 2.1.4 Manufacturing process development

#### 2.1.4.1 Manufacturing process development (intravenous infusion)

Table 2 shows the main changes made to the manufacturing process of the drug substance for the intravenous infusion. The formulation used in each clinical study was manufactured from the drug substance prepared by the following process: Processes M10 and M11 for phase I studies, Process M12 for phase II studies, and Processes M13, M14, and M15 (commercial process) for phase III studies. Comparability assessment of quality attributes was performed before and after the change of the manufacturing process for the drug substance, which confirmed the comparability of the drug substance. Before and after the manufacturing process change from Process M12 to Process M13, the comparability of the pharmacokinetics was confirmed using cynomolgus monkeys.

**Table 2. Main changes made to the manufacturing process during the development process of the drug substance (intravenous infusion)**

| | Change |
|---|---|
| Process M10 → Process M11 | Production scale |
| Process M11 → Process M12 | [redacted], [redacted] |
| Process M12 → Process M13 | Change in [redacted], addition of [redacted] chromatography, change in [redacted] |
| Process M13 → Process M14 | Production scale |
| Process M14 → Process M15 (commercial process) | Production scale |

#### 2.1.4.2 Manufacturing process development (subcutaneous injection)

Table 3 shows the main changes made to the manufacturing process of the drug substance for the subcutaneous injection. The formulation used in each clinical study was manufactured from the drug substance prepared by the following process: Processes M16 and M18 for phase I studies, and Process M18 for phase III studies. Comparability assessment of quality attributes was performed before and after the manufacturing process change for the drug substance, which confirmed the comparability of the drug substance.

**Table 3. Main changes made to the manufacturing process during the development process of the drug substance (subcutaneous injection)**

| | Change |
|---|---|
| Process M15 → Process M16 | Change in [redacted], Change in [redacted] |
| Process M16 → Process M18 | Change in [redacted], [redacted] scale |
| Process M18 → Process M21 (commercial process) | Addition of [redacted] |

### 2.1.5 Characterization

#### 2.1.5.1 Structure and characteristics

The drug substance was subjected to characterization tests described in Table 4.

**Table 4. Parameters evaluated in characterization tests**

| | |
|---|---|
| Primary structure | Amino acid sequence, posttranslational modification (C-terminal amino acid sequence, N-terminal amino acid sequence, deamidation, glycosylation, oxidation) |
| Higher order structure | Disulfide bond, secondary structure, tertiary structure |
| Physicochemical properties | Molecular weight, molecular variants, extinction coefficient |
| Carbohydrate structure | Monosaccharide component, sialic acid, N-linked oligosaccharide profile |
| Biological activities | BR3-Fc binding affinity, TACI-Fc binding affinity, BCMA-Fc binding affinity |
| | Binding inhibitory activity, [redacted] growth inhibitory activity |

As for biological activity, half maximal inhibitory concentration ($IC_{50}$) of belimumab against BLyS receptor (BAFF receptor 3 [BR3], transmembrane activator and calcium-modulator and cyclophilin ligand interactor [TACI], and B cell maturation antigen [BCMA]) was calculated by pharmacokinetic analysis using surface plasmon resonance (SPR). Also, it was confirmed that belimumab inhibited the binding of BLyS with its receptor in a dose-dependent manner, by an *in vitro* assay using [redacted] BLyS and [redacted] cells expressing 3 types of BLyS receptors (BR3, TACI, BCMA). Furthermore, it was confirmed that belimumab inhibited BLyS-induced cell proliferation in a concentration-dependent manner in the presence of [redacted] derived from mice.

In all of the above studies, the biological activity decreased in forcedly degraded samples containing high levels of aggregates, fragments, cross-linked forms, deamidated forms, or oxidized forms. In contrast, deglycosylated samples showed a similar biological activity as that of belimumab.

Belimumab showed no antibody-dependent cell cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) activity [see Section 3.2.2].

#### 2.1.5.2 Product-related substances/Product-related impurities

Based on the results of the characterization presented in Section "2.1.5.1 Structure and characteristics," [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] were identified as product-related substances. [redacted], [redacted], [redacted], and [redacted] were identified as product-related impurities. The product-related impurities are controlled by the specifications for the drug substance and the drug product.

#### 2.1.5.3 Process-related impurities

Host cell protein, host cell DNA, [redacted], [redacted], [redacted], [redacted], low molecule compounds, endotoxin, bioburden, extractables, and leachables were identified as process-related impurities. All process-related impurities have been shown to be completely removed during the manufacturing process. Endotoxin is controlled by the specifications for the drug

substance and for the drug product (bacterial endotoxin), and host cell protein and bioburden by the specifications for the drug substance (host cell protein and microbial limit).

### 2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification ([redacted]-high performance liquid chromatography [HPLC], [redacted], and peptide mapping), glycosylation profile, osmotic pressure, pH, charge variants, purity (SEC and capillary gel electrophoresis [CGE, reduced]), host cell protein, bacterial endotoxin, microbial limit, relative potency (binding inhibitory activity), and assay (ultraviolet-visible spectrophotometry).

### 2.1.7 Stability of drug substance

#### 2.1.7.1 Stability of drug substance (intravenous infusion)

Table 5 shows the main stability studies for the drug substance for the intravenous infusion.

**Table 5. Outline of main stability studies of drug substance for intravenous infusion**

| | Manufacturing process | Number of batches | Storage conditions | Test period | Storage form |
|---|---|---|---|---|---|
| Long-term testing | Process [redacted] | 3 | −80[redacted]°C and −40[redacted]°C | [redacted] months | [redacted] bag |
| Accelerated testing | | | −20[redacted]°C and 5[redacted]°C | [redacted] months | |
| Photostability testing | Process [redacted] | 1 | Overall illumination of ≥1.2 million lux·h, an integrated near ultraviolet energy of ≥200 W·h/m$^2$ | | Glass vial with [redacted] rubber stopper |

The long-term testing showed no clear change in the quality attributes throughout the test period.

The accelerated testing (−20[redacted]°C) showed no clear change in the quality attributes throughout the test period.

The accelerated testing (5[redacted]°C) showed a decrease in [redacted] and a tendency toward an increase in [redacted].

The photostability testing showed that the drug substance is photolabile.

Based on the above, a shelf life of [redacted] months has been proposed for the drug substance for the intravenous infusion when stored in a [redacted] bag at ≤−40°C protected from light.

#### 2.1.7.2 Stability of drug substance (subcutaneous injection)

Table 6 shows the main stability studies for the drug substance for the subcutaneous injection.

**Table 6. Outline of main stability studies of drug substance for subcutaneous injection**

| | Manufacturing process | Number of batches | Storage conditions | Test period | Storage form |
|---|---|---|---|---|---|
| Long-term testing | Process [redacted] | 3 | −40[redacted]°C | [redacted] months[a)] | [redacted] bag |
| | Process [redacted] | | | [redacted] months[a)] | |
| Accelerated testing | Process [redacted] | | −20[redacted]°C and 5[redacted]°C | [redacted] months | |
| | Process [redacted] | | | | |
| Photostability testing | Process [redacted] | 1 | Overall illumination of ≥1.2 million lux·h, an integrated near ultraviolet energy of ≥200 W·h/m$^2$ | | |

a) The test is ongoing for [redacted] months.

The long-term testing showed a tendency of increase in [redacted] but no clear change in other parameters throughout the test period.

The accelerated testing (−20[redacted]°C) showed an increase in [redacted] and a decrease in [redacted].

The accelerated testing (5[redacted]°C) showed a tendency toward an increase in [redacted] and a tendency toward a decrease in [redacted] and a tendency toward an increase in [redacted].

The photostability testing showed that the drug substance is unstable to light.

Based on the above, a shelf life of [redacted] months has been proposed for the drug substance for the subcutaneous injection when stored in a [redacted] bag at ≤−40°C protected from light.

## 2.2 Drug product

### 2.2.1 Description and composition of drug product and formulation development

#### 2.2.1.1 Description and composition of drug product and formulation development (intravenous infusion)

The intravenous infusion is an injectable product containing 136 or 432 mg of belimumab per vial for reconstitution before use. The drug product contains, as excipients, citric acid hydrate, sodium citrate hydrate, sucrose, and polysorbate 80. Each vial is overfilled with the drug product in excess of the nominal dose to allow, after reconstitution with 1.5 or 4.8 mL of water for injection, removal of 1.5 or 5.0 mL, respectively, of injectable solution containing 120 or 400 mg of belimumab.

#### 2.2.1.2 Description and composition of drug product and formulation development (subcutaneous injection)

The subcutaneous injection is an aqueous injectable solution containing 200 mg of belimumab per mL. The drug product contains, as excipients, sodium chloride, L-arginine hydrochloride, L-histidine hydrochloride hydrate, L-histidine, polysorbate 80, and water for injection. Marketing applications have been submitted for 2 types of products, i.e., (1) an autoinjector product that is a combination of a syringe prefilled with the drug solution and a pen injection device and (2) a syringe product composed of the above prefilled syringe that is equipped with a safety device. Both are classified as combination products among pharmaceutical products.

### 2.2.2 Manufacturing process

#### 2.2.2.1 Manufacturing process (intravenous infusion)

The manufacturing process for the drug product comprises thawing, pooling, and mixing of the drug substance, preparation of the formulation buffer, filtration of the formulation buffer to remove bioburden, dilution, filtration to remove bioburden, sterile filtration, filling and partial stoppering, lyophilization and stoppering, clamping, capping, inspection, packaging, labeling, testing, and storage. [redacted], [redacted], [redacted], [redacted], and [redacted] are defined as critical steps.

The manufacturing process of the drug product is subjected to process validation on a production scale.

#### 2.2.2.2 Manufacturing process (subcutaneous injection)

The manufacturing process for the drug product comprises thawing, pooling, and mixing of the drug substance, preparation of the formulation buffer, filtration of the formulation buffer to remove bioburden, dilution, filtration to remove bioburden, sterile filtration, filling and stoppering, inspection, device assembling, packaging, labeling, testing, and storage. [redacted], [redacted], [redacted], [redacted], and [redacted] are defined as critical steps.

The manufacturing process of the drug product is subjected to process validation on a production scale.

### 2.2.3 Manufacturing process development

#### 2.2.3.1 Manufacturing process development (intravenous infusion)

The formulation of the drug production was changed during the process of the product development. The drug product manufactured before the formulation change was used in phase I and II studies, and the drug product manufactured after the formulation change was used in phase III studies. The comparability assessment of the quality attributes was investigated between the drug products manufactured before and after the change of the manufacturing process, and results confirmed the comparability.

#### 2.2.3.2 Manufacturing process development (subcutaneous injection)

The formulation of the drug production was changed during the process of the product development. The drug product manufactured before the formulation change was used in early clinical studies, and the drug product manufactured after the formulation change was used in phase I and III studies which were conducted after the results of phase III studies on the intravenous infusion were obtained.

### 2.2.4 Control of drug product

#### 2.2.4.1 Control of drug product (intravenous infusion)

The proposed specifications for the intravenous drug product include strength, description, identification ([redacted]-HPLC and [redacted]), pH, charge variants, purity (SEC and CGE [reduced]), water content, bacterial endotoxin, reconstitution time, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, sterility, relative potency (binding-inhibitory activity), and assay (ultraviolet-visible spectrophotometry).

### 2.2.4.2 Control of drug product (subcutaneous injection)

The proposed specifications for the subcutaneous drug product include strength, description, identification ([redacted]-HPLC and [redacted]), osmotic pressure, pH, charge variants, purity (SEC and CGE [reduced]), bacterial endotoxin, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, relative potency (binding-inhibitory activity), and assay (ultraviolet-visible spectrophotometry).

## 2.2.5 Stability of drug product

### 2.2.5.1 Stability of drug product (intravenous infusion)

Table 7 shows the main stability studies for the intravenous infusion.

**Table 7. Outline of main stability studies for drug product**

| | Manufacturing process | Drug product specification | Number of batches | Storage conditions | Test period | Storage form |
|---|---|---|---|---|---|---|
| Long-term testing | Process [redacted] | 120 mg | 3 | 5 ± 3°C | 48 months[a)] | Glass vial with [redacted] rubber-stopper |
| | | 400 mg | | | | |
| Accelerated testing | | 120 mg | | 25[redacted]°C/60[redacted]%RH 40[redacted]°C/75[redacted]% RH | 6 months | |
| | | 400 mg | | | | |
| Photostability testing | | 120 mg | 2 | Overall illumination of ≥1.2 million lux·h, an integrated near ultraviolet energy of ≥200 W·h/m$^2$ | | |
| | | 400 mg | | | | |

a) The test is ongoing for [redacted] months.

The long-term testing showed no clear change throughout the test period in either of the products (120 and 400 mg products).

The accelerated testing (25[redacted]°C/60[redacted]% RH) showed a tendency toward an increase in [redacted] in both drug products.

The accelerated testing (40[redacted]°C/75[redacted]% RH) showed an increase in [redacted] and a decrease in [redacted] in both drug products.

The photostability testing showed that both drug products were photolabile.

Based on the above, a shelf life of 48 months has been proposed for the intravenous infusion when stored at 2°C to 8°C in a glass vial with [redacted] rubber-stopper protected from light in a paperboard box.

### 2.2.5.2 Stability of drug product (subcutaneous injection)

Table 8 shows the main stability studies for the subcutaneous injection. The stability studies were conducted using the prefilled syringes.

**Table 8. Outline of main stability studies for drug product**

| | Manufacturing process | Drug product specification | Number of batches | Storage conditions | Test period | Storage form |
|---|---|---|---|---|---|---|
| Long-term testing | Process [redacted] | 200 mg | 5 | 5 ± 3°C | 48 months[a)] | Glass syringe with [redacted] plunger stopper |
| | Process [redacted] | | 3 | | 18 months[a)] | |
| Accelerated testing | Process [redacted] | | 5 | 25[redacted]°C/60[redacted]%RH<br>40[redacted]°C/75[redacted]% RH | 6 months | |
| | Process [redacted] | | 3 | | | |
| Photostability testing | Process [redacted] | | 2 | Overall illumination of ≥1.2 million lux·h, an integrated near ultraviolet energy of ≥200 W·h/m$^2$ | | |

a) The test is ongoing for [redacted] months.

The long-term testing showed a tendency toward an increase in [redacted], a tendency toward a decrease in [redacted], and a tendency toward an increase in [redacted], but no clear change in other parameters throughout the test period.

The accelerated testing (25[redacted]°C/60[redacted]% RH) showed a tendency toward an increase in [redacted], a decrease in [redacted], and an increase in [redacted].

The accelerated testing (40[redacted]°C/75[redacted]% RH) showed an increase in [redacted], a decrease in [redacted] and an increase in [redacted], a decrease in purity ([redacted], [redacted]), and a decrease in [redacted].

The photostability testing showed that the drug product is photolabile.

Based on the above, a shelf life of 36 months has been proposed for the subcutaneous injection when stored at 2°C to 8°C in a glass syringe with [redacted] plunger stopper, protected from light in a paperboard box.

## 2.3 QbD

The QbD approach was applied to the development of the strategy for quality control of belimumab, including the identification of CQA listed in Table 9.

**Table 9. List of identified CQA**

| | |
|---|---|
| CQA of drug substance | [redacted], [redacted],[a)] [redacted], [redacted], [redacted], [redacted], endogenous viruses,[b)] adventitious viruses,[b)] host cell protein,[c)] [redacted],[c)] host cell DNA,[c)] [redacted],[c)] [redacted],[c)] carry-over of [redacted], [redacted][c)] |
| CQA common to drug substance and each drug product | [redacted], identification, [redacted], [redacted], [redacted], [redacted], insoluble particulate matter |
| CQA of intravenous infusion drug product | Purity ([redacted], [redacted], [redacted], [redacted]), bacterial endotoxin,[c)] sterility, [redacted], [redacted], [redacted], [redacted], [redacted] |
| CQA of subcutaneous injection drug product | Purity ([redacted], [redacted], [redacted]), bacterial endotoxin,[c)] sterility, [redacted], [redacted] |

a) Product-related impurities [see Section 2.1.5.2]
b) Controlled by in-process control test [see Section 2.1.3]
c) Process-related impurities [see Section 2.1.5.3]

## 2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance and the drug product is controlled appropriately.

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

As primary pharmacodynamic studies, binding to BLyS, the effect on the binding of BLyS and its receptor, and the effect on BLyS-induced cell proliferation were investigated. The effect on B cell count in cynomolgus monkey was evaluated as part of toxicology studies. As secondary pharmacodynamic studies, binding to TNF superfamily molecules, binding to immunoglobulin constant region (fragment crystallizable) (Fc) receptor, and Fc-medicated effects were investigated. No safety pharmacology study was conducted. Instead, safety pharmacology core battery studies were performed in 4-week and 6-month repeated intravenous dose toxicity studies in cynomolgus monkeys [see Section 5.2].

Pharmacological parameters are expressed in mean values unless specified otherwise.

### 3.1 Primary pharmacodynamics

#### 3.1.1 *In vitro* studies

##### 3.1.1.1 Binding to human BLyS (CTD 4.2.1.1.1 and 4.2.1.1.2)

BLyS is present on the cell membrane in the form of membrane-bound BLyS and, upon cleavage by furin-like protease, the extracellular domain is released as soluble BLyS (*Science*. 1999;285:260-3, *J Exp Med*. 1999;189:1747-56).

The binding activity of belimumab to human soluble BLyS was investigated by enzyme-linked immunosorbent assay (ELISA). The binding of belimumab with immobilized soluble human BLyS was inhibited by the addition of soluble BLyS in a concentration-dependent manner, with $IC_{50}$ being 8.5 nmol/L.

Using K-562 cell line expressing membrane-bound BLyS derived from human chronic myeloid leukaemia and peripheral mononuclear cells prepared from healthy donors, binding of belimumab to membrane-bound human BLyS was investigated by flow cytometry. Binding of belimumab to membrane-bound BLyS was observed in neither of the cell lines.

##### 3.1.1.3 Species specificity (CTD 4.2.1.1.4 to 4.2.1.1.6)

The binding affinity of belimumab to soluble BLyS of cynomolgus monkeys was measured twice by SPR. As a result, $K_D$ was 0.264 and 0.338 nmol/L, respectively, which was similar to $K_D$ for soluble human BLyS (0.274 and 0.250 nmol/L).

Measurement of the binding affinity of belimumab to soluble mouse BLyS by SPR showed that $K_D$ was 9.480 nmol/L, which was approximately 10 times that of soluble human BLyS (0.993 nmol/L).

#### 3.1.1.4 Effect on binding of BLyS with receptor (CTD 4.2.1.1.7)

In a competitive inhibition test using SPR, $IC_{50}$ of belimumab against the binding of soluble BLyS with 3 types of receptors (BR3, TACI, and BCMA) expressed on B cells was 69, 52, and 97 nmol/L, respectively.

#### 3.1.1.5 Effect on BLyS-induced cell proliferation (CTD 4.2.1.1.8 and 4.2.1.1.9)

Belimumab inhibited, in a concentration-dependent manner, human BLyS-induced proliferation of primary cultures of B cells isolated from mouse spleen cells and from human peripheral mononuclear cells, with $IC_{50}$ of 0.06 nmol/L for both cell types.

### 3.1.2 *In vivo* studies

#### 3.1.2.1 Effect in mice receiving human BLyS (CTD 4.2.1.1.10)

The effect of belimumab (0.05-5 mg/kg intravenous administration) or the same dose of negative control (human IgG1 antibody) on the human BLyS-induced increases in spleen weight, splenic B cell count, and serum IgA concentration in mice was investigated. Compared with animals in the negative control (human IgG1) group, those in the belimumab 5.0 mg/kg group showed suppressed increase in splenic weight and those in the ≥0.15 mg/kg group showed suppression of increases in splenic B cell count and in serum IgA concentration.

#### 3.1.2.2 Effect in mice (CTD 4.2.1.1.11)

Following an intravenous or intraperitoneal administration of belimumab to mice, the percentage of B cell count relative to the total white blood cell count decreased transiently, but this effect did not persist, becoming attenuated with repeated administrations. Anti-drug antibody (ADA) was detected after repeated administration of belimumab, from which it was considered that the above attenuating effect was due to ADA. After repeated administration, several mice had dyspnoea, with fatal outcome in some of them. These symptoms were considered to be due to anaphylactic reaction caused by ADA production by repeated administration of belimumab.

#### 3.1.2.3 Effect on B cell count in cynomolgus monkeys (CTD 4.2.3.2.1, 4.2.3.2.2, 4.2.3.5.3, and 4.2.3.7.7.1)

The effect of belimumab on B cell count was evaluated by toxicology studies (4-week and 6-month repeated-dose toxicity studies, reproductive and developmental toxicity study, and immunogenicity studies in cynomolgus monkeys). Repeated intravenous or subcutaneous administration of belimumab to cynomolgus monkeys caused a persistent decrease in B cell count in peripheral blood, spleen, and lymph nodes [see Section 5.2].

## 3.2 Secondary pharmacodynamics

### 3.2.1 Binding to TNF superfamily (CTD 4.2.1.2.1)

The binding activity of belimumab to 6 ligands of TNF superfamily (a proliferation-inducing ligand [APRIL], TNF-like ligand 1A [TL1A], homologous to lymphotoxin, exhibits inducible expression and competes with HSV glycoprotein D for binding to herpesvirus entry mediator, a receptor expressed on T lymphocytes [LIGHT], TNF-α, TNF-β [lymphotoxin α], and Fas ligand) other than BLyS was investigated by SPR. Belimumab did not bind to any of these ligands.

### 3.2.2 Binding to Fc receptor and Fc-mediated effect (CTD 4.2.1.2.3 and 4.2.1.2.4)

The binding affinity of belimumab to human neonatal Fc receptor (FcRn) and Fcγ receptor (FcγR)IIIa was investigated by SPR. $K_D$ of belimumab for human FcRn was 618 nmol/L, which was similar to that of raxibacumab, the antibody used as IgG1 control (590 nmol/L), and rituximab (genetical recombination) (318 nmol/L). $K_D$ of belimumab for human FcγRIIIa was 1.79 μmol/L, which was similar to that of rituximab (genetical recombination), the antibody used as IgG1 control (2.09 μmol/L), and human IgG1κ (2.68 μmol/L).

Using human lymphoma-derived U937 cell line expressing membrane-bound BLyS, human peripheral blood CD14-positive mononuclear cells, and ST486 cell line expressing BLyS receptor bound with soluble BLyS, ADCC activity of belimumab was investigated by flow cytometry. ADCC activity of belimumab was not detected in any of the cell lines studied. Using U937 cell line expressing membrane-bound BLyS and human peripheral CD14-positive mononuclear cells, CDC activity of belimumab was investigated by flow cytometry. CDC activity of belimumab was not detected in either of the cell lines studied.

## 3.3 Safety pharmacology

Safety pharmacology core battery parameters were investigated in 4-week and 6-month repeated intravenous dose toxicity studies in cynomolgus monkeys [see Sections 5.2.1 and 5.2.2]. Belimumab (5, 15, or 50 mg/kg) was administered intravenously to cynomolgus monkeys once every week for 4 weeks or once every 2 weeks for 6 months. As a result, belimumab had no effect either on the central nervous system or on the respiratory system, and no belimumab-related changes were observed in electrocardiogram.

## 3.R Outline of the review conducted by PMDA

The applicant's explanation about the role of BLyS in SLE and the mechanism of action of belimumab: BLyS, which belongs to TNF superfamily, suppresses B cell apoptosis and induces differentiation of B cells to plasma cells which produce immunoglobulin (*J Exp Med*. 2000;192:953-64). It is considered that activation of autoreactive B cells and differentiation of these cells into plasma cells play an important role in the pathogenesis of SLE (*Clin Immunol*. 2013;148:322-27, *Japanese journal of clinical immunology.* 2005;28:333-42). Based on observations such as that plasma BLyS concentration is higher in patients with autoimmune disease including SLE than in healthy adults (*Arthritis Rheum*. 2001;44:1313-9, *J Immunol*. 2001;166:6-10), that there is a correlation between BLyS concentration and disease activity of SLE (*Arthritis Rheum*. 2008;58:2453-9), and that transgenic mice overexpressing BLyS show autoimmune disease-like symptoms (*J Exp Med*. 1999;190:1697-710, *Proc Natl Acad Sci USA*. 2000;97:3370-5), it is considered that BLyS plays an important role in the pathogenesis of SLE. Belimumab was shown to suppress BLyS-induced B cell proliferation by binding with BLyS. Also, belimumab was shown to decrease B cell count in mice and cynomolgus monkeys. Based on the above, belimumab is expected to be effective in the treatment of SLE, a disease for which involvement of BLyS is suggested.

PMDA concluded that the submitted data demonstrate the anti-BLyS effect of belimumab and that belimumab is thus expected to be effective against SLE.

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

The applicant submitted results of the intravenous and subcutaneous administration studies of belimumab in cynomolgus monkeys, as data related to absorption, distribution, and excretion. Since antibody drugs including belimumab are considered to be degraded into peptide fragments and amino acids in the body, no metabolic studies were conducted. Belimumab concentration in serum (limit of quantitation [LOQ], 0.25-1.25 ng/mL), amniotic fluid (LOQ, 0.25 ng/mL), and milk (LOQ, 0.25 ng/mL) and ADA (limit of detection [LOD], 0.02-2.5 μg/mL) were measured by ELISA.

Pharmacokinetic parameters are expressed in mean or in mean ± standard deviation (SD) unless specified otherwise.

### 4.1 Absorption

#### 4.1.1 Single-dose administration (CTD 4.2.2.2)

A single dose of belimumab was administered to male and female cynomolgus monkeys intravenously at 5, 10, 30, 50, or 150 [only in females] mg/kg or subcutaneously at 10 or 30 mg/kg. Table 10 shows the pharmacokinetic parameter values observed. No clear sex difference was observed in the exposure, and absolute bioavailability (F) in subcutaneous administration was 79.0% to 92.1%. ADA was detected in 2 of 2 males and 1 of 2 females in the belimumab 50 mg/kg intravenous infusion (IV) group and in 1 of 2 females in the belimumab 30 mg/kg subcutaneous injection (SC) group. Among them, 1 female in the 50 mg/kg IV group and 1 female in the 30 mg/kg SC group showed decreased serum belimumab concentration.

**Table 10. Pharmacokinetic parameters following a single intravenous or subcutaneous administration of belimumab in cynomolgus monkeys**

| Route of administration | Dose | Sex | N | $C_{max}$ (μg/mL) | $AUC_{inf}$ (day·μg/mL) | $t_{1/2}$ (day) | CL or CL/F (mL/day/kg) | $V_{ss}$ or Vz/F (mL/kg) |
|---|---|---|---|---|---|---|---|---|
| IV | 5 mg/kg | M | 2 | 111 ± 2 | 901 ± 40 | 11.2 ± 0.7 | 5.6 ± 0.2 | 85.0 ± 2.1 |
| | | F | 2 | | | | | |
| | 10 mg/kg | M | 2 | 284 ± 49 | 1601 ± 65 | 7.8 ± 0.9 | 6.3 ± 0.3 | 70.0 ± 6.3 |
| | | F | 2 | | | | | |
| | 30 mg/kg | M | 2 | 852 ± 140 | 4807 ± 505 | 8.5 ± 1.9 | 6.4 ± 0.6 | 72.9 ± 6.0 |
| | | F | 2 | | | | | |
| | 50 mg/kg | M | 2 | 1230 ± 180[a)] | 8970 ± 320 [a)] | 14 ± 1.8[a)] | 5.6 ± 0.2[a)] | 108 ± 14[a)] |
| | | F | 2 | | | | | |
| | 150 mg/kg | F | 3 | 3778 ± 326 | 22,693 ± 3990 | 11.5 ± 1.7 | 6.8 ± 1.3 | 89.8 ± 11.4 |
| SC | 10 mg/kg | M | 2 | 91.1 ± 12.9 | 1264 ± 162 | 8.0 ± 0.9 | 8.0 ± 1.2 | 91.8 ± 7.1 |
| | | F | 2 | | | | | |
| | 30 mg/kg | M | 2 | 281 ± 55[b)] | 4421 ± 595[b)] | 10.8 ± 1.0[b)] | 6.9 ± 0.9[b)] | 109 ± 20[b)] |
| | | F | 2 | | | | | |

Mean ± SD. Data in the 5 and 50 mg IV groups are expressed in mean ± standard error (SE).
a) Excluding 1 female that was ADA positive and showed a decreased serum belimumab level at 8 days after administration.
b) Excluding 1 ADA-positive female.

#### 4.1.2 Repeated-dose administration (toxicokinetics) (CTD 4.2.2.2)

In the 4-week repeated intravenous dose toxicity study [see Section 5.2.1] and the 13-week repeated subcutaneous dose immunogenicity study [see Section 5.7.1] using male and female cynomolgus monkeys, toxicokinetics was investigated following intravenous administration of belimumab (5, 15, 50

mg/kg) once every week or subcutaneous administration of belimumab (1 mg/kg) twice or 4 time every week. Table 11 shows pharmacokinetic parameters of belimumab. ADA was detected in 1 of 5 females in the belimumab 15 mg/kg IV group, 2 of 5 males in the 50 mg/kg IV group, and 1 of 5 males in the 1 mg/kg SC 4 times weekly group. Decreased serum belimumab concentration was not observed in any of them.

**Table 11. Pharmacokinetic parameters following repeated intravenous or subcutaneous administration of belimumab to cynomolgus monkeys**

| Route of administration | Dosage and administration | Measuring time point | Sex | N | $C_{max}$ (μg/mL) | AUC (day·μg/mL) | $t_{1/2}$ (day) |
|---|---|---|---|---|---|---|---|
| IV[a)] | 5 mg/kg Once weekly | Week 4 | M | 2 | 153 ± 9 | 2868 ± 259 | 13.5 ± 0.9 |
| | | | F | 2 | | | |
| | 15 mg/kg Once weekly | Week 4 | M | 2 | 472 ± 22 | 9459 ± 1000 | 14.0 ± 1.6 |
| | | | F | 2 | | | |
| | 50 mg/kg Once weekly | Week 4 | M | 2 | 1713 ± 142 | 37,145 ± 3617 | 14.6 ± 1.1 |
| | | | F | 2 | | | |
| SC[b)] | 1 mg/kg Twice weekly | Week 1 | M | 5 | 22.2 ± 1.4 | 101 ± 12 | NA |
| | | | F | 5 | 19.9 ± 3.6 | 92.2 ± 14.3 | NA |
| | | Week 13 | M | 5 | 71.8 ± 12.6 | 443 ± 54 | 12.2 ± 2.7 |
| | | | F | 5 | 73.3 ± 9.3 | 446 ± 74 | 11.0 ± 3.5 |
| | 1 mg/kg 4 times weekly | Week 1 | M | 5 | 36.0 ± 4.8 | 124 ± 15 | NA |
| | | | F | 5 | 35.6 ± 3.4 | 129 ± 11 | NA |
| | | Week 13 | M | 5 | 126 ± 31 | 796 ± 218 | 10.9 ± 2.8 |
| | | | F | 5 | 122 ± 13 | 765 ± 84 | 10.9 ± 3.2 |

a) Mean ± SE; b) Mean ± SD; NA, Not applicable

## 4.2 Distribution (CTD 4.2.2.3)

In a study for effects on pre- and postnatal development, including maternal function, using pregnant cynomolgus monkeys, belimumab (5 or 150 mg/kg) was administered intravenously on Gestation Days 20 to 22 and Gestation Day 34, followed by administration of belimumab (5 or 150 mg/kg) once every 2 weeks until delivery (not later than Gestation Day 175), and toxicokinetics was investigated. Table 12 shows serum belimumab concentration in maternal animals, pups, and umbilical cord and belimumab concentration in amniotic fluid. Exposure of serum in pups and umbilical cord and of amniotic fluid to belimumab was observed.

**Table 12. Serum belimumab concentration in maternal animals, pups, and umbilical cord and belimumab concentration in amniotic fluid (μg/mL)**

| Dose | Maternal animals[a)] | | Pups[a)] | | Umbilical cord[b)] | | Amniotic fluid[b)] | |
|---|---|---|---|---|---|---|---|---|
| | N | Concentration | N | Concentration | N | Concentration | N | Concentration |
| 5 mg/kg | 10 | 12.9 ± 11.9 | 8 | 21.6 ± 26.4 | 7 | 35.7 ± 36.7 | 9 | 2.9 ± 3.3 |
| 150 mg/kg | 11 | 972 ± 303 | 6 | 370 ± 233 | 9 | 582 ± 382 | 8 | 52.2 ± 14.6 |

Mean ± SD

a) Measured on Lactation Day 7, b) Measured on Gestation Day 150

## 4.3 Excretion (CTD 4.2.2.5)

In the study for effects on pre- and postnatal development, including maternal function, using pregnant cynomolgus monkeys, belimumab (150 mg/kg) was administered intravenously to pregnant cynomolgus monkeys (n = 10) on Gestation Days 20 to 22 and Gestation Day 34, followed by administration of belimumab (150 mg/kg) once every 2 weeks until delivery (not later than Gestation Day 175). As a result, belimumab concentration in milk collected from 1 animal each on Lactation Days 7 and 28 was 1.9 μg/mL and 11.7 μg/mL, respectively, (0.14% and 4.3%, respectively, relative to serum belimumab concentration in maternal animals), showing excretion of belimumab into milk.

## 4.R Outline of the review conducted by PMDA

Based on the nonclinical pharmacokinetic data submitted, PMDA concluded that the behavior of belimumab within the body has been elucidated to a sufficient extent.

## 5. Toxicity and Outline of the Review Conducted by PMDA

As the toxicity studies of belimumab, repeated-dose toxicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other studies (immunogenicity, tissue cross-reactivity) were conducted. Belimumab binds to rodent soluble BLyS with an affinity of only approximately one tenth that to human soluble BLyS, whereas it binds to soluble BLyS of cynomolgus monkeys with a similar affinity as that to human soluble BLyS [see Section 3.1.1.3]. Therefore, toxicity studies of belimumab were conducted using cynomolgus monkeys. In repeated-dose toxicity studies and in reproductive and developmental studies, ADA production was observed in only a small number of animals [see Section 4.1.2]. In all studies conducted, it was determined that animals were exposed to belimumab during the administration period at a sufficiently high level for toxicological evaluation.

### 5.1 Single-dose toxicity

No single-dose toxicity study of belimumab was conducted. In the study for effects on pre- and postnatal development, including maternal function, using pregnant cynomolgus monkeys (CTD 4.2.3.5.3), belimumab was administered intravenously at doses up to 150 mg/kg. After the first dose, no belimumab-related acute toxicity findings or death was observed, from which the approximate lethal dose in intravenous administration was determined to be >150 mg/kg.

### 5.2 Repeated-dose toxicity

Four-week and 6-month intravenous dose toxicity studies were conducted using cynomolgus monkeys. As a result, the no observed adverse effect level (NOAEL) in the 6-month intravenous dose toxicity study (administered once every 2 weeks) was determined to be 50 mg/kg, and the estimated $AUC_{0-\tau}$ at this dose (9101 μg·day/mL) [5)] was 3.4 times the $AUC_{0-\tau}$ (2660 μg·day/mL) [6)] in intravenous administration of the clinical dose (10 mg/kg) in Japanese patients with SLE and 5.8 times the $AUC_{0-\tau}$ (781 μg·day/mL)[7)] in subcutaneous administration of the clinical dose (200 mg).

#### 5.2.1 Four-week repeated intravenous dose toxicity study in cynomolgus monkeys (CTD 4.2.3.2)

Belimumab (0 [vehicle[8)]], 5, 15, or 50 mg/kg) was administered intravenously to male and female cynomolgus monkeys once every week for a total of 4 doses. Some of the animals were allowed to undergo a 28-day recovery period after the last dose. In this study, flow cytometric analysis, etc., of peripheral mononuclear cells was performed.

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5) Estimate calculated from the value in the 50 mg/kg group in the single dose PK study (CTD 4.2.2.2)

6) Estimate calculated from the data of the clinical study in which multiple dose of belimumab (10 mg/kg) was administered intravenously to Japanese patients with SLE (CTD 5.3.3.5, Study BEL113750)

7) Estimate calculated from the data of the clinical study in which multiple dose of belimumab (200 mg) was administered subcutaneously to patients with SLE (CTD 5.3.3.5, Study BEL112341)

8) 10 mmol/L sodium citrate, 19 mg/mL glycine, 5.0 mg/mL sucrose, 0.1 mg/mL polysorbate 80, pH 7.1

No death or moribund sacrifice occurred. Animals at ≥5 mg/kg showed decreased lymphocyte count in ileum-related lymphatic tissues, decreased total or mature B cell count ratio in spleen and mesenteric lymph nodes, decreased total B cell ratio in spleen, and increased total T cell ratio and increased helper T cell ratio or cytotoxic T cell ratio in spleen and mesenteric lymph nodes as changes secondary to the decreased B cell ratio. Animals in the 50 mg/kg group showed increased spleen weight and splenic abscess supposedly related to the immunosuppressive effect of belimumab, and inflammation and cell infiltration in thyroid, mesenteric lymph nodes, etc. After the 28-day recovery period, 1 animal in the 50 mg/kg group showed necrotising granuloma in lymph nodes. Findings in ileum, spleen, and mesenteric lymph nodes, such as decreased lymphocyte count, decreased total and mature B cell ratios, and decreased total T cell ratio, were minor or mild changes due to the pharmacological action of belimumab and were reversible, from which the applicant explained that they are of little toxicological significance.

Based on the above, the NOAEL was determined to be 15 mg/kg.

### 5.2.2 Six-month repeated intravenous dose toxicity study in cynomolgus monkeys (CTD 4.2.3.2)

Belimumab (0 [vehicle[9)]], 5, 15, or 50 mg/kg) was administered intravenously to male and female cynomolgus monkeys once every 2 weeks for 3 months (a total of 7 doses) or for 6 months (a total of 13 doses). Some of the animals receiving 13 doses of belimumab were allowed to undergo an 8-month recovery period after the last dose. In this study, flow cytometric analysis, etc., of peripheral mononuclear cells was performed.

No death or moribund sacrifice occurred. Animals receiving 7 doses of belimumab at ≥5 mg/kg showed decreased total B cell ratio in spleen and mesenteric lymph nodes, decreased mature B cell ratio in spleen, and decreased size or count of lymphoid follicles in spleen. Animals receiving 7 doses of belimumab at ≥15 mg/kg showed decreased total and mature B cell counts in peripheral blood. Animals receiving 13 doses of belimumab at ≥5 mg/kg showed decreased total and mature B cell counts in peripheral blood, decreased splenic weight, decreased total B cell ratio in spleen and mesenteric lymph nodes, increased total T cell ratio and increased helper T cell ratio in spleen which were changes secondary to the decreased B cell ratio, and decreased size or count of lymphoid follicles in spleen. Animals receiving 13 doses of belimumab at ≥15 mg/kg showed decreased size or count of lymphoid follicles in spleen. The applicant explained that the above findings were due to the pharmacological action of belimumab and were reversible after the 8-month recovery period, and that they are therefore of little toxicological significance.

Based on the above, the NOAEL was determined to be 50 mg/kg.

## 5.3 Genotoxicity

Since belimumab is an antibody drug, it is considered not to directly act on DNA or other chromosomal components. Therefore, no genotoxicity study was conducted.

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9) 2.1 mg/mL citric acid, 19 mg/mL glycine, 5.0 mg/mL sucrose, 0.1 mg/mL polysorbate 80, pH 6.5

### 5.4 Carcinogenicity

In rodents, antibodies are rapidly produced against belimumab and against hamster anti-mouse BLyS antibody which is an antibody homologous to belimumab. Therefore, no carcinogenicity study was conducted in rodents. The applicant explained that belimumab is unlikely to pose a risk of cancer, taking account of the following:

- In the 6-month repeated intravenous dose toxicity study of belimumab in cynomolgus monkeys, proliferative changes suggestive of carcinogenicity or preneoplastic lesion were not observed [see Section 5.2.2].
- Belimumab inhibits the activity of BLyS which belongs to TNF superfamily. TNF-dependent tumor-eradicating capacity is considered to be cellular response to TNF receptor mediated by TNF-α or TNF-β (*Curr Med Res Opin.* 2015;31;557-74), whereas belimumab did not bind to either TNF-α or TNF-β [see Section 3.2.1].

### 5.5 Reproductive and developmental toxicity

A study for effects on pre- and postnatal development, including maternal function, was conducted in cynomolgus monkeys. The NOAEL in maternal animals and pups was determined to be 150 mg/kg. $AUC_{0-\tau}$ (27,441 μg·day/mL) was 10.3 times the $AUC_{0-\tau}$ (2660 μg·day/mL) [10)] in intravenous administration of the clinical dose (10 mg/kg) in Japanese patients with SLE and 17.6 times the $AUC_{0-\tau}$ (781 μg·day/mL)[11)] in subcutaneous administration of 200 mg. Belimumab was shown to cross the placenta [see Section 4.2] and be excreted into milk [see Section 4.3] in cynomolgus monkeys.

#### 5.5.1 Fertility and early embryonic development to implantation

Study of belimumab on fertility and early embryonic development to implantation was not conducted. In the 6-month intravenous dose toxicity study in cynomolgus monkeys, belimumab up to the maximum dose of 50 mg/kg did not show any effect on the weight or histopathological findings of the male or female reproductive organ, based on which it was determined that belimumab is unlikely to affect male or female fertility.

#### 5.5.2 Effects on pre- and postnatal development, including maternal function, in cynomolgus monkeys (CTD 4.2.3.5.3)

Belimumab (0 [vehicle[12)]], 5, 150 mg/kg) was administered intravenously to pregnant cynomolgus monkeys once every 2 weeks starting from Gestation Days 20 to 22 until cesarean section (Gestation Day 150) or spontaneous delivery. In this study, peripheral blood of maternal animals was subjected to flow cytometric analysis and to measurement of serum immunoglobulin. Necropsy was performed on fetuses after cesarean section on Gestation Day 150 and on newborn pups 366 to 368 days postpartum, and immunohistochemical examination was performed on lymphatic tissues.

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10) Estimate calculated from the data of the clinical study in which multiple dose of belimumab (10 mg/kg) was administered intravenously to Japanese patients with SLE (CTD 5.3.3.5, Study BEL113750)

11) Estimate calculated from the data of the clinical study in which multiple dose of belimumab (200 mg) was administered subcutaneously to patients with SLE (CTD 5.3.3.5, Study BEL112341)

12) 2.1 mg/mL citric acid, 19 mg/mL glycine, 5.0 mg/mL sucrose, 0.1 mg/mL polysorbate 80, pH 6.5

Maternal animals at ≥5 mg/kg showed decreased total and mature B cell counts and increased monocyte count in peripheral blood. It was determined that the findings observed in maternal animals were due to the pharmacological action of belimumab and that they are of little toxicological significance, judging from the observations that the cell counts returned to baseline by Lactation Day 365 and that there were no changes in clinical signs.

Fetuses at ≥5 mg/kg showed decreased splenic weight and decreased B cell density in inguinal and mesenteric lymph nodes and in spleen as findings caused by the pharmacological action of belimumab. Abortion or stillbirth was observed in 3 of 21 animals in the 0 mg/kg group, 6 of 25 animals in the 5 mg/kg group, and 3 of 20 animals in the 150 mg/kg group, but was considered unlikely related to belimumab, judging from the observation that the incidence was similar to the historical data in cynomolgus monkeys (*Am J Primatol*. 1996;40:41-53).

Belimumab was detected in serum of new born pups and decreased gradually over 182 days postpartum. Pups at ≥5 mg/kg showed decreased total and mature B cell counts in the peripheral blood on 7 and 28 days postpartum and decreased serum IgM concentration on 7 or 91 days postpartum. It was determined that these findings are of little toxicological significance, based on the facts that those observed in fetuses and new born pups were caused by the pharmacological action of belimumab, that they resolved 91 or 182 days postpartum in new born pups, and that there were no changes in clinical signs. Decreased B cell density in lymph nodes and spleen, observed in fetuses, were not observed in pups 1 year postpartum. Postnatal death occurred in 2 of 10 pups in the 5 mg/kg group and 1 of 8 pups in the 150 mg/kg group. No toxicological findings attributable to belimumab were observed in any of the pups, from which the death was considered to be due to premature delivery. The total motility of new born pups was similar to the historical data of Macaca including cynomolgus monkeys (*Lab Anim Sci*. 1989;39:205-12, *J Med Primatol*. 1975;4:8-22), from which it was considered that the death of pups is unlikely related to belimumab.

Based on the above, the NOAEL in maternal animals, fetuses, and pups was determined to be 150 mg/kg.

### 5.6 Local tolerance (CTD 4.2.3.6)

In the 8-week repeated subcutaneous dose local tolerance study in cynomolgus monkeys, 5 mL of vehicle[13)] or 200 mg/mL belimumab (244-294 mg/kg) was administered 3 doses at 2-week intervals to cynomolgus monkeys. No belimumab-associated changes were observed at the injection site (back), from which it was considered that belimumab has no local irritant effect.

In the 4-dose subcutaneous dose local tolerance study in cynomolgus monkeys, the following injections were given to animals in order to simultaneously observe the effect of belimumab on the injection site in a single and repeated subcutaneous administration. Thus, the intravenous infusion (lyophilized formulation) or the subcutaneous injection (liquid formulation), both at 80 mg/mL (25 mg/kg), placebo, and physiological saline were administered in a single dose at 3 sites at the back, and the intravenous infusion (lyophilized product) or the subcutaneous injection (liquid product), both at 80 mg/mL (25

[13)] 0.65 mg/mL L-histidine, 1.2 mg/mL L-histidine monohydrochloride, 6.7 mg/mL sodium chloride, 5.3 mg/mL L-arginine hydrochloride, 0.1 mg/mL polysorbate 80, pH 6.0

mg/kg), placebo, and physiological saline were administered at the back 4 doses at 2-day intervals. Erythema was observed at all injection sites, and the findings were not different between the vehicle group and the belimumab group, from which it was considered that neither the intravenous infusion nor the subcutaneous injection has a local irritant effect.

### 5.7 Other toxicity studies

#### 5.7.1 Immunogenicity (CTD 4.2.3.7.7)

Belimumab (0 [vehicle[14)]] or 1 mg/kg) was administered subcutaneously to male and female cynomolgus monkeys twice or 4 times every week for a total of 13 weeks, and animals were allowed to undergo a 9-week recovery period after the last administration.

ADA was detected in 1 of 10 animals in the 4 times weekly group only on Day 71 of the study. Animals in the twice and 4 times weekly groups showed decreased total B cell count in peripheral blood from Days 113 and 99, respectively, of the study. The decreased total B cell count was observed earlier in the 4 times weekly group than in the twice weekly group. The decreased B cell count persisted even during the recovery period. No belimumab-related changes were observed in the counts of white blood cells, lymphocytes, total T cells, helper T cells, cytotoxic T cells, or NK cells.

#### 5.7.2 Tissue cross-reactivity (CTD 4.2.3.7.7)

Tissue cross-reactivity of belimumab to the normal tissues of humans and cynomolgus monkeys was investigated. In cynomolgus monkey tissues, stains were detected in zymogen granules of pancreas and in basal laminae of uterine cervical epithelium. However, these findings were considered to be of no toxicological significance, based on the observation in the 6-month repeated intravenous dose toxicity study in cynomolgus monkeys, that the histopathological examination did not detect any effect of belimumab on pancreas or uterus [see Section 5.2.2]. No belimumab-specific staining was observed in human tissues.

### 5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that clinical use of belimumab does not pose any specific problems from the toxicological point of view.

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

The applicant submitted evaluation data, in the form of results from a Japanese clinical study in healthy adult subjects (CTD 5.3.3.1 [IV and SC], Study BEL116119), a Japanese clinical study in patients with SLE (CTD 5.3.3.2 [IV], Study BEL114243), foreign clinical studies in patients with SLE (CTD 5.3.3.2 [IV], Study LBSL01; CTD 5.3.3.1 [SC], Study BEL117100), etc. The applicant also submitted reference data, in form of results from a foreign clinical study (CTD 5.3.3.1 [SC], Study BEL114448), population pharmacokinetic analyses (CTD 5.3.3.5 [IV], Study HGS1006-POPPK; CTD 5.3.3.5 [SC], Study RA001550188), etc.

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[14)] 0.13 mg/mL citric acid, 2.8 mg/mL sodium citrate, 80 mg/mL sucrose, 0.4 mg/mL polysorbate 80, pH 6.5

Pharmacokinetic parameters are expressed in mean or in mean ± SD unless specified otherwise.

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

Serum belimumab concentration was measured by ELISA (limit of quantitation [LOQ], 138.5 ng/mL) or by immunological electrochemiluminescence (ECL) (LOQ, 100 ng/mL). ADA was measured by ELISA (limit of detection [LOD], 0.5-5 μg/mL) or by ECL (LOD, 0.1 μg/mL). Neutralizing antibody was detected by ELISA (LOD, 0.75-1.5 μg/mL) or by IECL (LOD, 0.39-0.4 μg/mL).

#### 6.1.1 Absolute bioavailability following subcutaneous administration (CTD 5.3.3.1 [SC], Study BEL114448 [February to September 2011])

In a foreign clinical study in healthy adults (N = 118), belimumab was administered subcutaneously at a dose of 200 or 240 mg in a single dose or 4 times at 1-week intervals, or intravenously at a dose of 240 mg in a single dose. Table 13 shows pharmacokinetic parameters observed. The absolute bioavailability following subcutaneous administration was estimated to be 73.5% to 81.8%.

**Table 13. Pharmacokinetic parameters following administration of belimumab to non-Japanese healthy adults**

| | No. of subjects | Dosage regimen | $C_{max}$ (μg/mL) | $AUC_{inf}$ (day·μg/mL) | $t_{1/2}$ (day) | $t_{max}$ (day) | F[a)] (%) |
|---|---|---|---|---|---|---|---|
| Single dose | 19 | 240 mg IV | 87.9 ± 17.5 | 1080 ± 346 | 18.2 ± 6.3 | 0.1 [0.05, 0.3] | NA |
| | 19 | 240 mg SC[b)] | 34.3 ± 9.9 | 830 ± 300 | 15.9 ± 5.3 | 3.9 [0.9, 9.8] | 76.1 |
| | 18 | 240 mg SC | 32.9 ± 9.2 | 860 ± 311 | 18.2 ± 6.0 | 4.9 [2.9, 13.9] | 81.8 |
| | 18 | 200 mg SC | 27.3 ± 11.0 | 666 ± 252 | 16.0 ± 5.1 | 5.9 [1.9, 13.9] | 73.5 |
| Multiple dose | 17 | 240 mg SC[b)] | 22.3 ± 5.2 | 807 ± 241 | 20.3 ± 5.2 | 5.4 [3.5, 9.3] | 74.7 |
| | 19 | 200 mg SC | 20.1 ± 5.0 | 694 ± 217 | 19.8 ± 4.9 | 5.3 [3.6, 8.6] | 77.9 |

Mean ± SD. Time to reach maximum serum concentration ($t_{max}$) is expressed in median [range]. NA, Not applicable.
a) F was calculated from the geometric mean ratio of $AUC_{0\text{-}inf}$ corrected for body weight.
b) Two consecutive subcutaneous administrations of 120 mg

#### 6.1.2 Comparison of pharmacokinetics among different formulations (CTD 5.3.1.2 [SC], Study BEL117100 [October 2013 to May 2014])

In a foreign clinical study in healthy adults (N = 81), a single dose of belimumab (200 mg) was administered subcutaneously using a prefilled syringe (PFS) or auto-injector (AI) formulation. Table 14 shows the pharmacokinetic parameters observed. The geometric mean ratios [90% confidence interval (CI)] of maximum observed serum drug concentration ($C_{max}$) and area under the serum concentration versus time curve from time zero to infinity ($AUC_{inf}$) with AI formulation relative to those with PFS formulation were 1.05 [0.94, 1.18] and 0.94 [0.83, 1.05], respectively. $AUC_{inf}$ tended to be higher following femoral injection compared with abdominal injection, but the applicant discussed that the difference was not marked, remaining within the range of inter-subject variability.

**Table 14. Pharmacokinetic parameters following a single dose of belimumab (200 mg) to non-Japanese healthy adults**

| Formulation/ injection site | No. of subjects | $C_{max}$ (μg/mL) | $AUC_{inf}$ (day·μg/mL) | $t_{1/2}$ (h) | $t_{max}$ (h) |
|---|---|---|---|---|---|
| PFS formulation | 38 | 26.6 ± 8.1 | 790 ± 309 | 424 ± 184 | 141 [47.5, 337] |
| AI formulation | 38 | 28.2 ± 8.3 | 743 ± 261 | 378 ± 134 | 96.8 [47.4, 238] |
| PFS formulation/abdominal | 20 | 25.3 ± 7.7 | 738 ± 306 | 411 ± 191 | 134 [68.0, 337] |
| AI formulation/abdominal | 18 | 26.1 ± 6.3 | 692 ± 170 | 378 ± 144 | 108 [47.7, 168] |
| PFS formulation/femoral | 18 | 28.1 ± 8.4 | 847 ± 311 | 438 ± 180 | 141 [47.5, 239] |
| AI formulation/femoral | 20 | 30.1 ± 9.4 | 789 ± 319 | 378 ± 127 | 96.8 [47.4, 238] |

Mean ± SD. $t_{max}$ is expressed in median [range].

## 6.2 Clinical pharmacology

### 6.2.1 Study in healthy adults (CTD 5.3.3.1 [IV and SC], Study BEL116119 [December 2011 to March 2012])

In a Japanese clinical study in healthy adults (N = 16), belimumab (200 mg) was administered intravenously or subcutaneously in a single dose. Table 15 shows the pharmacokinetic parameters observed. Absolute bioavailability following the subcutaneous administration was estimated to be 77.5%. No ADA was detected.

**Table 15. Pharmacokinetic parameters following a single dose of belimumab (200 mg) to Japanese healthy adults**

| Method of administration | No. of subjects | $C_{max}$ (μg/mL) | $AUC_{inf}$ (day·μg/mL) | $t_{1/2}$ (day) | $t_{max}$ (day) | F[a)] (%) |
|---|---|---|---|---|---|---|
| IV | 8 | 63.7 ± 10.6 | 1227 ± 241.3 | 18.1 ± 4.2 | 0.045 [0.045, 0.083] | - |
| SC | 8 | 27.2 ± 9.3 | 1079 ± 375.1 | 17.2 ± 7.3 | 6.5 [4.0, 14.0] | 77.5 |

Mean ± SD. $t_{max}$ is expressed in median [range].
a) F was calculated from the geometric mean ratio of $AUC_{0\text{-}inf}$ corrected for body weight.

### 6.2.2 Studies in patients

#### 6.2.2.1 Japanese patients with SLE (CTD 5.3.3.2 [IV], Study BEL114243 [July to November 2010])

In a Japanese clinical study in Japanese patients with SLE (belimumab administered to 8 of 12 patients), belimumab (1 or 10 mg/kg) was administered intravenously in a single dose. Table 16 shows pharmacokinetic parameters observed. No ADA was detected.

**Table 16. Pharmacokinetic parameters following single intravenous administration of belimumab to Japanese patients with SLE**

| Treatment group | No. of patients | $C_{max}$ (μg/mL) | $AUC_{inf}$ (day·μg/mL) | $t_{1/2}$ (day) | CL (mL/day/kg) | $V_{ss}$ (mL/kg) |
|---|---|---|---|---|---|---|
| 1 mg/kg | 4 | 20.5 ± 3.7 | 217 ± 35 | 12.6 ± 3.1 | 4.7 ± 0.8 | 81.1 ± 15.2 |
| 10 mg/kg | 4 | 223 ± 20 | 2847 ± 473 | 16.3 ± 5.0 | 3.6 ± 0.7 | 77.7 ± 16.5 |

Mean ± SD

#### 6.2.2.2 Patients with SLE (CTD 5.3.5.1 [IV], Study BEL113750 [May 2011 to September 2015])

In a multi-regional clinical study in patients with SLE (of 705 patients, 80 patients included in PK analysis), belimumab (10 mg/kg) was administered intravenously for 52 weeks at 4-week intervals (at 2-week intervals for the first 3 doses). Table 17 shows serum belimumab concentrations observed.

**Table 17. Serum belimumab concentration following multiple intravenous administration of belimumab (10 mg/kg) to patients with SLE**

| | $C_{max}$ (μg/mL) | | $C_{min}$ (μg/mL) | |
|---|---|---|---|---|
| | Week 2 | Week 24 | Week 8 | Week 52 |
| Japanese population (N = 39) | 271 (N = 37) | 258 (N = 34) | 64.8 (N = 38) | 63.2 (N = 34) |
| Overall population (N = 80) | 241 (N = 75) | 239 (N = 71) | 44.4 (N = 77) | 44.6 (N = 65) |

Median (number of patients analyzed)

### 6.2.2.3 Non-Japanese patients with SLE (CTD [IV] 5.3.3.2, Study LBSL01 [February 2002 to March 2003])

In a foreign clinical study in patients with SLE (57 of 70 patients received belimumab), belimumab (1, 4, 10, or 20 mg/kg) was administered intravenously once or twice at a 3-week interval. Table 18 shows the pharmacokinetic parameters observed. ADA was observed in 2 patients (1 in the 1 mg/kg single-dose group, 1 in the 20 mg/kg double-dose group), and neutralizing antibody was detected in 1 patient of them (1 mg/kg single-dose group).

**Table 18. Pharmacokinetic parameters following intravenous administration of belimumab to non-Japanese patients with SLE**

| Number of doses | Treatment group | No. of patients | $C_{max}$ (μg/mL) | $AUC_{inf}$ (day·μg/mL) | $t_{1/2}$ (day) | CL (mL/day/kg) | $V_{ss}$ (mL/kg) |
|---|---|---|---|---|---|---|---|
| 1 | 1 mg/kg | 7 | 22.3 ± 4.2 | 156 ± 46 | 8.5 ± 2.2 | 7.2 ± 3.2 | 73.3 ± 13.6 |
| | 4 mg/kg | 7 | 81.2 ± 24.6 | 629 ± 258 | 9.9 ± 2.2 | 7.2 ± 2.5 | 82.3 ± 22.3 |
| | 10 mg/kg | 7 | 192 ± 35 | 1510 ± 315 | 10.6 ± 2.9 | 6.9 ± 1.6 | 86.3 ± 16.8 |
| | 20 mg/kg | 6 | 524 ± 294 | 3384 ± 1424 | 11.3 ± 3.0 | 7.3 ± 4.4 | 112 ± 96 |
| 2 | 1 mg/kg | 6 | 20.6 ± 3.0 | 148 ± 30 | 9.7 ± 1.3 | 7.0 ± 1.4 | 76.5 ± 19.6 |
| | 4 mg/kg | 7 | 105 ± 28 | 729 ± 145 | 9.9 ± 3.0 | 5.7 ± 1.1 | 69.8 ± 22.7 |
| | 10 mg/kg | 7 | 241 ± 42 | 1849 ± 355 | 9.6 ± 2.2 | 5.6 ± 1.0 | 69.2 ± 13.6 |
| | 20 mg/kg | 6 | 368 ± 94 | 3221 ± 781 | 14.1 ± 5.3 | 6.5 ± 1.5 | 102 ± 30 |

Mean ± SD

### 6.2.2.4 Patients with SLE (CTD 5.3.5.1 [SC], Study BEL112341 [November 2011 to February 2015])

In a multi-regional clinical study in patients with SLE (of 836 patients, 554 patients included in PK analysis), belimumab (200 mg) was administered subcutaneously for 52 weeks at 1-week intervals. Table 19 shows serum belimumab concentrations observed.

**Table 19. Serum belimumab concentration following once weekly subcutaneous administration of belimumab (200 mg) to patients with SLE**

| | Serum belimumab concentration (μg/mL) | | | |
|---|---|---|---|---|
| | Day 28 | Day 56 | Day 112 | Day 168 |
| Japanese population (N = 13) | 78.5 (N = 12) | 102 (N = 13) | 105 (N = 13) | 114 (N = 13) |
| Overall population (N = 554) | 65.0 (N = 538) | 87.3 (N = 527) | 99.2 (N = 506) | 105 (N = 489) |

Median (number of patients analyzed)

### 6.2.2.5 Non-Japanese patients with SLE (CTD 5.3.5.2 [SC], Study 200339 [May 2014 to April 2015])

In a phase II study in non-Japanese patients with SLE (95 subjects who had undergone ≥3 cycles of treatment with intravenous injection of belimumab [28 days] or had completed the open-label phase of Study BEL112341), AI formulation of belimumab (200 mg) was self-administered subcutaneously once weekly, and pharmacokinetics was investigated. The subcutaneous administration of belimumab (200 mg) was started at 1 to 4 weeks after the last intravenous dose. Table 20 shows serum trough belimumab concentrations.

**Table 20. Serum belimumab concentration following subcutaneous administration of belimumab (200 mg) to non-Japanese patients with SLE**

| | $C_{trough}$ (μg/mL) | | | |
|---|---|---|---|---|
| | Baseline (N = 91) | Week 2 (N = 89) | Week 4 (N = 93) | Week 8 (N = 90) |
| Non-Japanese patients with SLE | 145 ± 91.7 | 136 ± 82.4 | 121 ± 53.3 | 121 ± 53.1 |

Mean ± SD

## 6.3 Population pharmacokinetic analysis (CTD 5.3.3.5 [IV], 2016N291332; CTD 5.3.3.5 [SC], RA001550188)

### 6.3.1 Intravenous administration

Population pharmacokinetic analysis (NONMEM Version 7.2) was performed using serum belimumab concentration data (8439 measuring points in 1683 patients) obtained from the multi-regional clinical study (Study BEL113750) and foreign clinical studies (Studies LBSL01, LBSL02, BEL110751, and BEL110752), both in patients with SLE.

Using, as the basic model, a linear 2-compartment model with the first order elimination process, the following covariates were selected: Study (Studies LBSL01 and LBSL02), use/non-use of steroid, baseline body weight, creatinine clearance, urine protein, albumin, IgG, and use/non-use of an angiotensin-converting enzyme inhibitor for clearance (CL); and study (Studies LBSL01 and LBSL02), baseline body weight, body mass index (BMI), hemoglobin, and white blood cell count for central volume of distribution (V1); and dose for peripheral volume of distribution (V2).

The population pharmacokinetic parameter values (relative standard error [%]) of belimumab estimated from the final model were as follows: CL, 217 (1.56) mL/day; V1, 2611 (0.925) mL; clearance between compartments (Q), 452 (7.39) mL/day; and V2, 2727 (3.98) mL. Table 21 shows pharmacokinetic parameters of belimumab at steady state in Japanese and non-Japanese patients with SLE, estimated from the final model.

**Table 21. Pharmacokinetic parameters at steady state following intravenous administration of belimumab (10 mg/kg) to patients with SLE (estimated values)**

| | $C_{max}$ (μg/mL) | $C_{min}$ (μg/mL) | $AUC_{0-\tau}$ (day·μg/mL) | $t_{1/2}$ (day) | CL (mL/day) | $V_{ss}$ (mL) |
|---|---|---|---|---|---|---|
| Japanese[a)] (N = 39) | 275 (11.6) | 48.2 (30.9) | 2660 (19.5) | 20.3 (20.0) | 201 (24.2) | 5138 (7.1) |
| Non-Japanese[b)] (N = 563) | 308 (21.3) | 46.2 (55.8) | 2809 (36.7) | 18.1 (27.0) | 232 (33.0) | 5241 (12.4) |

Geometric mean (inter-individual variability [CV%])

a) Study BEL113750, b) Studies BEL110751 and BEL110752

### 6.3.2 Subcutaneous administration

Population pharmacokinetic analysis (NONMEM Version 7.3) was performed using serum belimumab concentration data (4958 measuring points in 688 patients) obtained from the Japanese and foreign clinical studies in healthy adult subjects (Studies BEL116119 and BEL114448) and the multi-regional clinical study in patients with SLE (Study BEL112341).

Using, as the basic model, a linear 2-compartment model with the first order absorption process and the lag time, the following covariates were selected: Baseline body weight, albumin, and IgG for CL; baseline body weight and BMI for V1; baseline body weight for V2; and baseline body weight for Q.

The population pharmacokinetic parameter values (relative standard error [%]) of belimumab estimated from the final model were as follows: CL, 204 mL/day (6.8); V1, 2300 mL (9.8); Q, 698 mL/day (13.3); V2, 2650 mL (7.1); $K_a$, 0.24 $day^{-1}$ (5.7); F, 0.74 (6.8); and ALAG, 0.18 day (2.0). Table 22 shows pharmacokinetic parameters of belimumab at steady state in Japanese and Caucasian patients with SLE, estimated from the final model.

**Table 22. Pharmacokinetic parameters at steady state following subcutaneous administration of belimumab (200 mg) to patients with SLE (estimated values)**

| | $C_{max}$ (μg/mL) | $C_{min}$ (μg/mL) | $AUC_\tau$ (day·μg/mL) | $t_{1/2}$ (day) | CL (mL/day) | $V_{ss}$ (mL) |
|---|---|---|---|---|---|---|
| Japanese[a)] (N = 13) | 117 (33.9) | 101 (36.8) | 781 (34.8) | 14.9 (25.1) | 190 (26.9) | 3520 (24.1) |
| Caucasian[a)] (N = 333) | 106 (36.9) | 95.9 (39.0) | 718 (37.6) | 20.1 (44.1) | 207 (45.6) | 5467 (63.2) |

Geometric mean (inter-individual variability [CV%])
a) Study BEL112341

## 6.R Outline of the review conducted by PMDA

### 6.R.1 Ethnic differences of pharmacokinetics of belimumab

The applicant's explanation about the effect of ethnic factors on the pharmacokinetics of belimumab:
In the Japanese clinical studies (Studies BEL114243 and BEL116119) and in the foreign clinical studies (Studies LBSL01, BEL114448, and BEL117100), $AUC_{0-\infty}$ following a single dose intravenous administration of belimumab (10 mg/kg) and following a single subcutaneous administration of belimumab (200 mg) tended to be higher in Japanese subjects [see Sections 6.1.1, 6.2.1, 6.2.2.1, and 6.2.2.3]. On the other hand, race/ethnicity was not selected as a covariate in the population pharmacokinetic analysis, and $AUC_{0-\tau}$ in Japanese and non-Japanese subjects estimated from the population pharmacokinetic model did not show any significant difference [see Section 6.3].

It is unclear what caused a tendency toward higher exposure observed in Japanese subjects than in non-Japanese subjects in the Japanese clinical study. In any case, as shown in Table 23, data did not suggest any significant effect of the variation in the exposure on efficacy or safety.

**Table 23. SRI response rate and incidence of serious adverse events, classified by exposure**

| Dosage regimen | Q1[a)] | Q2[b)] | Q3[c)] | Q4[d)] |
|---|---|---|---|---|
| SRI response rate (%) [95% CI] | | | | |
| 10 mg/kg IV Q4W[e)] | 0.39 [0.32, 0.47] | 0.56 [0.48, 0.63] | 0.53 [0.45, 0.60] | 0.52 [0.45, 0.60] |
| 200 mg SC QW[f)] | 0.54 [0.46, 0.62] | 0.57 [0.49, 0.65] | 0.72 [0.64, 0.79] | 0.62 [0.54, 0.70] |
| Incidence of serious adverse events (%) | | | | |
| 10 mg/kg IV Q4W[e)] | 0.22 | 0.20 | 0.12 | 0.12 |
| 200 mg SC QW[f)] | 0.14 | 0.12 | 0.06 | 0.11 |

a) IV, ≤2204 day·μg/mL; SC, ≤566 day·μg/mL
b) IV, >2204 day·μg/mL and ≤2703 day·μg/mL; SC, >566 day·μg/mL and ≤739 day·μg/mL
c) IV, >2703 day·μg/mL and ≤3329 day·μg/mL; SC, >739 day·μg/mL and ≤920 day·μg/mL
d) IV, >3329 day·μg/mL; SC, >920 day·μg/mL
e) Studies BEL110751, BEL110752, and BEL113750
f) Study BEL112341

PMDA accepted the above explanation and concluded that, from the pharmacokinetic point of view, data do not show any clear ethnic difference that may affect the efficacy or safety of belimumab.

### 6.R.2 Dosage and administration of subcutaneous injection

PMDA asked the applicant to explain the reason for concluding that it is unnecessary to adjust the dose of the subcutaneous injection for body weight.

The applicant's explanation:

In study BEL114448 investigating the bioavailability following subcutaneous administration, the bioavailability of belimumab 200 mg once weekly was calculated to be 73.5%. Therefore, the multi-regional phase III study with the subcutaneous injection (Study BEL112341) employed the dosage regimen that was estimated to achieve the exposure (area under the serum concentration versus time curve [AUC] over 4 weeks) similar to that obtained by intravenous infusion. Using the population pharmacokinetic models of subcutaneous injection and intravenous infusion, a simulation was performed on changes over time of belimumab concentration following subcutaneous administration of belimumab 200 mg once weekly for 24 weeks and following intravenous infusion of belimumab 10 mg/kg once every 2 weeks (at Weeks 0, 2, and 4) followed by intravenous infusion once every 4 weeks, for a total of 24 weeks. As a result, the mean serum belimumab concentration at steady state following the subcutaneous administration (average serum drug concentration [$C_{ave}$], 104 μg/mL) was similar to $C_{ave}$ observed after the intravenous administration (110 μg/mL). Table 24 shows serum belimumab concentration estimated from the population pharmacokinetic analysis, classified by body weight quartile. Serum belimumab concentration differed among body weight groups. However, the efficacy and safety classified by body weight quartile were as shown in Table 25, with body weight showing no effect on efficacy or safety.

**Table 24. Serum belimumab concentration at steady state following subcutaneous injection, classified by body weight group**

| Dose regimen | Quartile[a)] | $C_{max}$ (μg/mL) | $C_{min}$ (μg/mL) | $C_{ave}$ (μg/mL) |
|---|---|---|---|---|
| 10 mg/kg IV Q4W[b)] | Q1 | 274 [266, 282] | 39.5 [36.3, 42.8] | 84.2 [80.1, 88.6] |
| | Q2 | 302 [293, 311] | 46.4 [42.6, 50.4] | 97.8 [93.1, 103] |
| | Q3 | 314 [305, 323] | 45.4 [41.7, 49.4] | 101 [95.7, 106] |
| | Q4 | 360 [350, 371] | 54.4 [49.5, 59.7] | 122 [115, 129] |
| 200 mg SC QW[c)] | Q1 | 133 [127, 139] | 119 [113, 125] | 128 [122, 134] |
| | Q2 | 114 [108, 121] | 103 [97.1, 109] | 110 [104, 117] |
| | Q3 | 101 [95.5, 106] | 90.1 [85.2, 95.2] | 96.8 [91.7, 102] |
| | Q4 | 82.6 [77.5, 88.1] | 73.5 [68.5, 78.7] | 79.3 [74.2, 84.7] |

Geometric mean [95% CI]

a) IV: Q1, ≤54 kg; Q2, >54 kg and ≤63 kg; Q3, >63 kg and ≤75 kg; Q4, >75 kg
SC: Q1, <55.05 kg; Q2, ≥55.05 kg and <65.15 kg; Q3, ≥65.15 kg and <78.25 kg; Q4, ≥78.25 kg

b) Studies BEL110751 and BEL110752, c) Study BEL112341

**Table 25. SRI response rate and incidence of adverse events at Week 52, classified by body weight quartile, in Study BEL112341**

| Quartile[a)] | SRI response rate | | Incidence of adverse events | |
|---|---|---|---|---|
| | Belimumab | Placebo | Belimumab | Placebo |
| Q1 | 64.0 (89/139) | 54.3 (38/70) | 76.3 (106/139) | 77.1 (54/70) |
| Q2 | 56.0 (79/141) | 48.5 (32/66) | 79.0 (113/143) | 84.8 (56/66) |
| Q3 | 65.2 (88/135) | 49.3 (36/73) | 81.5 (110/135) | 85.1 (63/74) |
| Q4 | 60.4 (84/139) | 41.4 (29/70) | 86.3 (120/139) | 90.0 (63/70) |

% (n/N)

a) Q1, <55.05 kg; Q2, ≥55.05 kg and <65.15 kg; Q3, ≥65.15 kg and <78.25; Q4, ≥78.25 kg

The above results show that, with the subcutaneous injection, the variations in pharmacokinetics due to the difference in body weight do not affect the efficacy or safety of belimumab. Therefore, it is unnecessary to adjust the dose of the subcutaneous injection according to body weight.

PMDA accepted the above explanation.

### 6.R.3 Anti-belimumab antibody

The applicant's explanation about the effect of ADA on the pharmacokinetics, efficacy, and safety of belimumab:

Table 26 shows the number of subjects who were ADA-positive in multi-regional phase III studies using the intravenous infusion (Studies BEL113750, BEL110751, and BEL110752) and in the multi-regional phase III study using the subcutaneous injection (Study BEL112341). The percentage of ADA-positive subjects tended to be higher in the group receiving 1 mg/kg of the intravenous infusion. However, since the analytical method employed in this clinical study may be interfered by BLyS, leading to "false positive" results, the observed difference in the percentage of ADA-positive cases was considered to be due to the analytical method.

**Table 26. Percentage of ADA-positive subjects**

| Route of administration | Study | Dose | Percentage of ADA-positive subjects |
|---|---|---|---|
| IV | Study BEL110751 | 1 mg/kg | 20.3 (55/271) |
| | | 10 mg/kg | 2.9 (8/273) |
| | Study BEL110752 | 1 mg/kg | 11.8 (34/288) |
| | | 10 mg/kg | 1.0 (3/290) |
| | Study BEL113750 | 10 mg/kg | 0.2 (1/470) |
| SC | Study BEL112341 (double-blind phase) | 200 mg | 0 |
| | Study BEL112341 (open-label phase) | 200 mg | 0.5 (3/662) |

% (n/N)

As for pharmacokinetics, serum belimumab concentrations in 11 ADA-positive subjects (7.28-82.1 μg/mL) in the 10 mg/kg group of Studies BEL110751 and BEL110752 were within the range of serum belimumab concentration in subjects who were ADA-negative at Week 8 of the follow-up period (median [first and third quartile] 13.1 [4.49, 23.4] μg/mL), except in 2 subjects who became ADA-positive for the first time during the follow-up period (serum belimumab concentration, 0.193 and 3.95 μg/mL).

As for efficacy, the percentage of SRI responders in Studies BEL110751 and BEL110752, classified by positive/negative ADA, was as shown in Table 27. As for safety, among 61 subjects who were continually ADA positive in Study BEL110751 or BEL110752, adverse events (administration site reaction and hypersensitivity) were observed in 2 subjects (3.3%) in the 1 mg/kg group and in 1 subject (1.6%) in the 10 mg/kg group, and all were non-serious.

**Table 27. Percentage and number of SRI responders at Week 52, classified by positive/negative ADA**

| Dose | ADA | Study BEL110751 | Study BEL110752 |
|---|---|---|---|
| 1 mg/kg | Positive (transient or persistent) | 50.9 (28/55) | 41.2 (14/34) |
| | Positive (persistent) | 48.5 (16/33) | 44.4 (4/9) |
| | Negative | 38.0 (82/216) | 52.8 (134/254) |
| 10 mg/kg | Positive (transient or persistent) | 50.0 (4/8) | 66.7 (2/3) |
| | Positive (persistent) | 50.0 (3/6) | 66.7 (2/3) |
| | Negative | 43.0 (114/265) | 57.5 (165/287) |

% (n/N)

In Studies BEL113750 and BEL112341, non-serious administration site reaction was observed in 1 of 4 ADA-positive subjects. However, no conclusion could be drawn regarding the effect of the ADA status on the efficacy or safety of belimumab because of the limited number of ADA-positive cases.

Thus, the studies suggest no effects of the ADA status on the pharmacokinetics, efficacy, or safety of belimumab. However, because of the limited number of subjects evaluated in clinical studies precluding any clear conclusions, immunogenicity of belimumab will be investigated continuously in clinical studies of belimumab on other diseases.

PMDA's view:
The currently available information does not suggest any clinical problem associated with ADA production. However, attention should be paid to the effect of ADA in patients in whom efficacy is substantially attenuated during the continued administration and in patients who show hypersensitivity.

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from clinical studies listed in Table 28.

**Table 28. List of clinical studies on efficacy and safety**

| | Region | Study identifier | Phase | Subjects | Number of subjects enrolled | Dosage regimen | Main endpoints |
|---|---|---|---|---|---|---|---|
| IV | Foreign | LBSL02 | II | Patients with SLE who have inadequately responded to conventional treatments | Double-blind phase:<br>(a) 114<br>(b) 111<br>(c) 111<br>(d) 113<br>Extended treatment phase:<br>345 | Q2W IV up to Week 4, followed by Q4W IV for 52 weeks at any of the following doses:<br>(a) Belimumab 1 mg/kg<br>(b) Belimumab 4 mg/kg<br>(c) Belimumab 10 mg/kg<br>(d) Placebo<br>Patients who completed 52-week administration received belimumab Q4W for 24 weeks. | Efficacy<br>Safety |
| | Multi-regional | BEL113750 | III | Patients with SLE who have inadequately responded to conventional treatments | (a) 470<br>(b) 235 | Q2W IV up to Week 4, followed by Q4W IV for 52 weeks at either of the following doses:<br>(a) Belimumab 10 mg/kg<br>(b) Placebo | Efficacy<br>Safety |
| | Foreign | BEL110751 | III | Patients with SLE who have inadequately responded to conventional treatments | (a) 271<br>(b) 273<br>(c) 275 | Q2W IV up to Week 4, followed by Q4W IV for 76 weeks at any of the following doses:<br>(a) Belimumab 1 mg/kg<br>(b) Belimumab 10 mg/kg<br>(c) Placebo | Efficacy<br>Safety |
| | Foreign | BEL110752 | III | Patients with SLE who have inadequately responded to conventional treatments | (a) 288<br>(b) 290<br>(c) 287 | Q2W IV up to Week 4, followed by Q4W IV for 52 weeks at any of the following doses:<br>(a) Belimumab 1 mg/kg<br>(b) Belimumab 10 mg/kg<br>(c) Placebo | Efficacy<br>Safety |
| SC | Multi-regional | BEL112341 | III | Patients with SLE who have inadequately responded to conventional treatments | (a) 556<br>(b) 280 | QW SC for 52 weeks at either of the following doses:<br>(a) Belimumab 200 mg<br>(b) Placebo | Efficacy<br>Safety |

## 7.1 Phase II studies

### 7.1.1 Foreign study (CTD 5.3.5.1, Study LBSL02 [October 2003 to June 2006])

A randomized, double-blind, parallel group, placebo-controlled study was conducted to investigate the efficacy and safety of belimumab in patients[15)] with SLE with disease activity despite standard treatments for SLE (target sample size, 412 subjects [≥95 per group]) in the US and Canada.

Belimumab (1 mg/kg, 4 mg/kg, 10 mg/kg) or placebo was to be administered intravenously at Weeks 0, 2, and 4, and then at 4-week intervals, for a total of 52 weeks, in combination with anti-SLE drugs.[16)] Patients who completed the 52-week double-blind phase were allowed to participate a 24-week open-label phase at 4 weeks after the end of the double-blind phase. Patients fully responsive to belimumab during the double-blind phase were to receive the same dose during the open-label phase. Patients who received placebo during the double-blind phase, patients who received belimumab during the double-blind phase but were poorly responsive, and patients who were considered to achieve a higher response at the maximum dose by the investigator were to receive 10 mg/kg once every 4 weeks. After the end of the open-label phase, patients who wished to continue the treatment with study drug were allowed to participate in an open-label extension study administering 10 mg/kg (Study BEL112626).

Of 476 randomized[17)] patients, 449 patients (114 in the 1 mg/kg group, 111 in the 4 mg/kg group, 111 in the 10 mg/kg group, 113 in the placebo group) who received at least one dose of the study drug were included in the modified intent-to-treat (mITT) population, and the mITT population was subjected to the safety and efficacy analyses. During the double-blind phase, treatment discontinuation occurred in 23.7% (27 of 114) of patients in the 1 mg/kg group, 15.3% (17 of 111) of patients in the 4 mg/kg group, 18.9% (21 of 111) of patients in the 10 mg/kg group, and 17.7% (20 of 113) of patients in the placebo group. The main reason of discontinuation was patient's request (9.6% [11 of 114] of patients in the 1 mg/kg group, 6.3% [7 of 111] of patients in the 4 mg/kg group, 6.3% [7 of 111] of patients in the 10 mg/kg group, 5.3% [6 of 113] of patients in the placebo group).

Table 29 and Figure 1 show change from baseline in Safety of Estrogens in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index (SELENA SLEDAI) at Week 24, the primary efficacy endpoint, and the time to first mild/moderate or severe SLE flare [see Section 10 for definition] during the double-blind phase.

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15) Main inclusion criteria: Patients with SLE who met the following criteria: (a) SELENA SLEDAI score at screening ≥4, (b) history of positive autoantibody (1 or more of the following: ANA、anti-dsDNA antibody, anti-Sm antibody, anti-RNP antibody, anti-SS-A antibody, anti-SS-B antibody, aCL antibody), (c) received anti-SLE drugs (steroid [5-40 mg prednisone equivalent/day in monotherapy, ≤40 mg prednisone equivalent/day in combination therapy], antimalarial drugs, NSAID, methotrexate (MTX), azathioprine, leflunomide, MMF) from ≥60 days before the start of the study drug, and (d) without complication with lupus nephritis with disease activity, or CNS lupus.

16) Concomitant use of the following anti-SLE drugs was permitted: Steroid (5-40 mg prednisone equivalent/day in monotherapy, ≤40 mg prednisone equivalent/day in combination therapy), antimalarial drugs, NSAID, MTX, azathioprine, leflunomide, and MMF. Concomitant drugs could be added, discontinued, and changed in dose. Concomitant use of the following drugs was prohibited: Other investigational products, cyclosporin (except eye drops), intravenous immunoglobulin, biological products, cyclophosphamide intravenous infusion, and high dose steroid of ≥100 mg prednisone equivalent/day.

17) Patients were assigned to treatment groups by stratified randomization using SELENA SLEDAI score (4-7 vs ≥8).

**Table 29. Change in SELENA SLEDAI score from baseline and time to first SLE flare (mITT population, LOCF)**

| | 1 mg/kg (N = 114) | 4 mg/kg (N = 111) | 10 mg/kg (N = 111) | Placebo (N = 113) |
|---|---|---|---|---|
| Baseline SELENA SLEDAI score | 9.9 ± 4.70 | 9.4 ± 4.73 | 9.5 ± 4.16 | 9.5 ± 5.37 |
| SELENA SLEDAI score at Week 24 | 7.3 ± 4.93 | 7.5 ± 4.57 | 6.8 ± 4.73 | 7.3 ± 5.15 |
| Percent change in SELENA SLEDAI score from baseline | −23.3 ± 47.3 | −11.3 ± 56.9 | −23.7 ± 44.5 | −17.2 ± 54.2 |
| Difference from placebo group [95% CI] | −6.10 [−19.4, 7.2] | 5.94 [−8.7, 20.6] | −6.48 [−19.6, 6.6] | |
| Patients with SLE flare | 88.6 (101) | 84.7 (94) | 86.5 (96) | 88.5 (100) |
| Median time (days) to the first SLE flare | 68.0 | 61.0 | 70.0 | 83.0 |

Mean ± SD or % (n)

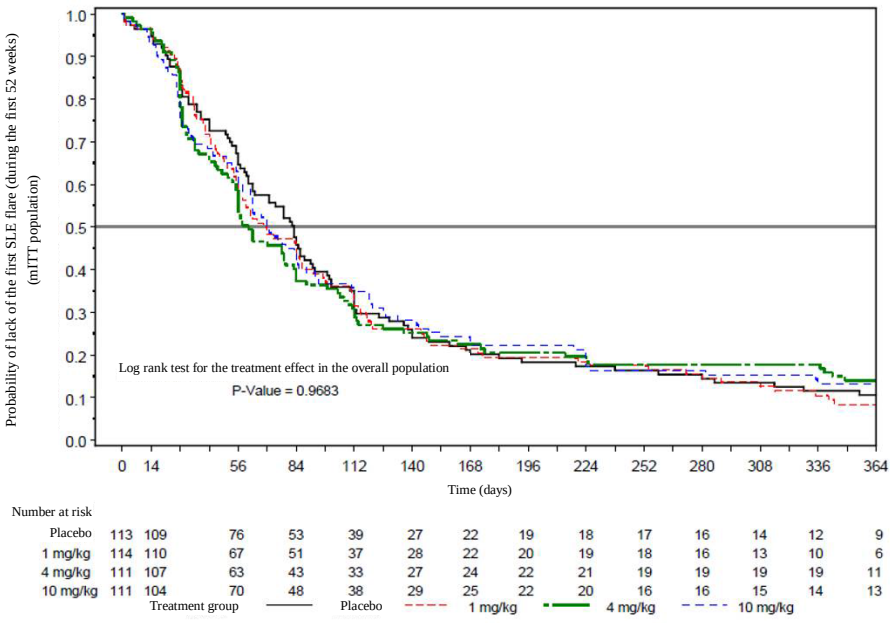


**Figure 1. Kaplan-Meier curve up to the first SLE flare (mITT population)**

In the double-blind phase (up to Week 52), adverse events were observed in 97.4% (111 of 114) of patients in the 1 mg/kg group, 96.4% (107 of 111) of patients in the 4 mg/kg group, 97.3% (108 of 111) of patients in the 10 mg/kg group, and 97.3% (110 of 113) of patients in the placebo group. Table 30 shows main events observed.

Death occurred in 1 patient in the 1 mg/kg group (completed suicide) and in 1 patient in the 10 mg/kg group (respiratory failure), but their causal relationship to the study drug was ruled out. Serious adverse events were observed in 18.4% (21 of 114) of patients in the 1 mg/kg group, 13.5% (15 of 111) of patients in the 4 mg/kg group, 16.2% (18 of 111) of patients in the 10 mg/kg group, and 19.5% (22 of 113) of patients in the placebo group. Table 31 shows main events observed. Adverse events leading to discontinuation was observed in 8.8% (10 of 114) of patients in the 1 mg/kg group, 4.5% (5 of 111) of patients in the 4 mg/kg group, 7.2% (8 of 111) of patients in the 10 mg/kg group, and 7.1% (8 of 113) of patients in the placebo group.

Adverse drug reactions were observed in 55.3% (63 of 114) of patients in the 1 mg/kg group, 47.7% (53 of 111) of patients in the 4 mg/kg group, 56.8% (63 of 111) of patients in the 10 mg/kg group, and 46.0% (52 of 113) of patients in the placebo group.

**Table 30. Adverse events reported by ≥10% of patients in any group during the double-blind phase**

| Event | 1 mg/kg (N =114) | 4 mg/kg (N = 111) | 10 mg/kg (N = 111) | Placebo (N = 113) |
|---|---|---|---|---|
| Arthralgia | 41 (36.0) | 37 (33.3) | 41 (36.9) | 42 (37.2) |
| Upper respiratory tract infection | 36 (31.6) | 36 (32.4) | 29 (26.1) | 33 (29.2) |
| Nausea | 31 (27.2) | 22 (19.8) | 33 (29.7) | 27 (23.9) |
| Headache | 29 (25.4) | 31 (27.9) | 35 (31.5) | 27 (23.9) |
| Fatigue | 27 (23.7) | 33 (29.7) | 27 (24.3) | 34 (30.1) |
| Diarrhoea | 19 (16.7) | 23 (20.7) | 17 (15.3) | 19 (16.8) |
| Depression | 17 (14.9) | 12 (10.8) | 10 (9.0) | 9 (8.0) |
| Arthritis | 16 (14.0) | 21 (18.9) | 18 (16.2) | 19 (16.8) |
| Urinary tract infection | 16 (14.0) | 19 (17.1) | 20 (18.0) | 18 (15.9) |
| Rash | 16 (14.0) | 17 (15.3) | 8 (7.2) | 12 (10.6) |
| Oedema peripheral | 15 (13.2) | 18 (16.2) | 15 (13.5) | 13 (11.5) |
| Back pain | 15 (13.2) | 15 (13.5) | 16 (14.4) | 16 (14.2) |
| Myalgia | 15 (13.2) | 10 (9.0) | 15 (13.5) | 14 (12.4) |
| Vomiting | 14 (12.3) | 15 (13.5) | 9 (8.1) | 13 (11.5) |
| Pain in extremity | 14 (12.3) | 13 (11.7) | 10 (9.0) | 8 (7.1) |
| Pyrexia | 13 (11.4) | 17 (15.3) | 16 (14.4) | 14 (12.4) |
| Cough | 13 (11.4) | 8 (7.2) | 13 (11.7) | 12 (10.6) |
| Sinusitis | 11 (9.6) | 15 (13.5) | 17 (15.3) | 21 (18.6) |
| Migraine | 11 (9.6) | 6 (5.4) | 15 (13.5) | 11 (9.7) |
| Alopecia | 10 (8.8) | 9 (8.1) | 11 (9.9) | 13 (11.5) |
| Mouth ulceration | 9 (7.9) | 12 (10.8) | 17 (15.3) | 11 (9.7) |
| Dizziness | 8 (7.0) | 12 (10.8) | 6 (5.4) | 8 (7.1) |
| Hypertension | 6 (5.3) | 5 (4.5) | 13 (11.7) | 5 (4.4) |
| Bronchitis | 5 (4.4) | 11 (9.9) | 14 (12.6) | 7 (6.2) |
| Infusion site reaction | 3 (2.6) | 12 (10.8) | 2 (1.8) | 6 (5.3) |

n (%)

**Table 31. Serious adverse events reported by ≥2 patients in pooled belimumab group during the double-blind phase (safety analysis population)**

| Event | 1 mg/kg (N =114) | 4 mg/kg (N = 111) | 10 mg/kg (N = 111) | Placebo (N = 113) |
|---|---|---|---|---|
| Transient ischaemic attack | 2 (1.8) | 1 (0.9) | 1 (0.9) | 0 |
| Pneumonia | 2 (1.8) | 1 (0.9) | 0 | 1 (0.9) |
| Cellulitis | 2 (1.8) | 1 (0.9) | 0 | 0 |
| Cholelithiasis | 1 (0.9) | 2 (1.8) | 0 | 0 |
| Bronchitis acute | 1 (0.9) | 1 (0.9) | 0 | 0 |
| Pneumonia bacterial | 1 (0.9) | 1 (0.9) | 0 | 0 |
| Asthma | 1 (0.9) | 1 (0.9) | 0 | 0 |
| Arteriosclerosis | 1 (0.9) | 1 (0.9) | 0 | 0 |
| Non-cardiac chest pain | 1 (0.9) | 0 | 1 (0.9) | 2 (1.8) |
| Pancreatitis | 0 | 2 (1.8) | 0 | 0 |
| Proteinuria | 0 | 0 | 2 (1.8) | 1 (0.9) |

n (%)

## 7.2 Phase III studies

### 7.2.1 Multi-regional clinical study (CTD 5.3.5.1, Study BEL113750 [May 2011 to September 2015])

A randomized, double-blind, parallel group, placebo-controlled study in patients[18)] with SLE with

[18)] Main inclusion criteria: Patients with SLE who met the following criteria: (a) SELENA SLEDAI score at screening ≥8, (b) autoantibody test positive twice (ANA titer ≥80× or anti-dsDNA antibody ≥30 IU/mL), (c) continuously received a constant dose of one or more of anti-SLE drugs (steroid [7.5-40 mg prednisone equivalent/day in monotherapy, ≤40 mg prednisone equivalent/day in combination therapy], antimalarial drugs, NSAID, MTX, azathioprine, leflunomide, MMF, mizoribine, calcineurin inhibitor, sirolimus, oral cyclophosphamide, 6-mercaptopurine, thalidomide) from ≥30 days before the start of the study drug, and (d) without complication with severe lupus nephropathy or acute lupus nephritis requiring acute-phase treatment, or CNS lupus requiring treatment.

disease activity despite standard treatments for SLE (target sample size, 630 subjects[19] [420 in the 10 mg/kg group, 210 in the placebo group]) was conducted to investigate the efficacy and safety of belimumab in Japan, China, and South Korea.

Belimumab (10 mg/kg) or placebo was to be administered as an intravenous infusion at Weeks 0, 2, and 4, then at 4-week intervals for a total of 52 weeks, in combination with anti-SLE drugs. It was allowed, within the scope of the rule, to add, discontinue, or change in dose of, the standard therapies that had been given from before the start of the study drug administration.[20] Patients who completed the 52-week double-blind phase were allowed to participate in the open-label phase in China while, in Japan and in South Korea, patients who met the eligibility criteria were allowed to participate in Study BEL114333 in which belimumab (10 mg/kg) was to be administered intravenously at 4-week intervals. In Study BEL114333, the concomitant anti-SLE drugs used in Study BEL113750 were to be continued and, if clinical symptoms improved or aggravated, it was allowed to add, discontinue, or change in dose of, the concomitant drugs.

Of 707 randomized patients,[21] 705 patients (470 in the 10 mg/kg group, 235 in the placebo group) who received at least one dose of the study drug were included in the safety analysis population. A total of 677 patients (451 in the 10 mg/kg group, 226 in the placebo group), excluding 28 patients in one study site in China where source material preparation and disease activity assessment were not performed in an appropriate manner, were included in mITT population and subjected to efficacy analysis. During the double-blind phase, treatment discontinuation occurred in 17.5% (79 of 451) of patients in the 10 mg/kg group and in 24.8% (56 of 226) of patients in the placebo group. The main reasons for the discontinuation included adverse events (6.0% [27 of 451] of patients in the 10 mg/kg group, 9.7% [22 of 226] of patients in the placebo group) and lack of efficacy (1.6% [7 of 451] of patients in the 10 mg/kg group, 4.9% [11 of 226] of patients in the placebo group).

The mITT population included a Japanese subpopulation consisting of 60 patients (39 in the 10 mg/kg group, 21 in the placebo group). In this Japanese subpopulation, treatment discontinuation during the double-blind phase occurred in 12.8% (5 of 39) of patients in the 10 mg/kg group and in 33.3% (7 of 21) of patients in the placebo group. Main reasons for the discontinuation were adverse events (5.1% [2 of 39] of patients in the 10 mg/kg group, 9.5% [2 of 21] of patients in the placebo group), patient's

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19) During the study, results of the double-blind phase were reviewed under blinding conditions and, based on the review results, the target number of subjects to be randomized was changed to not less than 702 (468 in the 10 mg/kg group, 234 in the placebo group).

20) Steroid (in mean daily total systemic dose): Dose increase was allowed up to Week 24. The dose increase should be adjusted within 25% of the baseline level or by ≤5 mg/day (whichever dose was higher) by Week 24. After Week 24, dose increase by >25% from baseline or by >5 mg/day (whichever was higher) was prohibited (a short-term high-dose administration for treatment other than SLE treatment was permitted). From Week 44 to Week 52, new dose increase exceeding baseline or the dose at Week 44 (whichever was higher) was prohibited. In patients who showed improvement in SLE activity for at least 4 weeks, the dose should be decreased targeted at ≤7.5 mg/day after Week 24 by the judgment of the investigator.
Antimalarial drugs: After Week 16, starting the administration or dose increase (exceeding the dose at baseline or at Week 16, whichever was higher) was prohibited.
Immunosuppressants/immunomodulators: Starting the administration after the start of the study drug administration or dose increase after Week 16 (exceeding the dose at baseline or at Week 16, whichever was higher) was prohibited.
NSAID and aspirin: Starting the administration after Week 44 or newly starting the administration (>1000 mg/day for aspirin) for ≥7 days was prohibited.
Other: concomitant use with injectable immunoglobulin, other biological products, injectable cyclophosphamide, or plasmapheresis was prohibited.

21) Patients were assigned to treatment groups by stratified randomization using SELENA SLEDAI score at screening (≤9 vs. ≥10), complements (decreased C3 or C4 vs. other), and country.

request (5.1% [2 of 39] of patients in the 10 mg/kg group, 9.5% [2 of 21] of patients in the placebo group), etc.

Table 32 shows SRI response rate [see Section 10 for definition] at Week 52, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison between the placebo group and the 10 mg/kg group, demonstrating the superiority of belimumab 10 mg/kg to placebo. Table 33 shows the results in the Japanese subpopulation.

**Table 32. SRI response rate at Week 52 (mITT population, LOCF)**

| | | 10 mg/kg | Placebo | Odds ratio to placebo[b] [95% CI]<br>*P* value[a), b)] |
|---|---|---|---|---|
| SRI response rate | | 53.8 (240/446) | 40.1 (87/217) | 1.99 [1.40, 2.82]<br>*P* = 0.0001 |
| Component index | ≥4 point reduction in SELENA SLEDAI score | 55.8 (249/446) | 41.9 (91/217) | |
| | No worsening in PGA | 77.4 (345/446) | 68.7 (149/217) | |
| | No new BILAG 1A/2B domain scores | 80.3 (358/446) | 68.2 (148/217) | |

% (n/N)
Patients who discontinued the study before Week 52 and patients who underwent non-permitted change in concomitant drugs were handled as nonresponders. In patients in whom assessment at Week 52 was performed, missing data were imputed by LOCF if any of the data of 3 parameters constituting SRI responder were missing.
a) Significance level of 5% (two-sided)
b) Logistic regression analysis comparing the 10 mg/kg group and the placebo group using baseline SELENA SLEDAI score (≤9 vs. ≥10), complements (decreased C3 or C4 vs. other), and country as covariates.

**Table 33. SRI response rate at Week 52 (Japanese subpopulation, mITT population)**

| | | 10 mg/kg | Placebo | Odds ratio to placebo[a)] [95% CI] |
|---|---|---|---|---|
| SRI response rate | | 46.2 (18/39) | 25.0 (5/20) | 2.57 [0.78, 8.47] |
| Component index | ≥4 point reduction in SELENA SLEDAI score | 48.7 (19/39) | 25.0 (5/20) | |
| | No worsening in PGA | 84.6 (33/39) | 60.0 (12/20) | |
| | No new BILAG 1A/2B domain scores | 84.6 (33/39) | 60.0 (12/20) | |

% (n/N). Patients who discontinued the study before Week 52 and patients who underwent non-permitted change in concomitant drugs were handled as nonresponders.
a) Logistic regression analysis comparing the 10 mg/kg group and the placebo group.

During the double-blind phase (up to Week 52), adverse events were observed in 74.9% (352 of 470) of patients in the 10 mg/kg group and in 75.7% (178 of 235) of patients in the placebo group. Table 34 shows main events observed.

Death occurred in 1 patient in the placebo group (respiratory failure), but its causal relationship to the study drug was ruled out. Serious adverse events were observed in 12.3% (58 of 470) of patients in the 10 mg/kg group and in 18.3% (43 of 235) of patients in the placebo group. Table 35 shows main events observed. Adverse events leading to discontinuation were observed in 6.2% (29 of 470) of patients in the 10 mg/kg group and in 9.4% (22 of 235) of patients in the placebo group.

Adverse drug reactions were observed in 28.9% (136 of 470) of patients in the 10 mg/kg group and in 23.4% (55 of 235) of patients in the placebo group.

**Table 34. Adverse events reported by ≥3% of patients in either group during the double-blind phase (safety analysis population)**

| Event | 10 mg/kg (N = 470) | Placebo (N = 235) | Event | 10 mg/kg (N = 470) | Placebo (N = 235) |
|---|---|---|---|---|---|
| Upper respiratory tract infection | 65 (13.8) | 39 (16.6) | Upper respiratory tract infection bacterial | 16 (3.4) | 13 (5.5) |
| Nasopharyngitis | 56 (11.9) | 26 (11.1) | Abdominal pain | 17 (3.6) | 8 (3.4) |
| Pyrexia | 30 (6.4) | 21 (8.9) | Urinary tract infection bacterial | 20 (4.3) | 2 (0.9) |
| Viral upper respiratory tract infection | 34 (7.2) | 15 (6.4) | Abdominal pain upper | 15 (3.2) | 6 (2.6) |
| Cough | 30 (6.4) | 16 (6.8) | Dizziness | 14 (3.0) | 7 (3.0) |
| Diarrhoea | 28 (6.0) | 14 (6.0) | Nausea | 17 (3.6) | 4 (1.7) |
| Herpes zoster | 29 (6.2) | 12 (5.1) | Hypokalaemia | 11 (2.3) | 8 (3.4) |
| Headache | 23 (4.9) | 16 (6.8) | Oropharyngeal pain | 7 (1.5) | 10 (4.3) |
| Urinary tract infection | 21 (4.5) | 11 (4.7) | Lupus nephritis | 7 (1.5) | 7 (3.0) |

n (%)

**Table 35. Serious adverse events reported by ≥2 patients in either group during the double-blind phase (safety analysis population)**

| Event | 10 mg/kg (N = 470) | Placebo (N = 235) | Event | 10 mg/kg (N = 470) | Placebo (N = 235) |
|---|---|---|---|---|---|
| Lupus nephritis | 5 (1.1) | 5 (2.1) | Abdominal pain | 2 (0.4) | 0 |
| Herpes zoster | 6 (1.3) | 2 (0.9) | Uterine leiomyoma | 2 (0.4) | 0 |
| Pyrexia | 2 (0.4) | 4 (1.7) | Hepatic function abnormal | 2 (0.4) | 0 |
| Pneumonia | 2 (0.4) | 1 (0.4) | Lung infection | 0 | 2 (0.9) |
| Appendicitis | 2 (0.4) | 0 | Salmonella sepsis | 0 | 2 (0.9) |
| Pyelonephritis acute | 2 (0.4) | 0 | Proteinuria | 0 | 2 (0.9) |
| Renal failure | 2 (0.4) | 0 | SLE arthritis | 0 | 2 (0.9) |

n (%)

In the Japanese subpopulation, adverse events during the double-blind phase (up to 52 weeks of administration) were observed in 100% (39 of 39) of patients in the 10 mg/kg group and in 90.5% (19 of 21) of patients in the placebo group. Table 36 shows main events observed.

No death occurred. Serious adverse events were observed in 23.1% (9 of 39) of patients in the 10 mg/kg group (Escherichia urinary tract infection, gastroenteritis, herpes zoster, contusion, fractured sacrum, ligament rupture, haemorrhoidal haemorrhage, cataract, and brain stem infarction in 1 patient each), and in 28.6% (6 of 21) of patients in the placebo group (SLE arthritis in 2 patients, pneumonia, allergic colitis, pancytopenia, pyrexia, anogenital warts, and erythema multiforme in 1 patient each). Adverse events leading to discontinuation were observed in 5.1% (2 of 39) of patients in the 10 mg/kg group and in 9.5% (2 of 21) of patients in the placebo group.

Adverse drug reactions were observed in 48.7% (19 of 39) of patients in the 10 mg/kg group and in 23.8% (5 of 21) of patients in the placebo group.

**Table 36. Adverse events reported by ≥2 patients in either group during the double-blind phase (safety analysis population [Japanese subpopulation])**

| Event | 10 mg/kg (N = 39) | Placebo (N = 21) | Event | 10 mg/kg (N = 39) | Placebo (N = 21) |
|---|---|---|---|---|---|
| Nasopharyngitis | 22 (56.4) | 9 (42.9) | Conjunctivitis | 2 (5.1) | 1 (4.8) |
| Contusion | 5 (12.8) | 3 (14.3) | Dermatitis contact | 3 (7.7) | 0 |
| Nausea | 7 (17.9) | 1 (4.8) | Gastroenteritis | 3 (7.7) | 0 |
| Back pain | 5 (12.8) | 1 (4.8) | Hordeolum | 3 (7.7) | 0 |
| Viral upper respiratory tract infection | 4 (10.3) | 2 (9.5) | Ocular hyperaemia | 2 (5.1) | 1 (4.8) |
| Constipation | 3 (7.7) | 2 (9.5) | Pneumonia | 2 (5.1) | 1 (4.8) |
| Hypertension | 4 (10.3) | 0 | Arthralgia | 2 (5.1) | 0 |
| Influenza | 3 (7.7) | 1 (4.8) | Arthropod bite | 2 (5.1) | 0 |
| Insomnia | 1 (2.6) | 3 (14.3) | Dyspepsia | 2 (5.1) | 0 |
| Iron deficiency anaemia | 1 (2.6) | 3 (14.3) | Gastrooesophageal reflux disease | 2 (5.1) | 0 |
| Myalgia | 3 (7.7) | 1 (4.8) | Haemorrhoids | 2 (5.1) | 0 |
| Oral herpes | 4 (10.3) | 0 | Headache | 2 (5.1) | 0 |
| Pyrexia | 2 (5.1) | 2 (9.5) | Herpes zoster | 2 (5.1) | 0 |
| Vertigo | 4 (10.3) | 0 | SLE arthritis | 0 | 2 (9.5) |
| Abdominal pain upper | 1 (2.6) | 2 (9.5) | Skin ulcer | 2 (5.1) | 0 |

n (%)

### 7.2.2 Foreign study (CTD 5.3.5.1, Study BEL110751 [February 2007 to March 2010])

A randomized, double-blind, parallel group, placebo-controlled study in patients[22)] with SLE with disease activity despite standard treatments for SLE (target sample size, 810 subjects [270 per group]) was conducted to investigate the efficacy and safety of belimumab in 19 countries or regions including the US, Mexico, and Germany.

Belimumab (1 mg/kg, 10 mg/kg) or placebo was to be administered at Weeks 0, 2, and 4, and then at 4-week intervals, for a total of 76 weeks, in combination with anti-SLE drugs. It was allowed, within the scope of the rule, to add, discontinue, or change in dose of, the standard therapies that had been given from before the start of the study drug administration.[23)] After the completion of the 76-week double-blind phase, patients were allowed to participate in the extension study (Study BEL112233 in the US, Study BEL112234 in other countries) intravenously administering belimumab (10 mg/kg) at 4-week intervals under open-label conditions, at the discretion of the investigator.

Of 826 randomized[24)] patients, 819 patients (271 in the 1 mg/kg group, 273 in the 10 mg/kg group, 275 in the placebo group) receiving at least 1 dose of the study drug were included in the mITT population

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22) Main inclusion criteria: Patients with SLE who met the following criteria: (a) SELENA SLEDAI score at screening ≥6, (b) autoantibody test positive twice (ANA titer ≥80× or anti-dsDNA antibody ≥30 IU/mL), (c) continuously received constant doses of anti-SLE drugs (steroid [7.5-40 mg prednisone equivalent/day in monotherapy, ≤40 mg prednisone equivalent/day in combination therapy], antimalarial drugs, NSAID, immunosuppressive therapy [e.g., MTX, azathioprine, leflunomide, MMF, calcineurin inhibitor, sirolimus, oral cyclophosphamide, 6-mercaptopurine, thalidomide]) from ≥30 days before the start of the study drug, and (d) without complication with lupus nephritis with severe disease activity, or CNS lupus.

23) Steroid (in mean daily total systemic dose): Dose change was allowed up to Week 24. The dose increase at Week 24 should be within 25% of the baseline level or by ≤5 mg/day. Dose increase by >25% from baseline or by >5 mg/day was prohibited during the period from Week 24 to Week 44 and from Week 52 to Week 68, and new dose increase during the period from Week 44 to Week 52 and Week 68 to Week 76 was prohibited.
Antimalarial drugs: After Week 16, starting the administration or dose increase was prohibited.
Immunosuppressants/immunomodulators: Newly starting the administration after the start of the study drug administration or dose increase after Week 16 was prohibited.
NSAID and aspirin (use for ≥7 days): Starting the administration after Week 44 was prohibited.
Other: Concomitant use with injectable immunoglobulin, other biological products, injectable cyclophosphamide, or plasmapheresis was prohibited.

24) Patients were assigned to treatment groups by stratified randomization using SELENA SLEDAI score at screening (≤9 vs.≥10), urine protein (<2 g/day vs. ≥2 g/day), and race (patients of African or native American lineage vs. other).

and subjected to safety and efficacy analyses. During the double-blind phase, treatment discontinuation occurred in 26.6% (72 of 271) of patients in the 1 mg/kg group, 30.0% (82 of 273) of patients in the 10 mg/kg group, and 32.4% (89 in 275) of patients in the placebo group. Main reasons for the discontinuation included subject's request (6.3% [17 of 271] of patients in the 1 mg/kg group, 7.3% [20 of 273] of patients in the 10 mg/kg group, 10.2% [28 of 275] of patients in the placebo group).

Table 37 shows SRI response rate after 52 weeks of administration, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison between the placebo group and the 10 mg/kg group, demonstrating the superiority of belimumab 10 mg/kg to placebo. In contrast, the paired comparison between the placebo group and the 1 mg/kg group did not show statistically significant difference.

**Table 37. SRI response rate at Week 52 (mITT population)**

| | | 1 mg/kg | 10 mg/kg | Placebo | Odds ratio to placebo[a)] [95% CI] *P* value[a) b)] | |
|---|---|---|---|---|---|---|
| | | | | | 1 mg/kg | 10 mg/kg |
| SRI response rate | | 40.6 (110/271) | 43.2 (118/273) | 33.5 (92/275) | 1.36 [0.95, 1.94] *P* = 0.0889 | 1.54 [1.08, 2.19] *P* = 0.0167 |
| Component index | ≥4 point reduction in SELENA SLEDAI score | 42.8 (116/271) | 46.5 (127/273) | 35.3 (97/275) | | |
| | No worsening in PGA | 72.7 (197/271) | 69.6 (190/273) | 62.9 (173/275) | | |
| | No new BILAG 1A/2B domain scores | 74.9 (203/271) | 69.2 (189/273) | 65.5 (180/275) | | |

% (n/N). Patients who discontinued the study before Week 52 and patients who underwent non-permitted change in concomitant drugs were handled as nonresponders.

a) Logistic regression analysis comparing each belimumab dose group and placebo group, using base line SELENA SLEDAI score (≤9 vs. ≥10), urine protein (<2 g/day vs. ≥2 g/day), and race (patients of African or native American lineage vs. other) as covariates.

b) Significance level of 5% (two-sided). Adjusted for multiplicity of testing by stratified sequential test using step-down procedure in the order of paired comparison between the belimumab 10 mg/kg group and the placebo group, followed by paired comparison between the belimumab 1 mg/kg group and the placebo group.

Adverse events were observed in 93.4% (253 of 271) of patients in the 1 mg/kg group, 92.7% (253 of 273) of patients in the 10 mg/kg group, and 92.0% (253 of 275) of patients in the placebo group. Table 38 shows main events observed.

Death occurred in 2 patients in the 1 mg/kg group (unknown cause and ovarian cancer in 1 patient each) and in 1 patient in the 10 mg/kg group (cardiac arrest/neuropsychiatric lupus/pleurisy/pleural effusion), but a causal relationship of the death to the study drug was ruled out for all patients. Serious adverse events were observed in 23.2% (63 of 271) of patients in the 1 mg/kg group, 22.3% (61 of 273) of patients in the 10 mg/kg group, and 19.6% (54 of 275) of patients in the 10 mg/kg group. Table 39 shows the main events observed. Adverse events leading to discontinuation were observed in 6.6% (18 of 271) of patients in the 1 mg/kg group, 8.4% (23 of 273) of patients in the 10 mg/kg group, and 8.4% (23 of 275) of patients in the placebo group.

Adverse drug reactions were observed in 44.3% (120 of 271) of patients in the 1 mg/kg group, 38.1% (104 of 273) of patients in the 10 mg/kg group, and 44.7% (123 of 275) of patients in the placebo group.

**Table 38. Adverse events reported by ≥5% of patients in any group during the double-blind phase (safety analysis population)**

| Event | 1 mg/kg (N = 271) | 10 mg/kg (N = 273) | Placebo (N = 275) | Event | 1 mg/kg (N = 271) | 10 mg/kg (N = 273) | Placebo (N = 275) |
|---|---|---|---|---|---|---|---|
| Upper respiratory tract infection | 53 (19.6) | 54 (19.8) | 58 (21.1) | Vomiting | 19 (7.0) | 24 (8.8) | 19 (6.9) |
| Headache | 56 (20.7) | 44 (16.1) | 38 (13.8) | Abdominal pain upper | 19 (7.0) | 11 (4.0) | 9 (3.3) |
| Urinary tract infection | 50 (18.5) | 44 (16.1) | 43 (15.6) | Influenza | 19 (7.0) | 9 (3.3) | 12 (4.4) |
| Arthralgia | 43 (15.9) | 41 (15.0) | 43 (15.6) | Vulvovaginal mycotic infection | 18 (6.6) | 15 (5.5) | 15 (5.5) |
| Nausea | 43 (15.9) | 46 (16.8) | 27 (9.8) | Rash | 17 (6.3) | 20 (7.3) | 12 (4.4) |
| Diarrhoea | 35 (12.9) | 33 (12.1) | 28 (10.2) | Viral upper respiratory tract infection | 17 (6.3) | 13 (4.8) | 12 (4.4) |
| Nasopharyngitis | 29 (10.7) | 43 (15.8) | 24 (8.7) | Depression | 16 (5.9) | 20 (7.3) | 10 (3.6) |
| Fatigue | 27 (10.0) | 21 (7.7) | 25 (9.1) | Pharyngitis | 16 (5.9) | 16 (5.9) | 14 (5.1) |
| Insomnia | 27 (10.0) | 17 (6.2) | 13 (4.7) | Anxiety | 16 (5.9) | 6 (2.2) | 10 (3.6) |
| Back pain | 26 (9.6) | 27 (9.9) | 21 (7.6) | Gastrooesophageal reflux disease | 16 (5.9) | 6 (2.2) | 6 (2.2) |
| Oedema peripheral | 26 (9.6) | 26 (9.5) | 21 (7.6) | Gastroenteritis | 15 (5.5) | 15 (5.5) | 11 (4.0) |
| Myalgia | 24 (8.9) | 19 (7.0) | 22 (8.0) | Oral herpes | 15 (5.5) | 11 (4.0) | 8 (2.9) |
| Pyrexia | 23 (8.5) | 29 (10.6) | 21 (7.6) | Dizziness | 14 (5.2) | 16 (5.9) | 11 (4.0) |
| Sinusitis | 21 (7.7) | 31 (11.4) | 28 (10.2) | Hypertension | 13 (4.8) | 15 (5.5) | 21 (7.6) |
| Cough | 21 (7.7) | 26 (9.5) | 15 (5.5) | Pain in extremity | 12 (4.4) | 25 (9.2) | 13 (4.7) |
| Abdominal pain | 20 (7.4) | 18 (6.6) | 16 (5.8) | Anaemia | 9 (3.3) | 11 (4.0) | 18 (6.5) |
| Bronchitis | 19 (7.0) | 32 (11.7) | 21 (7.6) | SLE arthritis | 8 (3.0) | 10 (3.7) | 15 (5.5) |

n (%)

**Table 39. Serious adverse events reported by ≥3 patients in any group during the double-blind phase (safety analysis population)**

| Event | 1 mg/kg (N = 271) | 10 mg/kg (N = 273) | Placebo (N = 275) | Event | 1 mg/kg (N = 271) | 10 mg/kg (N = 273) | Placebo (N = 275) |
|---|---|---|---|---|---|---|---|
| Pneumonia | 3 (1.1) | 5 (1.8) | 4 (1.5) | Infusion related reaction | 1 (0.4) | 3 (1.1) | 0 |
| Lupus nephritis | 2 (0.7) | 3 (1.1) | 5 (1.8) | Bronchitis | 0 | 3 (1.1) | 1 (0.4) |
| Urinary tract infection | 3 (1.1) | 3 (1.1) | 3 (1.1) | Non-cardiac chest pain | 0 | 0 | 4 (1.5) |
| Anaemia | 2 (0.7) | 4 (1.5) | 2 (0.7) | Pleurisy | 0 | 3 (1.1) | 0 |
| Pyrexia | 1 (0.4) | 4 (1.5) | 2 (0.7) | Renal failure acute | 0 | 0 | 3 (1.1) |
| Abdominal pain | 3 (1.1) | 0 | 1 (0.4) | Cholelithiasis | 2 (0.7) | 1 (0.4) | 3 (1.1) |

n (%)

### 7.2.3 Foreign study (CTD 5.3.5.1, Study BEL110752 [May 2007 to May 2009])

A randomized, double-blind, parallel-group, placebo-controlled study in patients[25)] with SLE with disease activity despite standard treatments for SLE (target sample size, 810 subjects [270 per group]) was conducted to investigate the efficacy and safety of belimumab in 13 countries or regions including Colombia, Taiwan, and Brazil.

Belimumab (1 mg/kg, 10 mg/kg) or placebo was to be administered intravenously at Weeks 0, 2, and 4, then at 4-week intervals, for a total of 52 weeks in combination with anti-SLE drugs. It was allowed, within the scope of the rule, to add, discontinue, or change in dose of, the standard therapies that had

25) Main inclusion criteria: Patients with SLE who met the following criteria: (a) SELENA SLEDAI score at screening ≥6, (b) autoantibody test positive twice (ANA titer ≥80× or anti-dsDNA antibody ≥30 IU/mL), (c) continuously received constant doses of anti-SLE drugs (steroid [7.5-40 mg prednisone equivalent/day in monotherapy, ≤40 mg prednisone equivalent/day in combination therapy], antimalarial drugs, NSAID, immunosuppressants/immunomodulators [e.g., MTX, azathioprine, leflunomide, MMF, calcineurin inhibitor, sirolimus, oral cyclophosphamide, 6-mercaptopurine, thalidomide]) from ≥30 days before the start of the study drug, and (d) without complication with lupus nephritis with severe disease activity, or CNS lupus.

been given from before the start of the study drug administration.[26)] After the completion of the 52-week double-blind phase, patients were allowed to participate in the extension study (Study BEL112234) to continuously receive belimumab (10 mg/kg), at the discretion of the investigator.

Of 867 randomized[27)] patients, 865 patients (288 in the 1 mg/kg group, 290 in the 10 mg/kg group, 287 in the placebo group) who received at least 1 dose of the study drug were included in the mITT population, and subjected to safety and efficacy analyses. During the double-blind phase, treatment discontinuation occurred in 16.7% (48 of 288) of patients in the 1 mg/kg group, 16.9% (49 of 290) of patients in the 10 mg/kg group, and 21.3% (61 of 287) of patients in the placebo group. Main reasons for the discontinuation included adverse events (5.6% [16 of 288] of patients in the 1 mg/kg group, 5.2% [15 of 290] of patients in the 10 mg/kg group, 6.6% [19 of 287] of patients in the placebo group).

Table 40 shows SRI response rate at Week 52, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison between the placebo group and each of the belimumab groups (1 mg/kg, 10 mg/kg), demonstrating the superiority of belimumab 1 and 10 mg/kg to placebo.

**Table 40. SRI response rate at Week 52 (mITT population)**

| | | 1 mg/kg | 10 mg/kg | Placebo | Odds ratio to placebo[a)] [95% CI] *P* value[a) b)] | |
|---|---|---|---|---|---|---|
| | | | | | 1 mg/kg | 10 mg/kg |
| SRI response rate | | 51.4 (148/288) | 57.6 (167/290) | 43.6 (125/287) | 1.55 [1.10, 2.19] *P* = 0.0129 | 1.83 [1.30, 2.59] *P* = 0.0006 |
| Component index | ≥4 point reduction in SELENA SLEDAI score | 53.1 (153/288) | 58.3 (169/290) | 46.0 (132/287) | | |
| | No worsening in PGA | 78.8 (227/288) | 79.7 (231/290) | 69.3 (199/287) | | |
| | No new BILAG 1A/2B domain scores | 78.5 (226/288) | 81.4 (236/290) | 73.2 (210/287) | | |

% (n/N). Patients who discontinued the study before Week 52 and patients who underwent non-permitted change in concomitant drugs were handled as nonresponders.

a) Logistic regression analysis comparing each belimumab dose group and placebo group, using base line SELENA SLEDAI score (≤9 vs. ≥10), urine protein (<2 g/day vs. ≥2 g/day), and race (patients of African or native American lineage vs. other) as covariates.

b) Significance level of 5%. (two-sided). Adjusted for multiplicity of testing by stratified sequential test using step-down procedure in the order of paired comparison of SLE response rate between the belimumab 10 mg/kg group and placebo group, followed by paired comparison between the belimumab 1 mg/kg group and the placebo group.

Adverse events were observed in 91.7% (264 of 288) of patients in the 1 mg/kg group, 91.7% (266 of 290) of patients in the 10 mg/kg group, and 91.6% (263 of 287) of patients in the placebo group. Table 41 shows main events observed.

Death occurred in 2 patients in the 1 mg/kg group (sepsis and ischaemic stroke in 1 patient each), 4 patients in the 10 mg/kg group (bacterial sepsis, diarrhoea infectious, completed suicide, and respiratory failure in 1 patient each), and 3 patients in the placebo group (myocardial infarction, cardiac arrest, and

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26) Steroid (in mean daily total systemic dose): Dose change was allowed up to Week 24. The dose increase at Week 24 should be within 25% of the baseline level or by ≤5 mg/day. Dose increase by >25% from baseline or by >5 mg/day was prohibited during the period from Week 24 to Week 44, and new dose increase during the period from Week 44 to Week 52 was prohibited.
Antimalarial drugs: After Week 16, starting the administration or dose increase was prohibited.
Immunosuppressants/immunomodulators: Starting the administration after the start of the study drug administration or dose increase after Week 16 was prohibited.
NSAID and aspirin (use for ≥7 days): Starting the administration after Week 44 was prohibited.
Other: Concomitant use with injectable immunoglobulin, other biological products, injectable cyclophosphamide, or plasmapheresis was prohibited.

27) Patients were assigned to treatment groups by stratified randomization using SELENA SLEDAI score at screening (≤9 vs. ≥10), urine protein (<2 g/day vs. ≥2 g/day), and race (patients of African descent or indigenous American descent vs. other).

death in 1 patient each). A causal relationship of death to the study drug could not be ruled out in 2 patients in the 10 mg/kg group (bacterial sepsis and diarrhoea infectious) and in 1 patient in the placebo group (myocardial infarction). In addition to the above, 1 patient in the 1 mg/kg group died of respiratory arrest approximately 15 weeks after discontinuation of belimumab administration due to renal failure acute (follow-up information from safety database, not related to the study drug).

Serious adverse events were observed in 16.3% (47 of 288) of patients in the 1 mg/kg group, 14.1% (41 of 290) of patients in the 10 mg/kg group, and 12.5% (36 of 287) of patients in the placebo group. Table 42 shows main events observed. Adverse events leading to discontinuation were observed in 5.6% (16 of 288) of patients in the 1 mg/kg group, 5.2% (15 of 290) of patients in the 10 mg/kg group, and 6.6% (19 of 287) of patients in the placebo group.

Adverse drug reactions were observed in 31.6% (91 of 288) of patients in the 1 mg/kg group, 36.2% (105 of 290) of patients in the 10 mg/kg group, and 39.4% (113 of 287) of patients in the placebo group.

**Table 41. Adverse events reported by ≥5% of patients in any group during the double-blind phase (safety analysis population)**

| Event | 1 mg/kg (N = 288) | 10 mg/kg (N = 290) | Placebo (N = 287) | Event | 1 mg/kg (N = 288) | 10 mg/kg (N = 290) | Placebo (N = 287) |
|---|---|---|---|---|---|---|---|
| Headache | 58 (20.1) | 66 (22.8) | 76 (26.5) | Nausea | 16 (5.6) | 23 (7.9) | 31 (10.8) |
| Upper respiratory tract infection | 41 (14.2) | 36 (12.4) | 47 (16.4) | Dizziness | 16 (5.6) | 15 (5.2) | 23 (8.0) |
| Urinary tract infection | 30 (10.4) | 26 (9.0) | 25 (8.7) | Pharyngitis | 16 (5.6) | 15 (5.2) | 7 (2.4) |
| Nasopharyngitis | 30 (10.4) | 20 (6.9) | 23 (8.0) | Vomiting | 16 (5.6) | 14 (4.8) | 13 (4.5) |
| Diarrhoea | 28 (9.7) | 30 (10.3) | 20 (7.0) | Anaemia | 13 (4.5) | 17 (5.9) | 13 (4.5) |
| Back pain | 25 (8.7) | 19 (6.6) | 25 (8.7) | Arthritis | 13 (4.5) | 15 (5.2) | 18 (6.3) |
| Hypertension | 25 (8.7) | 17 (5.9) | 30 (10.5) | Cystitis | 12 (4.2) | 23 (7.9) | 9 (3.1) |
| Cough | 23 (8.0) | 16 (5.5) | 25 (8.7) | Gastritis | 11 (3.8) | 15 (5.2) | 7 (2.4) |
| Influenza | 22 (7.6) | 33 (11.4) | 25 (8.7) | Dyspepsia | 11 (3.8) | 11 (3.8) | 15 (5.2) |
| Bronchitis | 22 (7.6) | 16 (5.5) | 7 (2.4) | Pruritus | 10 (3.5) | 17 (5.9) | 17 (5.9) |
| Arthralgia | 21 (7.3) | 33 (11.4) | 34 (11.8) | Insomnia | 9 (3.1) | 21 (7.2) | 14 (4.9) |
| Oedema peripheral | 20 (6.9) | 17 (5.9) | 21 (7.3) | Abdominal pain upper | 8 (2.8) | 13 (4.5) | 18 (6.3) |
| Gastroenteritis | 20 (6.9) | 12 (4.1) | 16 (5.6) | Dyspnoea | 6 (2.1) | 3 (1.0) | 15 (5.2) |
| Pyrexia | 18 (6.3) | 20 (6.9) | 18 (6.3) | Mouth ulceration | 5 (1.7) | 13 (4.5) | 18 (6.3) |
| Fatigue | 17 (5.9) | 18 (6.2) | 12 (4.2) | | | | |

n (%)

**Table 42. Serious adverse events reported by ≥3 patients in any group during the double-blind phase (safety analysis population)**

| Event | 1 mg/kg (N = 288) | 10 mg/kg (N = 290) | Placebo (N = 287) | Event | 1 mg/kg (N = 288) | 10 mg/kg (N = 290) | Placebo (N = 287) |
|---|---|---|---|---|---|---|---|
| Pyrexia | 4 (1.4) | 4 (1.4) | 1 (0.3) | Lupus nephritis | 3 (1.0) | 3 (1.0) | 0 |
| Urinary tract infection | 4 (1.4) | 2 (0.7) | 2 (0.7) | Abortion spontaneous | 1 (0.3) | 3 (1.0) | 1 (0.3) |
| Pneumonia | 1 (0.3) | 1 (0.3) | 5 (1.7) | Osteonecrosis | 3 (1.0) | 1 (0.3) | 0 |
| Cellulitis | 4 (1.4) | 1 (0.3) | 1 (0.3) | SLE arthritis | 0 | 3 (1.0) | 1 (0.3) |

n (%)

### 7.2.4 Multi-regional phase III study (CTD 5.3.5.1, Study BEL112341 [November 2011 to February 2015])

A randomized, double-blind, parallel group, placebo-controlled study in patients[28)] with SLE with disease activity despite standard treatments for SLE (target sample size, 816 subjects [544 in the 200 mg group, 272 in the placebo group]) was conducted to investigate the efficacy and safety of belimumab in 30 countries or regions including Japan, the US, and Brazil.

Belimumab (200 mg) or placebo was to be administered subcutaneously for 52 weeks at 1-week intervals in combination with anti-SLE drugs. It was allowed, within the scope of the rule, to add, discontinue, or change in dose of, the standard therapies that had been given before the start of the study drug administration.[29)] After the completion of the 52-week double-blind phase, patients were to participate in an open-label period and to receive belimumab (200 mg) at 1-week intervals for 6 months.

Of 839 randomized[30)] patients, 836 patients (556 in the 200 mg group, 280 in the placebo group) who received at least 1 dose of the study drug were included in the ITT population, and subjected to safety and efficacy analyses. During the double-blind phase, treatment discontinuation occurred in 16.7% (93 of 556) of patients in the 200 mg group and in 23.6% (66 of 280) of patients in the placebo group. Main reasons for the discontinuation included adverse events (7.2% [40 of 556] of patients in the 200 mg group, 8.9% [25 of 280] of patients in the placebo group).

The ITT population included a Japanese subpopulation consisting of 29 patients (13 in the 200 mg/kg group, 16 in the placebo group). In this Japanese subpopulation, treatment discontinuation during the double-blind phase occurred in 23.1% (3 of 13) of patients in the 200 mg group. Causes for the discontinuation were adverse events, lack of efficacy, and other (1 patient each).

Table 43 shows SRI response rate after 52 weeks of administration, the primary efficacy endpoint. A statistically significant difference was observed in the paired comparison between the placebo group and the 200 mg group, demonstrating the superiority of belimumab 200 mg to placebo. Table 44 shows the results obtained from the Japanese subpopulation.

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28) Main inclusion criteria: Patients with SLE who met the following criteria: (a) SELENA SLEDAI score at screening ≥8, (b) autoantibody test positive twice (ANA titer ≥80× or anti-dsDNA antibody ≥30 IU/mL), (c) continuously received constant dose of one or more of anti-SLE drugs (steroid [7.5-40 mg prednisone equivalent/day in monotherapy, ≤40 mg prednisone equivalent/day in combination therapy], antimalarial drugs, NSAID, immunosuppressants [MTX, azathioprine, leflunomide, MMF, mizoribine, calcineurin inhibitor, sirolimus, oral cyclophosphamide, 6-mercaptopurine, thalidomide]) from ≥30 days before the start of the study drug, and (d) without complication with severe lupus nephropathy or severe acute lupus nephritis requiring acute-phase treatment, or CNS lupus.

29) Steroid (in mean daily total systemic dose): Dose increase was allowed up to week 24. The dose increase should be adjusted within 25% of the baseline level or by ≤5 mg/day (whichever dose was higher) by Week 24. After Week 24, dose increase to >25% from baseline or by >5 mg/day (whichever was higher) was prohibited (a short-term high-dose administration for treatment other than SLE treatment was permitted). From Week 44 to Week 52, new dose increase exceeding baseline or the dose at Week 44 (whichever was higher) was prohibited. In patients who showed improvement in SLE activity for at least 8 weeks, the dose should be decreased targeted at ≤7.5 mg/day after Week 24, by the judgment of the investigator (subinvestigator).
Antimalarial drugs: After Week 16, starting the administration or dose increase (exceeding the dose at baseline or at Week 16, whichever was higher) was prohibited.
Immunosuppressants/immunomodulators: Starting the administration after the start of the study drug administration or dose increase after Week 16 (exceeding the dose at baseline or at Week 16, whichever was higher) was prohibited.
NSAID and aspirin: Starting the administration after Week 44 or starting the administration (>1000 mg/day for aspirin) for ≥7 days was prohibited.
Other: Concomitant use with injectable immunoglobulin, other biological products, cyclophosphamide intravenous infusion, or plasmapheresis was prohibited.

30) Patients were assigned to treatment groups by stratified randomization using SELENA SLEDAI score at screening (≤9 vs. ≥10), complements (decreased C3 or C4 vs. other), and race (black vs. other).

**Table 43. SRI response rate at Week 52 (ITT population)**

| | | 200 mg | Placebo | Odds ratio to placebo[a)] [95% CI]<br>*P* value[a) b)] |
|---|---|---|---|---|
| SRI response rate | | 61.4 (340/554[c)]) | 48.4 (135/279[c)]) | 1.68 [1.25, 2.25]<br>*P* = 0.0006 |
| Component index | ≥4 point reduction in SELENA SLEDAI score | 62.3 (345/554) | 49.1 (137/279) | |
| | No worsening in PGA | 81.2 (450/554) | 72.8 (203/279) | |
| | No new BILAG 1A/2B domain scores | 80.9 (448/554) | 74.2 (207/279) | |

% (n/N). Patients who discontinued the study before Week 52 and patients who underwent non-permitted change in concomitant drugs were handled as nonresponders.

a) Logistic regression analysis comparing the 200 mg group and the placebo group, using base line SELENA SLEDAI score (≤9 vs. ≥10), complements (decreased C3 or C4 vs. other) and race (black vs. other) as covariates.

b) Significance level of 5% (two-sided)

c) Three patients in the ITT population without baseline PGA assessment were excluded from SRI assessment.

**Table 44. SRI response rate at Week 52 (Japanese subpopulation, ITT population)**

| | | 200 mg | Placebo | Odds ratio to placebo[a)] [95% CI] |
|---|---|---|---|---|
| SRI response rate | | 53.8 (7/13) | 75.0 (12/16) | 1.02 [0.14, 7.65] |
| Component index | ≥4 point reduction in SELENA SLEDAI score | 61.5 (8/13) | 75.0 (12/16) | |
| | No worsening in PGA | 76.9 (10/13) | 100.0 (16/16) | |
| | No new BILAG 1A/2B domain scores | 69.2 (9/13) | 100.0 (16/16) | |

% (n/N)

a) Logistic regression analysis comparing the 200 mg group and the placebo group, using base line SELENA SLEDAI score (≤9 vs. ≥10) and complements (decreased C3 or C4 vs. other) as covariates.

During the double-blind phase (up to Week 52), adverse events were observed in 80.8% (449 of 556) of patients in the 200 mg group and in 84.3% (236 of 280) of patients in the placebo group. Table 45 shows main events observed.

Death occurred in 3 patients in the 200 mg group (tuberculosis of central nervous system, urosepsis, and bacterial sepsis in 1 patient each) and in 2 patients in the placebo group (cardiac arrest and thrombocytopenia in 1 patient each). A causal relationship of death to the study drug could not be ruled out for 2 patients in the 200 mg group (tuberculosis of central nervous system, urosepsis). Serious adverse events were observed in 10.8% (60 of 556) of patients in the 200 mg group and in 15.7% (44 of 280) of patients in the placebo group. Table 46 shows main events observed. Adverse events leading to discontinuation were observed in 7.2% (40 of 556) of patients in the 200 mg group and in 8.9% (25 of 280) of patients in the placebo group.

Adverse drug reactions were observed in 31.1% (173 of 556) of patients in the 200 mg group and in 26.1% (73 of 280) of patients in the placebo group.

**Table 45. Adverse events reported by ≥3% of patients in either group during the double-blind phase (safety analysis population)**

| Event | 200 mg (N = 556) | Placebo (N = 280) | Event | 200 mg (N = 556) | Placebo (N = 280) |
|---|---|---|---|---|---|
| Headache | 57 (10.3) | 26 (9.3) | Pyrexia | 21 (3.8) | 12 (4.3) |
| Viral upper respiratory tract infection | 49 (8.8) | 24 (8.6) | Influenza | 21 (3.8) | 8 (2.9) |
| Urinary tract infection bacterial | 42 (7.6) | 18 (6.4) | Bronchitis bacterial | 19 (3.4) | 8 (2.9) |
| Nasopharyngitis | 38 (6.8) | 22 (7.9) | Insomnia | 18 (3.2) | 20 (7.1) |
| Nausea | 38 (6.8) | 22 (7.9) | Herpes zoster | 18 (3.2) | 13 (4.6) |
| Arthralgia | 32 (5.8) | 11 (3.9) | Upper respiratory tract infection | 18 (3.2) | 9 (3.2) |
| Upper respiratory tract infection bacterial | 30 (5.4) | 14 (5.0) | Vomiting | 18 (3.2) | 7 (2.5) |
| Back pain | 28 (5.0) | 16 (5.7) | Abdominal pain upper | 18 (3.2) | 6 (2.1) |
| Diarrhoea | 28 (5.0) | 14 (5.0) | Abdominal pain | 17 (3.1) | 6 (2.1) |
| Hypertension | 25 (4.5) | 14 (5.0) | Pain in extremity | 16 (2.9) | 10 (3.6) |
| Cough | 22 (4.0) | 19 (6.8) | Dizziness | 14 (2.5) | 11 (3.9) |

n (%)

**Table 46. Serious adverse events reported by ≥2 patients in either group during the double-blind phase (safety analysis population)**

| Event | 200 mg (N = 556) | Placebo (N = 280) | Event | 200 mg (N = 556) | Placebo (N = 280) |
|---|---|---|---|---|---|
| Pneumonia | 4 (0.7) | 1 (0.4) | Abortion spontaneous | 2 (0.4) | 0 |
| Renal failure acute | 4 (0.7) | 0 | Bacterial sepsis | 2 (0.4) | 0 |
| Cellulitis | 3 (0.5) | 2 (0.7) | Myocardial infarction | 2 (0.4) | 0 |
| Pneumonia bacterial | 3 (0.5) | 2 (0.7) | Neuropsychiatric lupus | 2 (0.4) | 0 |
| Pyrexia | 3 (0.5) | 0 | Small intestinal obstruction | 2 (0.4) | 0 |
| Urosepsis | 3 (0.5) | 0 | Urinary tract infection bacterial | 2 (0.4) | 0 |
| Cerebrovascular accident | 2 (0.4) | 1 (0.4) | Thrombocytopenia | 0 | 3 (1.1) |
| Systemic lupus erythematosus rash | 2 (0.4) | 1 (0.4) | Lupus vasculitis | 0 | 2 (0.7) |
| Lupus nephritis | 2 (0.4) | 1 (0.4) | Nephrotic syndrome | 0 | 2 (0.7) |
| Nephritis | 2 (0.4) | 1 (0.4) | Headache | 0 | 2 (0.7) |
| Non-cardiac chest pain | 2 (0.4) | 1 (0.4) | Dysphagia | 0 | 2 (0.7) |

n (%)

In the Japanese subpopulation, adverse events during the double-blind phase (up to 52 weeks of administration) were observed in 92.3% (12 of 13) of patients in the 200 mg group and in 81.3% (13 of 16) of patients in the placebo group. Table 47 shows main events observed.

No death occurred. Serious adverse events were observed in 15.4% (2 of 13) of patients in the 200 mg group (endometrial cancer and lupus nephritis in 1 patient each) and in 12.5% (2 of 16) of patients in the placebo group (vertigo, cataract, and cellulitis in 1 patient each). Adverse events leading to discontinuation were observed in 7.7% (1 of 13) of patients in the 200 mg group.

Adverse drug reactions were observed in 46.2% (6 of 13) of patients in the 200 mg group and in 43.8% (7 of 16) of patients in the placebo group.

**Table 47. Adverse events reported by ≥2 patients in either group during the double-blind phase (safety analysis population [Japanese subpopulation])**

| Event | 200 mg (N = 13) | Placebo (N = 16) | Event | 200 mg (N = 13) | Placebo (N = 16) |
|---|---|---|---|---|---|
| Nasopharyngitis | 3 (23.1) | 5 (31.3) | Dizziness | 1 (7.7) | 2 (12.5) |
| Contusion | 3 (23.1) | 0 | Headache | 1 (7.7) | 5 (31.3) |
| Upper respiratory tract infection | 2 (15.4) | 2 (12.5) | Acne | 0 | 3 (18.8) |
| Ligament sprain | 2 (15.4) | 1 (6.3) | Bronchitis bacterial | 0 | 2 (12.5) |
| Metrorrhagia | 2 (15.4) | 0 | Stomatitis | 0 | 2 (12.5) |
| Cystitis bacterial | 1 (7.7) | 2 (12.5) | Cough | 0 | 2 (12.5) |
| Onychomycosis | 1 (7.7) | 2 (12.5) | Insomnia | 0 | 2 (12.5) |
| Dermatitis contact | 1 (7.7) | 2 (12.5) | | | |

n (%)

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Efficacy

#### 7.R.1.1 Development plan

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

Currently in Japan, SLE is diagnosed according to the SLE classification criteria proposed by the American College of Rheumatology (*Clinical Practice Manual for Systemic Lupus Erythematosus*. 2nd ed. Japan Medical Journal, Co., Ltd, 2012). Thus, there seems to be no major difference in SLE diagnosis or in the clinical system, including the treatment algorithm, between Japan and foreign countries. Also, the pharmacokinetics of belimumab in Japanese and non-Japanese patients with SLE does not show any clear difference possibly affecting the efficacy or safety [see Section 6.R.1]. Based on the above, it is possible to evaluate the efficacy and safety of belimumab in Japanese patients with SLE based on the clinical data package obtained from the multi-regional phase III study conducted in countries including Japan.

- **Target patient population**

Steroid therapy is the standard treatment for SLE. If SLE is resistant to steroid or if steroid causes any serious adverse drug reaction, the use of an immunosuppressant is considered. In steroid therapy, it is essential to decrease the dose as rapidly as possible (target dose level, ≤10 mg/day of steroid) in order to avoid complication by infection (*Lupus*. 2012;21:386-401) and to administer the lowest possible dose that maintains remission without flare-up. Based on the above, the phase III study of belimumab was conducted on patients with SLE with disease activity despite standard treatments for SLE such as steroid, immunosuppressants, and antimalarial drugs.

In the foreign phase II study (Study LBSL02) of belimumab intravenous infusion, no difference was observed between any of the belimumab dose groups (1 mg/kg, 4 mg/kg, or 10 mg/kg) and the placebo group in percent change in SELENA SLEDAI score at Week 24 from baseline (pre-defined primary efficacy endpoint) or in the time to first SLE flare during 52 weeks. On the other hand, a post-hoc analysis was performed to evaluate treatment difference between autoantibody (antinuclear antibody and anti-dsDNA antibody) -positive and -negative patients. SLE is often characterized by autoantibody-positivity. The analysis showed a tendency toward a greater difference in the outcome measures between belimumab and placebo in the autoantibody-positive subgroup than in the autoantibody-negative subgroup (see Table 48). Therefore, the population of autoantibody-positive patients was investigated in the phase III study. Autoantibody-positive patients show serological activity, suggesting that they have clinically higher disease activity. Taking account of the inhibitory effect of belimumab against B

cell proliferation, autoantibody-positive patients are considered to be more eligible for treatment with belimumab than autoantibody-negative patients.

**Table 48. Efficacy in autoantibody-positive and -negative patients (Study LBSL02, mITT population)**

| | Autoantibody positive | | | | Autoantibody negative | | | |
|---|---|---|---|---|---|---|---|---|
| | 1 mg/kg (N = 78) | 4 mg/kg (N = 79) | 10 mg/kg (N = 78) | Placebo (N = 86) | 1 mg/kg (N = 36) | 4 mg/kg (N = 32) | 10 mg/kg (N = 33) | Placebo (N = 27) |
| Percent change in SELENA SLEDAI score at Week 24 from baseline (mean ± SD) | −25.5 ± 43.8 | −6.8 ± 57.7 | −30.0 ± 39.4 | −15.6 ± 54.4 | −18.6 ± 54.5 | −22.3 ± 54.3 | −8.9 ± 52.5 | −22.5 ± 54.1 |
| Difference from placebo [95% CI] | −9.94 [−25.3, 5.4] | 8.75 [−8.5, 26.0] | −14.41 [−29.2, 0.4] | | 3.91 [−23.7, 31.6] | 0.19 [−28.2, 28.6] | 13.62 [−14.0, 41.3] | |
| SRI response rate at Week 52 (% [n]) | 48.7 (38) | 43.0 (34) | 46.2 (36) | 29.1 (25) | 44.4 (16) | 50.0 (16) | 45.5 (15) | 55.6 (15) |
| Odds ratio to placebo [95% CI] | 2.32 [1.22, 4.41] | 1.84 [0.97, 3.51] | 2.09 [1.10, 3.98] | | 0.64 [0.23, 1.75] | 0.80 [0.29, 2.24] | 0.67 [0.24, 1.85] | |

- **Efficacy endpoint**

The applicant's explanation about the primary endpoint in the phase III study:

Although there are several sets of criteria for SLE that are used across countries including Japan, there is no consensus on the parameter that can be commonly used in clinical settings. SLE causes systemic inflammatory lesions but the symptoms that manifest themselves vary from patient to patient. Based on the results of the foreign phase II study (Study LBSL02), SLE responder index (SRI), a composite endpoint consisting of (1) SELENA SLEDAI score that evaluates the overall disease activity, (2) British Isles Lupus Assessment Group (BILAG) score that evaluates specific worsening of the lesion of each organ, and (3) PGA, an overall assessment by a physician of unscorable worsening, was developed (*Arthritis Rheum.* 2009;61:1143-51), and used as the primary efficacy endpoint for the phase III study. The criterion for each component was as follows: Since ≥3 point increase in SELENA SLEDAI score is regarded as worsening of disease activity (*Arthritis Rheum.* 1991;34:937-44, *Lupus.* 1999;8:685-91) and ≥4 point reduction defined as improvement (*J Rheumatol.* 2000;27:377-9), ≥4 point reduction in SELENA SLEDAI score was specified as a criterion for improvement of SLE symptoms. No new BILAG A (severe) organ domain score or 2 new BILAG B (moderate) organ domain scores were confirmed for no worsening in a specific organ system. PGA score of <0.3 was used as a proof for the absence of overall worsening. Patients who met all of the 3 criteria were defined as SRI responders.

The applicant's explanation about the effect of race on efficacy evaluation:

In the pooled analysis of Studies BEL110751 and BEL110752 on belimumab intravenous infusion, the subpopulation analysis by race of SRI response rate at Week 52 showed that, as shown in Table 49, in the Black/African American subpopulation, SRI response rate tended to be higher in the placebo group than in the belimumab group, showing an interaction.[31)] In contrast, SRI response rate tended to be higher in each dose group compared with the placebo group in subpopulations of Caucasian, Asian, indigenous Alaskan, and indigenous Americans. Thus, there was no statistically significant interaction between treatment and race except Black/African American. In Study BEL112341 on belimumab subcutaneous injection, SRI response rate tended to be higher in the belimumab group than in the placebo group in all races. The above results of the pooled analysis of Studies BEL110751 and

[31)] The significance level of interactions between treatment and subgroup was 0.05 in the pooled analysis of Studies BEL110751 and BEL110752 and 0.10 in Study BEL112341.

BEL110752 were presumably caused at least partly by the bias in the baseline disease characteristics between the belimumab group and the placebo group among the Black/African American subgroup.

**Table 49. SRI response rate at Week 52, classified by race (Study BEL110751 + Study BEL110752, mITT population; Study BEL112341, ITT population)**

| | Study BEL110751 + Study BEL110752 | | | Study BEL112341 | |
|---|---|---|---|---|---|
| | 1 mg/kg (N = 559) | 10 mg/kg (N = 563) | Placebo (N = 562) | 200 mg (N = 556) | Placebo (N = 280) |
| SRI response | 258 (46.2) | 285 (50.6) | 218 (38.8) | 340/554 (61.4) | 135/279 (48.4) |
| SRI responders by race | | | | | |
| Caucasian | 125/268 (46.6) | 133/260 (51.2) | 94/270 (34.8) | 210/336 (62.5) | 81/165 (49.1) |
| Asian | 44/112 (39.3) | 59/127 (46.5) | 41/116 (35.3) | 70/120 (58.3) | 32/63 (50.8) |
| Black/African American | 15/48 (31.3) | 18/50 (36.0) | 22/50 (44.0) | 24/55 (43.6) | 12/30 (40.0) |
| Indigenous Alaskan or indigenous American | 74/131 (56.5) | 75/126 (59.5) | 61/125 (48.8) | 36/43 (83.7) | 10/21 (47.6) |

n (%) or n/N (%)

PMDA accepted the above explanation and considers it possible to evaluate the efficacy and safety of belimumab in patients with SLE based on the submitted clinical data package, with the focus on the results of the multi-regional phase III study in which Japanese patients participated. Also, it is acceptable that patients with active, autoantibody-positive SLE who have inadequately responded to conventional anti-SLE drugs were selected as the target patients for the confirmatory study on belimumab. Furthermore, since SLE is a systemic inflammatory disease with diverse clinical features, it is acceptable that SRI, a composite of indices consisting of (1) SELENA SLEDAI score, (2) BILAG, and (3) physician's overall assessment, was used in the multi-regional phase III study as the primary endpoint that allows systematic assessment of the SLE-associated symptoms in each organ.

### 7.R.1.2 Efficacy results

The applicant's explanation about the efficacy of belimumab intravenous infusion:

The multi-regional phase III study (Study BEL113750) including Japan confirmed the superiority of belimumab 10 mg/kg to placebo in SRI response rate at Week 52, the primary endpoint, and the Japanese subpopulation showed similar results to those in the overall population, as shown in Tables 32 and 33 [see Section 7.2.1]. The foreign phase III studies (Studies BEL110751 and BEL110752) confirmed the superiority of belimumab 10 mg/kg to placebo in SRI response rate at Week 52, the primary efficacy endpoint (Tables 37 and 40 [see Section 7.2]). The time to first severe SLE flare,[32)] a secondary endpoint, and the percentage of patients who achieved decrease both in mean daily dose of steroid by ≥25% from baseline and in daily dose to ≤7.5 mg/day throughout the period from Week 40 to Week 52, another secondary endpoint, were similar between Study BEL113750 and foreign phase III studies, showing a tendency of superiority in the belimumab 10 mg/kg group to the placebo group (Tables 50 and 51).

[32)] Patients diagnosed with SLE flare based on SELENA SLEDAI score >12 points alone were excluded. Data were cut off at the last hospital visit before Week 52. Among the deaths, in patients without severe SLE flare, data were cut off on the day of death or study discontinuation.

**Table 50. Time to first severe SLE flare (up to Week 52, mITT population)**

| | Study BEL113750 | | | | Study BEL110751 + Study BEL110752 | |
|---|---|---|---|---|---|---|
| | Overall population | | Japanese subpopulation | | | |
| | 10 mg/kg (N = 451) | Placebo (N = 226) | 10 mg/kg (N = 39) | Placebo (N = 21) | 10 mg/kg (N = 563) | Placebo (N = 562) |
| No. of patients with severe SLE flare (%) | 54 (12.0) | 50 (22.1) | 3 (7.7) | 5 (23.8) | 88 (15.6) | 133 (23.7) |
| Median (day) | Incalculable | Incalculable | Incalculable | Incalculable | Incalculable | Incalculable |
| Hazard ratio [95% CI][a) b)] | 0.50 [0.34, 0.73] | | 0.31 [0.07, 1.28] | | 0.64 [0.49, 0.84] | |

a) Study BEL113750: Cox proportional hazard model with SELENA SLEDAI score (≤9 vs. ≥10), country, and baseline complements (decreased C3 or C4 vs. other) as covariates. In the Japanese subpopulation, only the treatment group was used as the independent variable.

b) Study BEL110751 + Study BEL110752: Cox proportional hazard model with baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline urine protein (<2 g/day vs. ≥2 g/day), race (patients of African or of native American lineage vs. other), and study as covariates.

**Table 51. Percentage of patients whose average steroid dose has been reduced by ≥25% from baseline to ≤7.5 mg/day throughout the period from Week 40 to Week 52 (mITT population)**

| | Study BEL113750 | | | | Study BEL110751 + Study BEL110752 | |
|---|---|---|---|---|---|---|
| | Overall population | | Japanese subpopulation | | | |
| | 10 mg/kg (N = 451) | Placebo (N = 226) | 10 mg/kg (N = 39) | Placebo (N = 21) | 10 mg/kg (N = 563) | Placebo (N = 562) |
| Patients who achieved steroid dose reduction | 55/352 (15.6) | 20/184 (10.9) | 2/23 (8.7) | 0/14 (0) | 58/324 (17.9) | 39/318 (12.3) |
| Odds ratio to placebo [95% CI]][b), c)] | 1.68 [0.95, 2.96] | | Not estimable | | 1.57 [1.01, 2.45] | |

n/N (%)

a) Among patients with baseline average steroid dose >7.5 mg/day, patients whose average steroid dose has been reduced by ≥25% from baseline to ≤7.5 mg/day.

b) Study BEL113750: Logistic regression analysis with the treatment group, baseline steroid dose, baseline SELENA SLEDAI score (≤9 vs. ≥10), complements (decreased C3 or C4 vs. other), and race (Black vs. other) as covariates. In the Japanese subpopulation, only the treatment group was used as the independent variable.

c) Study BEL110751 + Study BEL110752: Logistic regression analysis with baseline steroid dose, study, baseline SELENA SLEDAI score (≤9 vs. ≥10), baseline urine protein (<2 g/24 hr vs. ≥2 g/24 hr), and race (AIA vs. other) as covariates.

The applicant's explanation about the efficacy of belimumab subcutaneous injection:

The multi-regional phase III study (Study BEL112341) including Japan confirmed the superiority of the belimumab 200 mg group to the placebo group in SRI response rate at Week 52, the primary efficacy endpoint, as shown in Table 43 [see Section 7.2.4]. The time to first severe SLE flare,[33)] a secondary endpoint, and the percentage of patients whose average steroid dose has been reduced by ≥25% from baseline to ≤7.5 mg/day throughout the period from Week 40 to Week 52, another secondary endpoint, were as shown in Tables 52 and 53, respectively, demonstrating a tendency toward superiority of belimumab 200 mg to placebo.

[33)] Patients diagnosed with severe SLE flare based on modified SFI were included. Patients diagnosed with SELENA SLEDAI score >12 points alone were not to be a severe SLE flare.

**Table 52. Time to first severe SLE flare**
**(Study BEL112341, up to Week 52, ITT population)**

| | Overall population | | Japanese subpopulation | |
|---|---|---|---|---|
| | 200 mg (N = 556) | Placebo (N = 280) | 200 mg (N = 13) | Placebo (N = 16) |
| No. of patients with SLE flare (%) | 59 (10.6) | 51 (18.2) | 2 (15.4) | 0 (0) |
| Median (day) | Incalculable | Incalculable | Incalculable | Incalculable |
| Hazard ratio to placebo [95% CI][a)] | 0.51 [0.35, 0.74] | | Not estimable | |

a) Cox proportional hazard model with SELENA SLEDAI score (≤9 vs. ≥10), baseline complements (decreased C3 or C4 vs. other), and race (Black vs. other) as covariates. In the Japanese subpopulation, race is not included in covariates.

**Table 53. Percentage of patients whose average steroid dose has been reduced by ≥25% from baseline to ≤7.5 mg/day throughout the period from Week 40 to Week 52 (Study BEL112341, ITT population)**

| | Overall population | | Japanese subpopulation | |
|---|---|---|---|---|
| | 200 mg (N = 556) | Placebo (N = 280) | 200 mg (N = 13) | Placebo (N = 16) |
| Patients who achieved steroid dose reduction[a)] | 61/335 (18.2) | 20/168 (11.9) | 1/8 (12.5) | 0/11 (0) |
| Odds ratio to placebo [95% CI][b)] | 1.65 [0.95, 2.84] | | Not estimable | |

n/N (%)

a) Among patients with baseline average steroid dose >7.5 mg/day, patients whose average steroid dose has been reduced by ≥25% from baseline to ≤7.5 mg/day.

b) Logistic regression analysis with SELENA SLEDAI score (≤9 vs. ≥10), complements (decreased C3 or C4 vs. other), and race (Black vs. other) as covariates.

PMDA asked the applicant to explain the reason(s) for the failure of the Japanese subpopulation to show similar efficacy results as in the overall population in Study BEL112341 (Table 44 [see Section 7.2.4]).

The applicant's explanation:

In the Japanese subpopulation of Study BEL112341, imbalances in baseline disease characteristics were observed, including a higher percentage of patients with higher disease activity (SELENA SLEDAI score ≥10) in the placebo group (38.5% [5 of 13] of patients in the 200 mg group, 75.0% [12 of 16] of patients in the placebo group), resulting in a higher percentage of patients with higher disease activity in the placebo group than in the belimumab group. Presumably, this result was caused partly by the fact that patients were not stratified by country in this study. SLE causes different disease activities with diverse clinical symptoms from patient to patient and repeats remission and flare and, as a result, disease activity-related SELENA SLEDAI score may improve (≥4 point reduction) accidentally. The higher the baseline SELENA SLEDAI score, the higher the possibility of accidental decrease in the score. As shown in Table 54, SRI response rate tends to be higher in patients with higher baseline SELENA SLEDAI score compared with patients with lower score.

These results suggested that the bias in the baseline disease characteristics between the belimumab group and the placebo group in the small Japanese subpopulation partly contributed to the higher SRI response rate observed in the placebo group.

**Table 54. SRI response rate at Week 52**
**(Study BEL112341, ITT population; Study BEL113750, mITT population)**

| Baseline SELENA SLEDAI score | Study BEL112341 | | Study BEL113750 | |
|---|---|---|---|---|
| | 200 mg (N = 556) | Placebo (N = 280) | 10 mg/kg (N = 451) | Placebo (N = 226) |
| ≤9 | 48.5 (98/202) | 41.4 (46/111) | 35.7 (76/213) | 30.9 (29/94) |
| ≥10 | 68.8 (242/352) | 53.0 (89/168) | 70.4 (164/233) | 47.2 (58/123) |

% (n/N)

PMDA asked the applicant to explain the efficacy in each organ lesion, because SLE causes diverse clinical symptoms different from patient to patient.

The applicant's explanation:
Table 55 shows the improvement rate in SELENA SLEDAI score, classified by organ system, in phase III studies. Belimumab was generally effective in improving various organ lesions that patients with SLE had, particularly lesions of mucocutaneous and musculoskeletal systems which are clinical pathologies commonly observed in patients with SLE. Belimumab also improved BILAG score of each organ lesion at Week 52 as observed with SELENA SLEDAI score, generally showing improvement in lesions of all organ systems.

**Table 55. Improvement rate in SELENA SLEDAI score at Week 52, classified by organ system**
**(Study BEL113750 and Study BEL110751 + Study BEL110752, mITT population;**
**Study BEL112341, ITT population)**

| | Study BEL113750 | | Study BEL110751 + Study BEL110752 | | | Study BEL112341 | |
|---|---|---|---|---|---|---|---|
| | 10 mg/kg (N = 451) | Placebo (N = 226) | 1 mg/kg (N = 559) | 10 mg/kg (N = 563) | Placebo (N = 562) | 200 mg (N = 556) | Placebo (N = 280) |
| Central nervous system | 100 (1/1) | 0 (0/2) | 60.0 (9/15) | 63.2 (12/19) | 9.1 (1/11) | 57.1 (4/7) | 50.0 (1/2) |
| Vascular system | 66.7 (42/63) | 57.6 (19/33) | 52.8 (19/36) | 73.7 (28/38) | 40.5 (15/37) | 63.0 (29/46) | 27.8 (5/18) |
| Musculoskeletal system | 74.1 (103/139) | 54.7 (41/75) | 58.3 (211/362) | 56.5 (208/368) | 49.2 (183/372) | 64.4 (282/438) | 50.5 (110/218) |
| Renal system | 61.8 (84/136) | 41.0 (32/78) | 47.8 (43/90) | 49.4 (42/85) | 42.4 (39/92) | 42.4 (25/59) | 36.6 (15/41) |
| Mucocutaneous system | 61.9 (229/370) | 53.0 (97/183) | 51.1 (233/456) | 54.8 (249/454) | 45.0 (211/469) | 64.1 (312/487) | 54.4 (135/248) |
| Immune system | 27.8 (114/410) | 12.9 (26/202) | 20.2 (90/445) | 27.3 (124/455) | 10.0 (44/439) | 29.7 (127/427) | 16.1 (34/211) |
| Hematological system (including pyrexia) | 38.5 (15/39) | 37.0 (10/27) | 50.9 (29/57) | 33.3 (18/54) | 45.8 (22/48) | 44.9 (22/49) | 36.0 (9/25) |
| Cardiovascular and respiratory system | 50.0 (1/2) | 66.7 (2/3) | 47.2 (17/36) | 54.1 (20/37) | 56.3 (18/32) | 69.0 (20/29) | 55.6 (10/18) |

Upper row, %; Lower row, patients showing reduction in score from baseline/patients with baseline score of ≥0

PMDA's view on the efficacy of belimumab intravenous infusion and belimumab subcutaneous injection:
The phase III studies of belimumab intravenous infusion (Studies BEL113750, BEL110751, and BEL110752) and the phase III study of belimumab subcutaneous injection (Study BEL112341) in patients with SLE with disease activity who have inadequately responded to conventional treatments confirmed the superiority of both belimumab (10 mg/kg) intravenous infusion at 4-week interval and belimumab (200 mg) subcutaneous injection at 1-week interval to placebo in SRI response rate at Week 52, the primary endpoint. Also, results of each secondary efficacy endpoint suggest the efficacy of

belimumab, and tendency of improvement was observed in each organ system (Table 55). Based on the above, efficacy of belimumab against SLE has been demonstrated.

In Study BEL113750 on belimumab intravenous infusion, SRI response rate at Week 52, the same primary endpoint as used in the above studies, showed similar results in Japanese subpopulation as observed in the overall population. In Study BEL112341 on belimumab subcutaneous injection, SRI response rate at Week 52 the primary endpoint, did not show similar results in the Japanese subpopulation as those in the overall population. However, PMDA understands the applicant's explanation that the discrepancy was partly due to the imbalance of patient characteristics between treatment groups due to the limited number of patients in the Japanese subpopulation. Also, taking account of the results of the secondary endpoints in the Japanese subpopulation of Study BEL112341, those of the primary endpoint in the Japanese subpopulation of Study BEL112341 do not rule out the efficacy of belimumab subcutaneous injection in Japanese patients. Therefore, there is no particular problem in evaluating the efficacy of belimumab subcutaneous injection in Japanese patients with SLE based on the results of the overall population in Study BEL112341.

### 7.R.2 Safety

#### 7.R.2.1 Summary of safety data

The applicant explained the safety of belimumab, based on the pooled data of 3 foreign comparative studies on belimumab intravenous infusion (Studies LBSL02, BEL110751, and BEL110752) (IV-CRD pooled analysis), the pooled data of 3 foreign comparative studies on belimumab intravenous infusion (Studies LBSL02, BEL110751, and BEL110752) and of Study BEL112341 on belimumab subcutaneous injection (IV/SC-CRD pooled analysis), the data of Study BEL113750 on belimumab intravenous infusion, and the data of Study BEL112341 on belimumab subcutaneous injection, etc., as follows:
Tables 56 and 57 show the outline of adverse events in Study BEL113750, IV-CRD pooled analysis, and Study BEL112341.

**Table 56. Summary of adverse events in studies on belimumab intravenous infusion (up to Week 52; safety analysis population in Study BEL113750, mITT population in IV-CRD pooled analysis)**

| | Study BEL113750 | | | | IV-CRD pooled analysis | | | |
|---|---|---|---|---|---|---|---|---|
| | Overall population | | Japanese subpopulation | | | | | |
| | 10 mg/kg (N = 470) | Placebo (N = 235) | 10 mg/kg (N = 39) | Placebo (N = 21) | 1 mg/kg (N = 673) | 4 mg/kg (N = 111) | 10 mg/kg (N = 674) | Placebo (N = 675) |
| All adverse events | 352 (74.9) | 178 (75.7) | 39 (100.0) | 19 (90.5) | 626 (93.0) | 107 (96.4) | 625 (92.7) | 624 (92.4) |
| Death | 0 | 1 (0.4) | 0 | 0 | 5 (0.7) | 0 | 6 (0.9) | 3 (0.4) |
| Serious adverse events | 58 (12.3) | 43 (18.3) | 9 (23.1) | 6 (28.6) | 125 (18.6) | 15 (13.5) | 117 (17.4) | 107 (15.9) |
| Adverse events leading to discontinuation | 29 (6.2) | 22 (9.4) | 2 (5.1) | 2 (9.5) | 42 (6.2) | 4 (3.6) | 45 (6.7) | 48 (7.1) |
| Adverse drug reactions | 136 (28.9) | 55 (23.4) | 19 (48.7) | 5 (23.8) | 270 (40.1) | 53 (47.7) | 269 (39.9) | 285 (42.2) |

n (%)

**Table 57. Summary of adverse events in the study of belimumab subcutaneous injection (up to Week 52; ITT population in Study BEL112341)**

| | Overall population | | Japanese subpopulation | |
|---|---|---|---|---|
| | 200 mg (N = 556) | Placebo (N = 280) | 200 mg (N = 13) | Placebo (N = 16) |
| All adverse events | 449 (80.8) | 236 (84.3) | 12 (92.3) | 13 (81.3) |
| Death | 3 (0.5) | 2 (0.7) | 0 | 0 |
| Serious adverse events | 60 (10.8) | 44 (15.7) | 2 (15.4) | 2 (12.5) |
| Adverse events leading to discontinuation | 40 (7.2) | 25 (8.9) | 1 (7.7) | 0 |
| Adverse drug reactions | 173 (31.1) | 73 (26.1) | 6 (46.2) | 7 (43.8) |

n (%)

Table 58 shows adverse events reported by ≥10% of patients in any group in the IV-CRD pooled analysis.

**Table 58. Adverse events reported by ≥10% of patients in any group (IV-CRD pooled analysis, mITT population)**

| | 1 mg/kg (N = 673) | 4 mg/kg (N = 111) | 10 mg/kg (N = 674) | Placebo (N = 675) |
|---|---|---|---|---|
| Headache | 138 (20.5) | 30 (27.0) | 142 (21.1) | 140 (20.7) |
| Upper respiratory tract infection | 128 (19.0) | 36 (32.4) | 118 (17.5) | 130 (19.3) |
| Arthralgia | 100 (14.9) | 32 (28.8) | 109 (16.2) | 112 (16.6) |
| Urinary tract infection | 92 (13.7) | 19 (17.1) | 87 (12.9) | 82 (12.1) |
| Nausea | 88 (13.1) | 22 (19.8) | 99 (14.7) | 82 (12.1) |
| Diarrhoea | 81 (12.0) | 23 (20.7) | 80 (11.9) | 62 (9.2) |
| Fatigue | 71 (10.5) | 33 (29.7) | 66 (9.8) | 70 (10.4) |
| Back pain | 64 (9.5) | 15 (13.5) | 60 (8.9) | 62 (9.2) |
| Oedema peripheral | 62 (9.2) | 19 (17.1) | 56 (8.3) | 54 (8.0) |
| Pyrexia | 52 (7.7) | 17 (15.3) | 65 (9.6) | 52 (7.7) |
| Vomiting | 49 (7.3) | 15 (13.5) | 46 (6.8) | 44 (6.5) |
| Rash | 46 (6.8) | 17 (15.3) | 35 (5.2) | 35 (5.2) |
| Bronchitis | 43 (6.4) | 12 (10.8) | 60 (8.9) | 35 (5.2) |
| Depression | 41 (6.1) | 12 (10.8) | 35 (5.2) | 25 (3.7) |
| Dizziness | 38 (5.6) | 12 (10.8) | 37 (5.5) | 42 (6.2) |
| Arthritis | 35 (5.2) | 21 (18.9) | 40 (5.9) | 41 (6.1) |
| Pain in extremity | 35 (5.2) | 13 (11.7) | 40 (5.9) | 27 (4.0) |
| Sinusitis | 34 (5.1) | 15 (13.5) | 49 (7.3) | 54 (8.0) |
| Mouth ulceration | 23 (3.4) | 12 (10.8) | 36 (5.3) | 35 (5.2) |

n (%)

Death occurred in 1 patient in the placebo group in Study BEL113750 (respiratory failure); in 14 patients in IV-CRD pooled analysis (5 patients in the 1 mg/kg group [sepsis, death, completed suicide, ovarian cancer, ischaemic stroke], 6 patients in the 10 mg/kg group [respiratory failure in 2 patients, cardiac arrest, bacterial sepsis, diarrhoea infectious, and completed suicide in 1 patient each], and 3 patients in the placebo group [cardiac arrest, myocardial infarction, death]); and in 5 patients in Study BEL112341 (3 patients in the 200 mg group [tuberculosis of central nervous system, urosepsis, bacterial sepsis], 2 patients in the placebo group [cardiac arrest, thrombocytopenia]). The mortality tended to be higher in the belimumab group compared with the placebo group. Of these, a causal relationship to the study drug could not be ruled out for bacterial sepsis, diarrhoea infectious, myocardial infarction, tuberculosis of central nervous system, and urosepsis. In Study BEL114333 in patients with SLE who completed the double-blind phase in Study BEL113750 and patients with SLE who completed the open-label phase of Study BEL112341, death occurred in 2 patients (endocarditis infective, accidental fall). In the pooled

data of 3 long-term extension studies on belimumab intravenous infusion (Studies BEL112626,[34] BEL112233,[35] and BEL112234[36]) (IV-LTC pooled analysis), death occurred in 20 patients (cardiac arrest in 2 patients, lung infection pseudomonal, pneumonia, pneumonia bacterial, pneumonia cytomegaloviral, pulmonary haemorrhage, respiratory failure, sepsis, septic shock, coronary artery disease, hypertensive heart disease, ischaemic stroke, retroperitoneal haemorrhage, acute respiratory distress syndrome, pancreatitis acute, completed suicide, toxicity to various agents, thrombotic thrombocytopenic purpura, and cardiogenic shock in 1 patient each). The most common cause of death was infection. Table 59 shows the mortality in each clinical study, which was not significantly different from that in patients with SLE reported in literature (0.17-1.66 per 100 person-years) (*Arthritis Rheum.* 2001;45:191-202, *Arthritis Rheum.* 2010;62:2458-66, etc.).

**Table 59. Mortality per 100 person-years**

| | Study BEL113750 | | IV-CRD pooled analysis | | IV-LTC pooled analysis | | Study BEL112341 | |
|---|---|---|---|---|---|---|---|---|
| | 10 mg/kg | Placebo | 10 mg/kg | Pooled belimumab | Placebo | Pooled belimumab | 200 mg | Placebo |
| Total exposure (person-years) | 428 | 206 | 627 | 1353 | 623 | 6894 | 511 | 248 |
| Death | 0 | 1 (0.5) | 6 (1.0) | 11 (0.8) | 3 (0.5) | 20 (0.3) | 3 (0.6) | 2 (0.8) |

Number of patients (mortality)

The incidence of serious adverse events did not show any clear difference between the placebo group and each belimumab group in any of the analyses. Serious adverse events[37] reported by >1% of patients in any group were lupus nephritis (1.1% in the 10 mg/kg group, 2.1% in the placebo group), pyrexia (0.4%, 1.7%), and herpes zoster (1.3%, 0.9%) in Study BEL113750; pneumonia (1.0% in the 1 mg/kg group, 0.9% in the 10 mg/kg group, 1.5% in the placebo group), pyrexia (0.7%, 1.3%, 0.4%), urinary tract infection (1.0%, 0.7%, 0.6%), and cellulitis (1.0%, 0.1%, 0.3%) in IV-CRD pooled analysis; and thrombocytopenia (0% in the 200 mg group, 1.1% in the placebo group) in Study BEL112341. In Study BEL114333, serious adverse events were observed in 13.7% (77 of 564) of patients. Main events observed included lupus nephritis in 7 patients and osteonecrosis in 6 patients. In IV-LTC pooled analysis, serious adverse events were observed in 39.6% (514 of 1299) of patients. Main events were non-cardiac chest pain (2.2%), pneumonia (2.2%), cellulitis (1.9%), pyrexia (1.8%), and pneumonia bacterial (1.7%).

The incidence of adverse events leading to treatment discontinuation did not show any clear difference between the placebo group and each belimumab group in any of the analyses. Events reported by ≥2 patients in any group were renal failure (0.6% in the 10 mg/kg group, 0% in the placebo group), lupus nephritis (0.4%, 1.3%), pyrexia (0.4%, 1.3%), and lung infection (0%, 0.9%) in Study BEL113750; lupus nephritis (0.6% in the 1 mg/kg group, 0.9% in the 10 mg/kg group, 1.2% in the placebo group), infusion related reaction (0.3%, 0.7%, 0.1%), pneumonia (0.3%, 0.1%, 0%), systemic lupus erythematosus rash (0%, 0.1%, 0.3%), SLE arthritis (0.1%, 0%, 0.3%), myositis (0%, 0%, 0.3%), respiratory failure (0%, 0.3%, 0%), myocardial infarction (0%, 0.1%, 0.3%), pyrexia (0.1%, 0%, 0.3%), pregnancy (0.3%, 0.1%, 0.1%), and vasculitis (0.3%, 0%, 0.1%) in IV-CRD pooled analysis; and lupus

34) A long-term extension study in patients who have responded sufficiently in Study LBSL02
35) A long-term extension study in patients who wished to continue Study BEL110751 in the US
36) A long-term extension study in patients who wished to continue Study BEL110751 or BEL110752 in countries other than the US and in patients enrolled in Study BEL112232 in Mexico.
37) The 4 mg/kg group in IV-CRD pooled analysis was not included in the analysis.

nephritis (0.7% in the 200 mg group, 0.7% in the placebo group), nephritis (0.4%, 0%), nephrotic syndrome (0%, 0.7%), proteinuria (0%, 0.7%), pulmonary tuberculosis (0.2%, 0.7%), and thrombocytopenia (0%, 1.1%) in Study BEL112341.

### 7.R.2.2 Adverse events possibly related to belimumab

Taking account of the occurrences of adverse events in clinical studies, pharmacological action of belimumab, and disease characteristics in patients with SLE, PMDA reviewed the data focused on the following events.

The applicant explained the safety of belimumab, based on the pooled data of Japanese and foreign clinical studies in patients with SLE. Details are presented in the subsections below.

**(a) Infection**

**(1) Serious infection**

The applicant's explanation about the occurrences of serious infection:

As belimumab suppresses BLyS, resulting in decreases in B cells and immunoglobulins, it may increase the risk of infection.

Tables 60 and 61 show the incidences of infection in Study BEL113750, IV-CRD pooled analysis, and Study BEL112341. Main events observed were upper respiratory tract infection, nasopharyngitis, and urinary tract infection. The incidence of adverse events classified as "Infections and infestations" in SOC tended to be higher in the belimumab group than in the placebo group in IV-CRD pooled analysis and in Study BEL113750, whereas the incidence of serious events was not significantly different between the placebo group and the belimumab group. The incidence rate of serious infection in clinical studies was not significantly different from the incidence rate of serious infection in patients with SLE (33,565 patients, 83,959 person-years) in clinical studies, calculated using Medicaid Analytic eXtract (MAX) of the US (10.81 [95% CI; 10.59, 11.04] per 100 person-years).

The most common cause of death observed in Study BEL113750, IV-CRD pooled analysis, and Study BEL112341 was infection [see Section 7.R.2.1], and fatal infection was observed only in the belimumab group. Most of the fatal cases had used steroid and other immunosuppressants. The incidence rate of death due to infection was 0.35 [95% CI; 0.14, 0.71] per 100 person-years in the belimumab group and 0.11 [0.00, 0.60] per 100 person-years in the placebo group, with the incidence rate ratio being 3.25 [0.42, 146.28].[38)] The incidence rate was not significantly different from that in patients with SLE reported in literature (0.17-1.66 per 100 person-years) (*Arthritis Rheum*. 2001;45:191-202, *Arthritis Rheum.* 2010;62:2458-66, etc.).

[38)] Pooled data of Study BEL112341 and IV-CRD pooled analysis up to Week 76 of administration.

**Table 60. Incidence of infection in phase III studies (up to Week 52; safety analysis population in Study BEL113750, mITT population in IV-CRD pooled analysis, ITT population in Study BEL112341)**

| | Study BEL113750 | | | | IV-CRD pooled analysis | | | Study BEL112341 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall population | | Japanese subpopulation | | | | | Overall population | | Japanese subpopulation | |
| | 10 mg/kg (N = 470) | Placebo (N = 235) | 10 mg/kg (N = 39) | Placebo (N = 21) | 10 mg/kg (N = 674) | Pooled belimumab (N = 1458) | Placebo (N = 675) | 200 mg (N = 556) | Placebo (N = 280) | 200 mg (N = 13) | Placebo (N = 16) |
| Infections and infestations (SOC) | 240 (51.1) | 119 (50.6) | 33 (84.6) | 14 (66.7) | 472 (70.0) | 1035 (71.0) | 444 (65.8) | 308 (55.4) | 159 (56.8) | 7 (53.8) | 10 (62.5) |
| Fatal infections and infestations (SOC) | 0 | 0 | 0 | 0 | 2 (0.3) | 3 (0.2) | 0 | 3 (0.5) | 0 | 0 | 0 |
| Serious infections and infestations (SOC) | 25 (5.3) | 13 (5.5) | 3 (7.7) | 1 (4.8) | 34 (5.0) | 83 (5.7) | 35 (5.2) | 23 (4.1) | 15 (5.4) | 0 | 1 (6.3) |
| Opportunistic infection[a)] | 13 (2.8) | 5 (2.1) | 0 | 0 | 9 (1.3) | 15 (1.0) | 8 (1.2) | 2 (0.4) | 1 (0.4) | 0 | 0 |
| Active tuberculosis | 2 (0.4) | 2 (0.9) | 0 | 0 | 0 | 0 | 0 | 2 (0.4) | 2 (0.7) | 0 | 0 |
| Herpes zoster | 29 (6.2) | 12 (5.1) | 2 (5.1) | 0 | 21 (3.1) | 46 (3.2) | 25 (3.7) | 18 (3.2) | 13 (4.6) | 1 (7.7) | 0 |
| Sepsis | 1 (0.2) | 2 (0.9) | 0 | 0 | 6 (0.9) | 12 (0.8) | 3 (0.4) | 6 (1.1) | 3 (1.1) | 0 | 0 |

n (%)

a) The sponsor assessed, before the release of the database, whether adverse events observed met the criteria for opportunistic infection.

**Table 61. Incidenc rates of infection and serious infection per 100 person-years (up to Week 52; safety analysis population in Study BEL113750, mITT population in IV-CRD pooled analysis, ITT population in Study BEL112341**

| | IV-CRD pooled analysis | | | Study BEL113750 | | Study BEL112341 | |
|---|---|---|---|---|---|---|---|
| | 10 mg/kg (627 person-years) | Pooled belimumab (1353 person-years) | Placebo (623 person-years) | 10 mg/kg (428 person-years) | Placebo (206 person-years) | 200 mg (511 person-years) | Placebo (248 person-years) |
| SOC "Infections and infestations" | | | | | | | |
| Adverse events | 1213 (193.6) | 2725 (201.3) | 1178 (189.1) | 484 (113.0) | 219 (106.1) | 665 (130.0) | 342 (137.6) |
| Serious | 42 (6.7) | 105 (7.8) | 50 (8.0) | 29 (6.8) | 18 (8.7) | 31 (6.1) | 17 (6.8) |
| Noteworthy infection among adverse events | | | | | | | |
| No. of patients with infection[a)] | 40 (6.4) | 99 (7.3) | 39 (6.3) | 41 (9.6) | 22 (10.7) | 34 (6.6) | 21 (8.5) |
| Serious | 11 (1.8) | 21 (1.6) | 5 (0.8) | 13 (3.0) | 8 (3.9) | 9 (1.8) | 3 (1.2) |
| Opportunistic infection[b)] | 10 (1.6) | 17 (1.3) | 9 (1.4) | 15 (3.5) | 6 (2.9) | 2 (0.4) | 1 (0.4) |
| Serious | 4 (0.6) | 6 (0.4) | 0 | 7 (1.6) | 3 (1.5) | 1 (0.2) | 0 |
| Opportunistic infection (except tuberculosis and herpes zoster)[b)] | 3 (0.5) | 5 (0.4) | 3 (0.5) | 4 (0.9) | 1 (0.5) | 0 | 1 (0.4) |
| Serious | 2 (0.3) | 2 (0.1) | 0 | 2 (0.5) | 0 | 0 | 0 |
| Active tuberculosis[a)] | 0 | 0 | 0 | 3 (0.7) | 3 (1.5) | 2 (0.4) | 2 (0.8) |
| Serious | 0 | 0 | 0 | 3 (0.7) | 3 (1.5) | 1 (0.2) | 1 (0.4) |
| Herpes zoster[a)] | 22 (3.5) | 49 (3.6) | 25 (4.0) | 30 (7.0) | 12 (5.8) | 19 (3.7) | 13 (5.2) |
| Serious | 3 (0.5) | 7 (0.5) | 3 (0.5) | 7 (1.6) | 2 (1.0) | 1 (0.2) | 0 |
| Disseminated | 3 (0.5) | 5 (0.4) | 0 | 5 (1.2) | 2 (1.0) | 1 (0.2) | 0 |
| Sepsis[a)] | 6 (1.0) | 12 (0.9) | 3 (0.5) | 1 (0.2) | 2 (1.0) | 7 (1.4) | 3 (1.2) |
| Serious | 6 (1.0) | 12 (0.9) | 1 (0.2) | 1 (0.2) | 2 (1.0) | 5 (1.0) | 2 (0.8) |

Number of events (incidence rate per 100 person-years)

a) Medical dictionary for regulatory activities (MedDRA) SMQ was used after partial modification

b) Assessment by the sponsor

As for opportunistic infection in IV/SC-CRD pooled analysis (52 weeks), adverse events assessed as opportunistic infection by the sponsor were observed in 9 of 955 patients (0.9%) in the pooled placebo group and in 17 of 2014 patients (0.8%) in the pooled belimumab group. Adverse events (PT) reported by ≥2 patients in either group were herpes zoster, oesophageal candidiasis, herpes zoster cutaneous disseminated, and herpes zoster disseminated. The incidence of serious opportunistic infection was higher in the belimumab group compared with the placebo group.

In IV/SC-CRD pooled analysis, herpes zoster was observed in 64 patients (3.2%) in the pooled belimumab group and in 38 patients (4.0%) in the placebo group. The incidence of serious herpes zoster was 0.4% in the belimumab group and 0.3% in the placebo group. In Study BEL113750, herpes zoster was observed in 29 patients (6.2%) in the belimumab group and in 12 patients (5.1%) in the placebo group. In East Asians, the incidence of herpes zoster tended to be higher than that in IV-CRD pooled analysis. As for Japanese, herpes zoster was observed in 2 patients in the 10 mg/kg group of Study BEL113750 and in 1 patient in Study BEL112341. The event was serious in 1 patient in Study BEL113750.

As for sepsis, the incidence (52 weeks) in IV/SC-CRD pooled analysis was 0.9% (0.9% in the 10 mg/kg group, 1.1% in the 200 mg group) in the pooled belimumab group and 0.6% in the pooled placebo group. Among events classified as sepsis, urosepsis was the most commonly observed; it was observed in 4 patients in the pooled belimumab group (0.2% in the pooled belimumab group, 0% in the pooled placebo group). The incidence of serious sepsis (52 weeks) was 0.8% (0.9% in the 10 mg/kg group, 0.7% in the 200 mg group) in the pooled belimumab group and 0.3% in the pooled placebo group. Serious sepsis (PT) reported by ≥2 patients in either group was urosepsis, bacterial sepsis, Escherichia sepsis, and sepsis.

In phase III studies (Studies BEL110751, BEL110752, BEL113750, and BEL112341), patients with acute or chronic infection requiring treatment for tuberculosis were to be excluded. Active tuberculosis was not observed in IV-CRD pooled analysis, but observed in 2 patients in the belimumab 10 mg group (disseminated tuberculosis/meningitis tuberculous in 1, tuberculous pleurisy in 1) and in 2 patients in the placebo group (tuberculosis liver/spleen tuberculosis in 1 patient, lymph node tuberculosis in 1 patient) in Study BEL113750. In Study BEL112341, active tuberculosis was observed in 2 patients in the belimumab group (pulmonary tuberculosis and tuberculosis of central nervous system in 1 patient each), and in 2 patients in the placebo group (pulmonary tuberculosis in 2 patients). The events were serious in 1 patient in the placebo group (pulmonary tuberculosis) and in 1 patient in the belimumab group (tuberculosis of central nervous system), and resulted in death in the patient with tuberculosis of central nervous system. Active tuberculosis was not observed in Japanese patients.

In phase III studies (Studies BEL110751, BEL110752, BEL113750, and BEL112341), an HBV test was performed at screening to check whether patients met HBV-related exclusion criteria.[39)] In Study BEL113750, 78 patients who were positive for HBV core antibody at screening were assigned to the belimumab group, but no HBV DNA was detected in any of them throughout the double-blind phase, showing no flare-up of hepatitis B. In Study BEL112626, acute hepatitis C was observed in 1 patient,

39) Patients positive for the surface antigen of hepatitis B virus (HBsAg) were to be excluded. In Japan in Study BEL112341 and in Study BEL113750, (1) patients who were negative for HBsAg but positive for hepatitis B virus core antibody (HBcAb) and (2) patients who were HBsAg- and HBcAb-negative but positive for hepatitis B virus surface antibody (HBsAb) and had no history of HBV vaccination were to be excluded. In China in Study BEL113750, patients who were HBsAg-negative and HBcAb-positive were eligible for the study if they were HBV DNA-negative.

but HBs antigen and HCV antibody were negative at screening in this patient. According to the data obtained from clinical studies and spontaneous reports (reports from consumers that were not confirmed by medical professionals were excluded) by March 8, 2016 after the approval of belimumab intravenous infusion in foreign countries, 1 event each of acute hepatitis and acute hepatitis B was reported as serious adverse events for which a causal relationship to belimumab could not be ruled out.

Also, according to the data obtained from clinical studies and spontaneous reports up to March 8, 2016 after the approval of belimumab intravenous infusion in foreign countries, the following were reported as serious adverse events for which a causal relationship to belimumab could not be ruled out: 3 events each of tuberculosis and pulmonary tuberculosis, 2 events each of mycobacterial infection and tuberculous pleurisy, and 1 event each of spleen tuberculosis, tuberculosis of central nervous system, disseminated tuberculosis, cutaneous tuberculosis, meningitis tuberculous, Mycobacterium abscessus infection, and Mycobacterium chelonae infection.

Based on the above, the applicant considers that there is no significant difference between the belimumab group and the placebo group in the incidence of opportunistic infection, active tuberculosis, herpes zoster, or sepsis.

PMDA's view on the risk of belimumab causing serious infection:
Given the mechanism of action of belimumab, the immunosuppressive effect of belimumab may causes infection, tuberculosis, and reactivation of viruses such as hepatitis B virus. Also, multiple cases of death caused by infection such as sepsis and tuberculosis were reported only in the belimumab group. Taking account of the above, it is essential to take strict safety measures against serious infection in administering belimumab, by alerting physicians to the following: (1) belimumab may possibly cause serious infection such as sepsis, tuberculosis, opportunistic infection, and herpes zoster, (2) before belimumab administration, patients should be thoroughly interviewed, tested, and screened for eligibility for the treatment, (3) belimumab should not be administered to patients with serious infection or with active tuberculosis, and (4) treatment should be performed in cooperation with a physician experienced in the treatment of infection such as tuberculosis. Only a limited number of patients were investigated in clinical studies, and it is unknown currently whether long-term administration of belimumab increases the risk of infection in Japanese patients with SLE. Therefore, incidences of serious infection, including those in long-term administration, should be continuously investigated in the post-marketing surveillance, etc., and information thus obtained should be appropriately provided to healthcare professionals.

**(b) PML**

The applicant's explanation about the incidence of PML:
PML causes nerve disorders, possibly leading to death. It is reported that the risk of PML is higher in patients with SLE compared with the general population or patients with other rheumatic diseases (*Arthritis Rheum*. 2009;60:3761-5, *Arthritis Rheum*. 2012;64:3043-51, etc.).

Up to the data cut-off ([redacted]), PML was reported in 3 patients receiving belimumab (2 patients in spontaneous reports, 1 patient in an ongoing clinical study [Study BEL115467, post-marketing clinical study investigating noteworthy adverse events]), with the incidence rate of PML being 6.23 per 100,000 person-years [95% CI; 1.28, 18.20]. After the data lock, another case of PML

was spontaneously reported. Of the 4 patients, 2 patients died and 2 patients recovered with sequelae. In the data obtained from clinical studies and spontaneous reports by March 8, 2016 after the approval of belimumab intravenous infusion in foreign countries, 5 events of PML, 2 events of JC virus infection, and 1 event of positive JC virus test were reported as serious adverse events for which a causal relationship to belimumab could not be ruled out.

All patients who experienced PML had received immunosuppressants and high dose steroid, and the relationship between PML and immunosuppressants such as MMF and steroid is reported (*Arthritis Rheum*. 2012;64:3043-51). Taking account of these, it is difficult currently to draw any conclusion on the causal relationship between belimumab and PML.

Because of the limited information on the risk of PML in patients with SLE, the incidence rate of PML in patients with SLE is unknown. The incidence rate of PML in patients receiving combination of conventional anti-SLE drugs is reported to be 2.4 per 100,000 person-years [95% CI; 0.1, 13.2] (*Neurology*. 2010;75:1326-32) or 4 per 100,000 person-years (*Arthritis Rheum*. 2009;60:3761-5), which was not significantly different from the incidence observed after belimumab administration.

Thus, the limited data currently available suggest that the incidence rate of belimumab-induced PML does not show any tendency toward an increase compared with the incidence of PML induced by conventional anti-SLE drugs. However, since there are reports of PML resulting in nerve disorder or in death in patients receiving belimumab, caution will be provided on the risk of PML in the package insert.

PMDA's view:
Because of the extremely limited number of patients studied, it is difficult to draw any clear conclusion on the risk of belimumab causing PML. Nevertheless, given that belimumab has an immunosuppressive effect and that there are reports of PML resulting in nerve disorder or death in patients receiving belimumab, the possibility cannot be excluded that belimumab may increase the risks of PML. Since PML may lead to a serious outcome, cautions should be provided in the package insert to pay close attention to occurrence of PML in administering belimumab, to monitor patients for their conditions during and after the treatment with belimumab and, in case of symptoms such as disturbed consciousness and cognitive disorder, to take appropriate measures. Also, because of the limited number of patients investigated in clinical studies, incidences of PML, including those in long-term administration, should be continuously investigated in the post-marketing surveillance, etc., and information thus obtained should be appropriately provided to healthcare professionals.

**(c) Post-infusion systemic reaction**

The applicant's explanation about the incidences of administration site reaction and post-infusion systemic reaction[40)]:
Occurrences of post-infusion systemic reaction, including hypersensitivity, were reported after administration of protein drugs including monoclonal antibodies.

Table 62 shows the incidences of post-infusion systemic reaction in Study BEL113750, IV-CRD pooled analysis, and Study BEL112341. The incidence of post-infusion systemic reaction in IV-CRD pooled

40) "Post-infusion systemic reaction" was defined as PT events that are included in category A (main anaphylaxis) of "Anaphylactic reaction" in SMQ, excluding "Anaphylactic transfusion reaction" and "First use syndrome," and adding "Infusion related reaction," "Drug hypersensitivity," and "Hypersensitivity," and occurred on the day of the study drug administration or within 3 days after the administration.

analysis was higher in the belimumab 10 mg/kg group than in the placebo group. Most of the events were mild, whereas 1 patient in the 10 mg/kg group experienced mild to moderate dyspnoea, pruritus, rash erythematous, and eyelid oedema, and the study drug administration was discontinued in this patient. Another 1 patient in the 10 mg/kg group experienced serious angioedema and hypotension, and the study drug administration was interrupted. In Studies BEL113750 and BEL112341, no clinically significant difference was observed in the incidence of post-infusion systemic reaction between the belimumab group and the placebo group. Among the patients of the Japanese subpopulation, the incidence of post-infusion systemic reaction was similar between the 10 mg/kg group and the placebo group in Study BEL113750, while anaphylactic reaction (broad search) was observed in 2 patients in the placebo group in Study BEL112341.

**Table 62. Incidence of post-infusion systemic reaction in phase III studies (up to Week 52; safety analysis population in Study BEL113750, mITT population in IV-CRD pooled analysis, ITT population in Study BEL112341)**

| | Study BEL113750 | | | | IV-CRD pooled analysis | | Study BEL112341 | |
|---|---|---|---|---|---|---|---|---|
| | Overall population | | Japanese subpopulation | | | | | |
| | 10 mg/kg (N = 470) | Placebo (N = 235) | 10 mg/kg (N = 39) | Placebo (N = 21) | 10 mg/kg (N = 674) | Placebo (N = 675) | 200 mg (N = 556) | Placebo (N = 280) |
| No. of patients with post-infusion systemic reaction | 64 (13.6) | 32 (13.6) | 3 (7.7) | 2 (9.5) | 80 (11.9) | 65 (9.6) | 38 (6.8) | 25 (8.9) |
| Anaphylactic reaction (narrow search[a)]) | 4 (0.9) | 4 (1.7) | 0 | 0 | 16 (2.4) | 7 (1.0) | 2 (0.4) | 1 (0.4) |
| Anaphylactic reaction (broad search[b)]) | 61 (13.0) | 29 (12.3) | 3 (7.7) | 2 (9.5) | 80 (11.9) | 65 (9.6) | 38 (6.8) | 24 (8.6) |
| Anaphylactic reaction (algorithmic search[c)]) | 4 (0.9) | 1 (0.4) | 0 | 0 | 17 (2.5) | 10 (1.5) | 2 (0.4) | 1 (0.4) |
| Serious anaphylactic reaction by Sampson criteria[d)] | 0 | 0 | 0 | 0 | 2 (0.3) | 0 | 0 | 0 |
| Serious and acute post-infusion systemic reaction/hypersensitivity, according to the applicant's assessment | 0 | 0 | 0 | 0 | 6 (0.9) | 2 (0.3) | 0 | 0 |

n (%)

a) One or more events classified as PT in category A of "Anaphylactic reaction" (SMQ).
b) One or more events classified as PT in category A, B, C, or D of "Anaphylactic reaction" (SMQ).
c) Events that correspond to any of the following: (a) one or more events of category A PT, (b) 2 adverse events, with one event each of category B and category C PT, and (c) 2 adverse events, with one event of category D PT and one event of category B or C PT.
d) Assessed based on the symptoms in 4 main regions that develop at the same time after exposure to allergen (mucocutaneous tissue, dyspnea, decreased blood pressure, gastrointestinal symptom) (*J Allergy Clin Immunol*. 2006;117:391-7).

PMDA's view:

In IV-CRD pooled analysis, the incidence of post-infusion systemic reaction in the belimumab 10 mg/kg group was higher than that in the placebo group, with some of the events being serious. Since belimumab is a monoclonal antibody product, the possibility cannot be excluded that it induces hypersensitivity reactions including shock and anaphylaxis. Therefore, a caution statement regarding post-infusion systemic reaction should be included in the package insert. Also, incidences of hypersensitivity reaction and administration site reaction should be continuously investigated in the post-marketing surveillance, etc., and information thus obtained should be appropriately provided to healthcare professionals.

**(d) Malignant tumor**

The applicant's explanation about the incidence of malignant tumor:

Since belimumab has an immunosuppressive effect, it may increase the risk of malignant tumor.

Table 63 shows the incidences of malignant tumor in Study BEL113750, IV-CRD pooled analysis, and Study BEL112341. No major difference was observed in the incidence of malignant tumor between the placebo group and the belimumab group in any of the studies. Among Japanese patients, endometrial cancer was observed in 1 patient in the belimumab 200 mg group of Study BEL112341.

**Table 63. Incidence of malignant tumor in phase III studies (up to Week 52, ITT population)**

| | Study BEL113750 | | IV-CRD pooled analysis | | Study BEL112341 | |
|---|---|---|---|---|---|---|
| | 10 mg/kg (N = 470) | Placebo (N = 235) | 10 mg/kg (N = 674) | Placebo (N = 675) | 200 mg (N = 556) | Placebo (N = 280) |
| Malignant tumor | 1 (0.2) | 0 | 3 (0.4) | 2 (0.3) | 2 (0.4) | 1 (0.4) |
| Malignant tumor except NMSC | 1 (0.2) | 0 | 0 | 1 (0.1) | 2 (0.4) | 1 (0.4) |

n (%)

The incidence rate of malignant tumor other than nonmelanoma skin cancer (NMSC) per 100 person-years was 0.2 in the placebo group, 0 in the belimumab 10 mg group, and 0.1 in the pooled belimumab group in IV-CRD pooled analysis; 0 in the placebo group and 0.2 in the belimumab 10 mg/kg group in Study BEL113750; and 0.4 in the placebo group and 0.4 in the belimumab 200 mg group in Study BEL112341, showing no major difference between the placebo group and the belimumab group. Table 64 shows the incidence rate of malignant tumor in IV-LTC pooled analysis including the long-term extension study of belimumab intravenous infusion. No clinically significant trend was observed in the incidence rates of events over time in each category of malignant neoplasm.

**Table 64. Incidence rate of malignant tumor over time (IV-LTC pooled analysis, mITT population)**

| Time to onset (year) | Entire period | 0-1 | 1-2 | 2-3 | 3-4 | 4-5 | 5-6 | 6-7 | 7-8 | 8-9 | 9-10 | 10- |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Person-years | 6894 | 1273 | 1203 | 1053 | 925 | 811 | 626 | 375 | 183 | 160 | 118 | 43 |
| Malignant tumor | 48 (0.7) | 3 (0.2) | 5 (0.4) | 10 (1.0) | 8 (0.9) | 6 (0.7) | 4 (0.6) | 5 (1.3) | 0 | 3 (1.9) | 4 (3.4) | 0 |
| Malignant tumor except NMSC | 35 (0.5) | 1 (<0.1) | 2 (0.2) | 7 (0.7) | 7 (0.8) | 6 (0.7) | 3 (0.5) | 3 (0.8) | 0 | 2 (1.3) | 4 (3.4) | 0 |
| Solid cancer | 28 (0.4) | 1 (<0.1) | 2 (0.2) | 5 (0.5) | 6 (0.6) | 4 (0.5) | 3 (0.5) | 1 (0.3) | 0 | 2 (1.3) | 4 (3.4) | 0 |
| Blood cancer | 4 (<0.1) | 0 | 0 | 2 (0.2) | 1 (0.1) | 0 | 0 | 1 (0.3) | 0 | 0 | 0 | 0 |
| All skin cancers | 16 (0.2) | 2 (0.2) | 3 (0.2) | 3 (0.3) | 1 (0.1) | 2 (0.2) | 1 (0.2) | 3 (0.8) | 0 | 1 (0.6) | 0 | 0 |
| NMSC | 13 (0.2) | 2 (0.2) | 3 (0.2) | 3 (0.3) | 1 (0.1) | 0 | 1 (0.2) | 2 (0.5) | 0 | 1 (0.6) | 0 | 0 |
| Other than NMSC | 3 (<0.1) | 0 | 0 | 0 | 0 | 2 (0.2) | 0 | 1 (0.3) | 0 | 0 | 0 | 0 |

Number of patients (incidence rate per 100 person-years)

In the data obtained from clinical studies and spontaneous reports by March 8, 2016 after the approval of belimumab intravenous infusion in foreign countries, 80 events coded to "Neoplasms benign, malignant and unspecified (incl. cysts and polyps)" (SOC) were reported as serious adverse events for which a causal relationship to belimumab could not be ruled out. The events reported at least twice were breast cancer (9 events), lymphoma, B-cell lymphoma, acute myeloid leukaemia, neoplasm malignant, and basal cell carcinoma (3 events each); renal cell carcinoma, thyroid cancer, papillary thyroid cancer,

non-small cell lung cancer, skin cancer, squamous cell carcinoma of skin, and Bowen's disease (2 events each).

In a cohort study in patients diagnosed with SLE (9547 patients from 23 study sites in 6 countries [Canada, US, UK, Iceland, Sweden, and South Korea]; 76,948 person-years, mean follow-up period 8.1 years), a total of 410 events of neoplasm malignant except NMSC were reported, with the incidence rate being 0.53 per 100 person-years (*Arthritis Rheum*. 2005;52:1481-90). In a cohort study which was a study on the cohort renewed from the above one (16,409 patients from 30 study sites in 9 countries [Canada, US, UK, Iceland, Sweden, Denmark, Spain, Germany, and South Korea]; 121,283 person-years in total, mean follow-up period 7.4 years), a total of 644 events of neoplasm malignant were reported, with the incidence rate being 0.53 per 100 person-years (*Journal of Autoimmunity*. 2013;42:130-5). The incidence rate of malignant tumor in patients receiving belimumab was similar to that observed in the overall population of patients with SLE studied.

PMDA's view:
Currently, a causal relationship between belimumab and malignant tumor is unclear. The number of patients investigated in clinical studies is not sufficiently large for evaluating the risk of malignant tumor and, given the immunosuppressive mechanism of belimumab, the possibility cannot be excluded that the belimumab affects the body's cancer-suppressing mechanism. Therefore, a caution statement regarding the risk of malignant tumor should be included in the package insert. Also, incidences of malignant tumor in patients with SLE receiving belimumab should be continuously investigated in the post-marketing surveillance, etc., and information thus obtained should be appropriately provided to healthcare professionals.

**(e) Depression and suicide/self-injury**

The applicant's explanation about the incidence of depression and suicide/self-injury:
It is shown that patients with SLE have a high risk of developing psychiatric events such as depression and suicidal tendency (*Ann Rheum Dis.* 2010;69:529, *Lupus*. 2016;25:185-92).

Table 65 shows the incidences of depression and suicide/self-injury in Study BEL113750, IV-CRD pooled analysis, and Study BEL112341. No clinically meaningful difference was observed in the incidence in the belimumab group compared with the placebo group. Study BEL113750 showed that 1 patient in the 10 mg/kg group had suicidal ideation, and 1 patient in the placebo group showed suicidal behavior. However, none of these events led to death, neither was there suicide/self-injury resulting in treatment discontinuation. As for Japanese patients, depression was observed in 3 patients (7.7%) in the belimumab 10 mg/kg group in Study BEL113750 (depression, anxiety disorder, and depressed mood in 1 patient each) and in 1 patient (4.8%) in the placebo group (anxiety), while no suicide attempt or self-injury was observed.

**Table 65. Incidence of depression and suicide/self-injury in phase III studies (up to Week 52; safety analysis population in Study BEL113750, mITT population in IV-CRD pooled analysis, ITT population in Study BEL112341)**

| | Study BEL113750 | | | | IV-CRD pooled analysis | | Study BEL112341 | |
|---|---|---|---|---|---|---|---|---|
| | Overall population | | Japanese subpopulation | | | | | |
| | 10 mg/kg (N = 470) | Placebo (N = 235) | 10 mg/kg (N = 39) | Placebo (N = 21) | 10 mg/kg (N = 674) | Placebo (N = 675) | 200 mg (N = 556) | Placebo (N = 280) |
| No. of patients with depression and suicide/self-injury | 10 (2.1) | 6 (2.6) | 3 (7.7) | 1 (4.8) | 59 (8.8) | 56 (8.3) | 17 (3.1) | 10 (3.6) |
| Depression[a)] | 9 (1.9) | 6 (2.6) | 3 (7.7) | 1 (4.8) | 58 (8.6) | 56 (8.3) | 15 (2.7) | 10 (3.6) |
| Serious depression[b)] | 0 | 0 | 0 | 0 | 4 (0.6) | 2 (0.3) | 0 | 0 |
| Suicide/self-injury[b)] | 1 (0.2) | 1 (0.4) | 0 | 0 | 1 (0.1) | 1 (0.1) | 2 (0.4) | 0 |
| Serious suicide/self-injury[b)] | 1 (0.2) | 1 (0.4) | 0 | 0 | 1 (0.1) | 1 (0.1) | 1 (0.2) | 0 |
| No. of patients with serious suicide/self-injury[c)] | 1 (0.2) | 1 (0.4) | 0 | 0 | 1 (0.1) | 1 (0.1) | 2 (0.4) | 0 |
| Suicidal behaviour[c)] | 0 | 1 (0.4) | 0 | 0 | 1 (0.1) | 0 | 0 | 0 |
| Completed suicide[c)] | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 0 | 0 |
| Suicidal ideation[c)] | 1 (0.2) | 0 | 0 | 0 | 0 | 0 | 2 (0.4) | 1 (0.4)[d)] |
| Self injurious behaviour[c)] | 0 | 0 | 0 | 0 | 0 | 1 (0.1) | 0 | 0 |

n (%)
a) MedDRA SMQ (Study BEL113750, Ver. 18.1; IV-CRD pooled analysis, Ver. 17.1) was used with partial modification.
b) MedDRA SMQ (Study BEL113750, Ver. 18.1; IV-CRD pooled analysis, Ver. 17.1)
c) Assessment by the sponsor
d) Not included in the aggregated data but added after the data cut-off.

In the data obtained from clinical studies and spontaneous reports by March 8, 2016 after the approval of belimumab intravenous infusion in foreign countries, 74 events coded to "Psychiatric disorders" (SOC) were reported as serious adverse event for which a causal relationship to belimumab could not be ruled out. They included 12 events of depressed mood disorders and disturbances (HLGT) (depression [8 events], major depression [3 events], depressed mood [1 event]) and 36 events of suicidal and self-injurious behaviours NEC (HLGT) (suicidal ideation [30 events], suicide attempt [4 evens], intentional self-injury and suicidal behavior [1 event each]).

PMDA's view:

Psychiatric symptom such as depression and suicide/self-injury may be observed as a central nervous system symptom of central nervous system lupus (CNS lupus) in patients with SLE, which makes it difficult to definitely conclude a causal relationship between belimumab administration and depression or suicide/self-injury currently. However, given that death due to completed suicide occurred in the belimumab group, that the incidence of psychiatric events such as depression is high in patients with SLE, and that the risk of developing psychiatric symptoms is particularly high in patients treated with a high dose steroid (*Psychosomatics*. 2012;53:103-15), a precautionary statement regarding the risk of depression and suicide/self-injury should be included in the package insert. Caution is required in administering belimumab to patients with a past history, or high risk, of these diseases. Also, incidences of depression and suicide/self-injury during treatment with belimumab, including those occurring in the long-term treatment, should be continuously investigated in the post-marketing surveillance, etc., and any new findings should be appropriately provided to healthcare professionals.

**(f) Interstitial lung disease**

The applicant's explanation about the incidence of interstitial lung disease:

Interstitial lung disease is one of the pathological hallmarks of SLE. Acute lupus pneumonitis occurs in 0.5% to 11.7% of patients with SLE, and chronic interstitial pneumonia in 3% to 5% (*Clinical Practice Manual for Systemic Lupus Erythematosus*. 2nd ed. Japan Medical Journal, Co., Ltd.; 2012:247-61, *Murray & Nadel's Textbook of Respiratory Medicine*. 4th ed. Elsevier Inc.; 1620-2).

As adverse events related to interstitial pneumonia, adverse events[41)] coded to "Interstitial lung disease (narrow search)" (SMQ) in MedDRA as well as lupus pneumonitis and organising pneumonia among adverse events in broad search were tabulated. Table 66 shows the incidence of events related to interstitial pneumonia in IV/SC-CRD pooled analysis and IV-LTC pooled analysis. No significant difference was observed in the incidence between the belimumab group and the placebo group. The incidence of interstitial pneumonia in patients included in the IV-LTC pooled analysis[42)] was 3.7% (11 of 296 patients) in Study BEL112626 (exposure, 2416 person-years), 1.1% (3 of 268 patients) in Study BEL112233 (exposure, 1468 person-years), and 0.8% (6 of 735 patients) in Study BEL112234 (exposure, 3254 person-years) (data cut-off on [redacted]), which was within the range of the incidence reported in literature on the interstitial pneumonia among patients with SLE (*Clinical Practice Manual for Systemic Lupus Erythematosus*. 2nd ed. Japan Medical Journal, Co., Ltd.; 2012:247-61, *Murray & Nadel's Textbook of Respiratory Medicine*. 4th ed. Elsevier Inc.;1620-2). Interstitial pneumonia was also reported in 1 subject not included in IV-LTC pooled analysis, during the open-label phase of Study LBSL02. Interstitial pneumonia was not reported in any of the Japanese patients.

41) Alveolitis, bronchiolitis, interstitial lung disease, lung infiltration, pneumonitis, pulmonary fibrosis, and pulmonary vasculitis
42) Interstitial lung disease was not observed in Study 200339 on belimumab subcutaneous injection.

**Table 66. Incidences of interstitial pneumonia (IV/SC-CRD pooled analysis and IV-LTC pooled analysis)**

| Study | | Adverse event | No. of subjects | | Belimumab (10 mg/kg or 200 mg) | Placebo | All subjects |
|---|---|---|---|---|---|---|---|
| | | | Belimumab (10 mg/kg or 200 mg) | Placebo | | | |
| IV/SC-CRD pooled analysis[a)] | BEL113750 | Interstitial lung disease | 470 | 235 | 0 | 0.9 (2) | |
| | | Lupus pneumonitis | | | 0.2 (1) | 0 | |
| | BEL110751 | Interstitial lung disease | 273 | 275 | 0.4 (1) | 0 | |
| | | Organising pneumonia | | | 0 | 0.4 (1) | |
| | BEL110752 | Lupus pneumonitis | 290 | 287 | 0.3 (1) | 0 | |
| | BEL112341 | Pulmonary fibrosis | 556 | 280 | 0 | 0.4 (1) | |
| | | Alveolitis | | | 0.2 (1) | 0 | |
| IV-LTC pooled analysis | BEL112626[b)] | Interstitial lung disease | 296 | | | | 1.4 (4) |
| | | Lupus pneumonitis | | | | | 0.7 (2) |
| | | Pulmonary fibrosis | | | | | 1.0 (3) |
| | | Lung infiltration | | | | | 0.7 (2) |
| | BEL112233[c)] | Pneumonitis | 268 | | | | 0.4 (1) |
| | | Pulmonary fibrosis | | | | | 0.4 (1) |
| | | Bronchiolitis | | | | | 0.4 (1) |
| | BEL112234[c)] | Interstitial lung disease | 735 | | | | 0.3 (2) |
| | | Lupus pneumonitis | | | | | 0.1 (1) |
| | | Pulmonary fibrosis | | | | | 0.3 (2) |
| | | Lung infiltration | | | | | 0.1 (1) |

% (number of patients)

a) Data collected during the following periods were analyzed: 76 weeks in Study BEL110751, 52 weeks in Study BEL110752, 52 weeks (treatment phase) and 24 weeks (extension phase) in Study LBSL02, 52 weeks (double-blind phase) and 24 weeks (open-label phase) in Study BEL112341.

b) Phase IIb long-term extension study administering belimumab intravenously to patients who have responded sufficiently to the treatment in Study LBSL02.

c) A long-term extension study in patients who successfully completed Study BEL110751 or BEL110752 (Study BEL112233 in American patients, Study BEL112234 in non-American patients). Mexican patients receiving belimumab subcutaneous injection in Study BEL112232 also participated in Study BEL112234.

PMDA's view:

Currently, there is no clear indication of increased risk of interstitial lung disease. However, since interstitial lung disease and pulmonary fibrosis were observed in clinical studies, and since the possibility cannot be excluded that the risk of interstitial lung disease may be further increased by a long-term administration of belimumab in combination with other immunosuppressants and steroid, caution against the possible occurrence of interstitial lung disease during belimumab administration should be provided. Also, it is reported that the incidence of drug-induced lung disorder is higher in Japanese patients compared with non-Japanese patients (*Consensus statement for the diagnosis and treatment of drug-induced lung injuries*. 1st ed. Medical Review Co., Ltd.; 2012:7-10). In addition, the number of Japanese patients investigated and the evaluation period in clinical studies are not sufficient for assessing the risk of interstitial lung disease. Therefore, incidences of interstitial lung disease during belimumab administration, including those in the long-term administration, should be continuously investigated in the post-marketing surveillance, etc., and information thus obtained should be appropriately provided to healthcare professionals.

Based on the above review, the following precautions should be provided: (1) Attention should be paid to serious infection and post-infusion systemic reactions during and after treatment with belimumab, (2) because serious events may occur, the treatment should be performed in cooperation with a physician/medical institution fully capable of handling emergency situations and, in case of abnormality, appropriate measures should be taken, and (3) belimumab should be used by physicians with adequate knowledge of belimumab and with sufficient knowledge and experience with SLE treatment.

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

### 7.R.3 Clinical positioning

#### 7.R.3.1 Clinical positioning of belimumab

The applicant's explanation about the clinical positioning of belimumab:

The standard treatment for SLE is drug therapy with steroid, immunosuppressants, antimalarial drugs, and non-steroidal anti-inflammatory drug (NSAID), and treatment with antimalarial drugs and steroid is recommended for patients with SLE not accompanied by severe organ lesion. In patients with SLE with severe organ lesion, combination therapy with high dose steroid and immunosuppressants is started promptly and, after remission, the treatment is continued at reduced doses as maintenance therapy. In phase III studies of belimumab in patients with SLE (Studies BEL110751, BEL110752, BEL113750, and BEL112341), patients who had continuously received a constant dose of steroid,[43)] antimalarial drugs, immunosuppressants, or NSAID, alone or in combination, from ≥30 days before the start of study drug treatment were to receive belimumab or placebo in addition to the above drugs. In all of the above phase III studies, the therapeutic agent most commonly used at baseline was steroid (76% to 98%), followed by antimalarial drug (63% to 71%), immunosuppressant (42% to 65%), and NSAID (20% to 41%). In the Japanese subpopulation, steroid (97% to 100%) was the most commonly used, followed by immunosuppressant (77% to 83%), and NSAID (35%). Thus, from the results of the above phase III studies, the intended patient population for treatment with belimumab are patients who have been receiving the standard therapy for SLE, mainly with steroid, immunosuppressant, and antimalarial drug. It is therefore considered appropriate to use belimumab in combination with the standard therapy for SLE.

PMDA's view:

In Japan also, drugs such as steroid are used as the standard therapy for SLE. Taking account of the fact that the clinical studies on belimumab were conducted in patients with SLE with high disease activity despite standard treatment, belimumab should be used in combination with these drugs in patients who have inadequately responded to conventional anti-SLE drugs.

#### 7.R.3.2 Patients to be treated with belimumab

The applicant's explanation about the target patients for treatment with belimumab:

Patients with SLE become positive for many autoantibodies such as anti-nuclear antibody (ANA), anti-dsDNA antibody, anti-Ro antibody, and anti-Sm antibody. Among them, the sensitivity of ANA was ≥95% for patients with SLE, and the specificity of anti-dsDNA antibody was ≥95% for patients with SLE (*The Medical Frontline, supplementary volume, Introduction to new diagnosis and treatment: Systemic lupus erythematosus*. Saishin Igaku, Co., Ltd., 2010:p85-7). As described in Section 7.R.1, belimumab was more effective in the autoantibody-positive patient population than in the autoantibody-negative patient population. The efficacy of belimumab was demonstrated in the phase III study conducted in autoantibody-positive patients with SLE who tested positive twice for autoantibodies (ANA titer ≥80× or anti-dsDNA antibody ≥30 IU/mL). In the study, ≥95% of patients were positive for autoantibodies at baseline. On the other hand, no clear correlation was observed between the efficacy of

43) 0 to 40 mg/day in prednisone equivalent

belimumab and baseline anti-dsDNA titer, as shown in Table 67. Taking account of these findings, together with the inter-individual variability for anti-dsDNA titer and the large difference in the reference range among testing laboratories, no criteria for anti-dsDNA titer are necessary to identify patients eligible for treatment with belimumab.

**Table 67. SRI response rate at Week 52, classified by baseline anti-dsDNA titer**

| | Anti-dsDNA antibody titer (IU/mL) | Belimumab 10 mg/kg or 200 mg | Placebo | Odds ratio to placebo [95% CI][a)] |
|---|---|---|---|---|
| Studies BEL110751 and BEL110752 | <30 | 49.4 (82/166) | 44.8 (82/183) | 1.23 [0.80, 1.88] |
| | ≥30 and <150 | 58.2 (110/189) | 42.7 (67/157) | 1.89 [1.23, 2.91] |
| | ≥150 | 44.7 (93/208) | 31.1 (69/222) | 1.78 [1.20, 2.65] |
| Study BEL113750 | <30 | 61.3 (49/80) | 52.4 (22/42) | 1.44 [0.68, 3.06] |
| | ≥30 and <500 | 53.0 (157/296) | 40.7 (57/140) | 1.64 [1.09, 2.47] |
| | ≥500 | 48.6 (34/70) | 22.9 (8/35) | 3.19 [1.27, 7.98] |
| Study BEL112341 | <30 | 59.2 (90/152) | 46.5 (40/86) | 1.67 [0.98, 2.84] |
| | ≥30 and <600 | 63.1 (195/309) | 48.7 (75/154) | 1.80 [1.22, 2.67] |
| | ≥600 | 59.1 (55/93) | 51.3 (20/39) | 1.38 [0.65, 2.92] |

% (n/N)
a) Logistic regression analysis

In clinical studies on belimumab, SELENA SLEDAI score and BILAG score, which are used to assess the disease activity of SLE, were used as inclusion criteria and as efficacy outcome measures, and the efficacy of belimumab was demonstrated in studies which used SELENA SLEDAI score of ≥6 or ≥8 as an inclusion criterion. Also, data presented in Table 68 suggests a correlation between efficacy and baseline disease activity. On the other hand, no clear measures defined in guidelines, etc. for determining treatment policy is currently available. In routine clinical practice, physicians perform comprehensive assessment of the clinical symptoms of the patient and the presence/absence and severity of organ lesions to determine the doses of the steroid and the use of immunosuppressants, etc. Thus, given the current situation where there are no commonly used assessment indices in clinical practice, it is practically impossible to clearly define the criteria for assessment of disease activity in patients eligible for treatment with belimumab.

**Table 68. SRI response rate at Week 52, classified by baseline SELENA SLEDAI score**

| | Baseline SELENA SLEDAI score | Belimumab 10 mg/kg or 200 mg | Placebo | Odds ratio to placebo [95% CI][a)] |
|---|---|---|---|---|
| Studies BEL110751 and BEL110752 | ≤9 points | 36.7 (98/267) | 32.7 (86/263) | 1.16 [0.81, 1.67] |
| | ≥10 points | 63.2 (187/296) | 44.1 (132/299) | 2.22 [1.59, 3.10] |
| Study BEL113750 | ≤9 points | 35.7 (76/213) | 30.9 (29/94) | 1.24 [0.74, 2.09] |
| | ≥10 points | 70.4 (164/223) | 47.2 (58/123) | 2.66 [1.69, 4.19] |
| Study BEL112341 | ≤9 points | 48.5 (98/202) | 41.4 (46/111) | 1.33 [0.83, 2.13] |
| | ≥10 points | 68.8 (242/352) | 53.0 (89/168) | 1.95 [1.34, 2.85] |

% (n/N)
a) Logistic regression analysis

Based on the above, although the Precautions for Indications section includes the statement “belimumab should be used in patients with active, autoantibody-positive SLE who are receiving standard treatment,” patients to be treated with belimumab should be identified by the comprehensive assessment by a physician experienced in SLE treatment, based on the clinical symptoms of each patient and past treatments, in addition to the disease activity and presence/absence of autoantibody.

PMDA's view:

Taking account of the results of the clinical studies, etc., the patient population for treatment with belimumab should be set as patients with active, autoantibody-positive SLE who have inadequately responded to conventional anti-SLE drugs. Also, given the large variations in reference ranges of laboratory tests among study sites, in addition to diverse clinical symptoms and serological findings, physicians highly experienced in the diagnosis and treatment of SLE should carefully determine the use of belimumab after carefully assessing its expected benefits that may be diverse depending on the conditions of individual patients, based on a good understanding of the clinical study results including the eligibility criteria and the characteristics of patients enrolled.

Furthermore, healthcare professionals should be informed that the efficacy of belimumab is unclear in patients with severe SLE, such as lupus nephritis with severe disease activity and CNS lupus, who were excluded from clinical studies.

### 7.R.4 Indication

PMDA's view:

As described in Section 7.R.1, the submitted clinical data have demonstrated the efficacy of belimumab in the treatment of SLE. On the other hand, as described in Section 7.R.3, belimumab is positioned as an add-on therapy for patients with active, autoantibody-positive SLE who have inadequately responded to conventional treatments, and thus the indication of belimumab should be "Treatment of patients with systemic lupus erythematosus who have inadequately responded to conventional treatments," and precautions should be provided, in the Precautions for Indications section of the package insert, that belimumab should be used in patients with active, autoantibody-positive SLE who have inadequately responded to appropriate treatments with anti-SLE drugs. Also, information on eligibility criteria, etc., in clinical studies should be provided as reference information for determining the eligibility of patients for treatment with belimumab.

The above conclusion of PMDA on the indication will be discussed at the Expert Discussion.

### 7.R.5 Dosage and administration

The applicant's explanation about the proposed dosage and administration:

As for belimumab intravenous infusion, once every 4 weeks administration at 1 to 10 mg/kg results in serum belimumab concentration exceeding BLyS in the circulating blood (2-10 ng/mL), as estimated from the serum belimumab concentration in the phase I study (Study LBSL01) in patients with SLE. Also, adminitration of belimumab at 2-week intervals for the first 3 doses was considered to promptly lead to the steady state serum concentration. In the foreign phase II study (Study LBSL02), administration of belimumab (1, 4, or 10 mg/kg) at Weeks 0, 2, and 4, and once every 4 weeks thereafter, did not show clear dose response in the primary efficacy end point, i.e., percent change in SELENA SLEDAI score at Week 24 from baseline, or in the time to first SLE flare. However, results of the post-hoc analysis showed that, in autoantibody-positive patients, efficacy tended to be observed earlier in the 10 mg/kg group than in the 1 mg/kg group, as assessed from percent decrease in SELENA SLEDAI score from baseline. Based on the above, in foreign phase III studies (Studies BEL110751 and BEL110752), the doses at 1 mg/kg and 10 mg/kg were tested as the low and high doses, respectively,

with possible efficacy. Results of these studies showed that both doses were effective, and that 10 mg/kg tended to be more effective than 1 mg/kg. The results did not suggest any concern about tolerability.

In the phase I study (Study BEL114243) in Japanese patients with SLE, the pharmacokinetics following intravenous administration of belimumab (1 mg/kg, 10 mg/kg) was not significantly different from that observed in non-Japanese patients with SLE, and the treatment was well-tolerated [see Section 6.2]. In Study BEL113750, the dose 10 mg/kg selected from the foreign phase III studies (Studies BEL110751 and BEL110752) was used based on the above results. Results of Study BEL113750 demonstrated the efficacy of belimumab (10 mg/kg) administered at 4-week intervals and did not suggest any tolerability problem.

Based on the above, the proposed dosage and administration was "10 mg/kg on Days 0, 14, and 28, and at 4-week intervals thereafter."

As for belimumab subcutaneous injection, the dosage and administration in Study BEL112341 was 200 mg once weekly, based on the following results. The study demonstrated the efficacy of belimumab (200 mg) once weekly administered subcutaneously, and did not suggest any tolerability problem.

- From the bioavailability of belimumab observed following subcutaneous administration at 200 mg once weekly (Study BEL114448), it was expected by simulation that exposure was similar to that achieved by administering belimumab intravenous infusion by the dosage and administration approved in foreign countries (10 mg/kg as an intravenous infusion on Days 0, 14, and 28, and at 4-week intervals thereafter) [see Section 6.R.2].
- The pharmacokinetics of belimumab following a single subcutaneous administration at 200 mg in Japanese healthy adult subjects in Study BEL116119 was not significantly different from that in non-Japanese subjects [see Section 6.2].

Based on the above, the proposed dosage and administration for belimumab was "200 mg once weekly."

The applicant explained the timing of assessing whether to continue belimumab administration and the appropriateness of interruption in responders, as follows:
In the phase III studies of belimumab (pooled studies of Studies BEL110751 and BEL110752, and Study BEL112341), the number of patients who showed SRI response lasting to Week 52 continued to increase up to Week 52, with the SRI response rate tending to remain at a constant level at approximately 6 months after the start of administration. Also, the risk of severe SLE flare decreased and the steroid dose tended to show a clinically significant decrease over 52 weeks. These results suggest that the decision of whether to further continue belimumab will be made approximately 6 months after the start of treatment, based on the effect on improvement of serological abnormal levels, steroid dose-reducing effect, flare-preventing effect, QOL improvement, etc.

There are limited investigations on interruption of belimumab in patients in whom the standard drugs for SLE were maintained at reduced doses after decrease in disease activity of SLE. In the ongoing Study BEL116027 evaluating the interruption of belimumab and rebound in patients with SLE with low activity, there are, currently, no safety-related signals suggestive of increased risk of worsening induced by the interruption of belimumab.

PMDA's view:

As for belimumab intravenous infusion, the proposed dosage and administration of belimumab ("10 mg/kg as an intravenous infusion on Days 0, 14, and 28, and 4-week intervals thereafter") is appropriate. As for belimumab subcutaneous injection, it is difficult to say that the relationship between exposure and efficacy or safety has been thoroughly investigated. However, given the results of Study BEL112341, it is acceptable to set the dosage and administration as "subcutaneous administration of 200 mg once weekly." As for the timing of assessing whether to continue belimumab treatment and the appropriateness of interruption in responders, currently available information should be provided, and when new findings become available, the information should be disclosed in an appropriate manner. Also, since there are only limited data on efficacy and safety in switching between belimumab intravenous infusion and belimumab subcutaneous injection, the switching should be performed carefully while patient conditions are closely monitored, and further investigated in the post-marketing surveillance, etc.

### 7.R.6 Self-administration

The applicant explained the efficacy and safety of self-administered belimumab as follows, based on the results of self-administration in the Japanese subpopulation of Study BEL112341:

In Study BEL112341, the first and the second doses of belimumab were to be self-administered under the supervision of a physician, etc., at the medical institution. The third and subsequent doses were to be self-administered at home or, in patients unable to self-inject belimumab, to be administered subcutaneously by a caregiver.

In the Japanese subpopulation of this study, most of the patients could continue self-administration, and results suggested a certain level of efficacy. The incidences of adverse events in the Japanese subpopulation of this study (Table 47 [see Section 7.2.4] and Table 57 [see Section 7.R.2]) were not significantly different from those in the Japanese subpopulation of Study BEL113750 on belimumab intravenous infusion (Table 36 [see Section 7.2.1] and Table 56 [see Section 7.R.2]).

The above results suggest that there are no particular problems in the efficacy or safety of belimumab self-administered by Japanese patients with SLE.

PMDA's view:

Currently, results of clinical studies do not suggest any specific problems regarding the safety or efficacy of self-administration of belimumab. However, a physician should carefully evaluate the necessity of self-administration, and provide sufficient training to the patient. Belimumab should be self-administered only when the patient understands the risk of belimumab treatment and the method to deal with the risk, and is confirmed to self-administer belimumab reliably. Also, the following caution should be provided: After switching to self-administration, if adverse drug reactions of belimumab, such as infection, are suspected or if continuing self-administration becomes difficult, the self-administration should be discontinued immediately and appropriate measures should be taken. Safety measures, such as preparation of information materials, should be taken by referring to the situations of approved biological products. In addition, because of the limited information on the safety and efficacy of self-administration in Japanese patients with SLE, continued investigation in the post-marketing surveillance, etc., is necessary.

### 7.R.7 Post-marketing investigations

The applicant plans to conduct a post-marketing surveillance covering all patients with SLE receiving Benlysta in order to confirm the safety and efficacy of Benlysta, including those in the long-term administration, in routine clinical use after the market launch.

As reviewed in Section 7.R.2, PMDA considers that the safety profile of belimumab is acceptable, judging from the results of clinical studies on belimumab. However, taking account of the facts that, in routine clinical practice, belimumab may be used in patients with more severe SLE than patients treated in clinical studies, that, given the mechanism of action of belimumab, the possibility cannot be excluded that serious adverse events such as serious infection including tuberculosis, malignant tumor, PML, etc., may occur due to the immunosuppressive effect of belimumab, and that there is only an extremely limited experience of long-term administration of belimumab in Japanese patients in clinical studies, it is necessary to conduct a post-marketing surveillance covering all patients receiving belimumab to promptly delineate the safety profile of belimumab, including the occurrences of unknown adverse events, and also to continue careful investigation on the safety and efficacy of belimumab.

Belimumab should be used by physicians with adequate knowledge of belimumab and with sufficient knowledge and experience of SLE treatment, and adverse drug reactions such as serious infection should be addressed in cooperation with other departments and institutions. In order to promote proper use of belimumab, information should be provided to physicians and other healthcare professionals, by using materials, and the coordination with other departments and institutions should be ensured in routine clinical practice in the post-marketing surveillance, etc.

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

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

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

The assessment is currently ongoing. Results and PMDA's conclusion will be reported in Review Report (2).

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

The assessment is currently ongoing. Results and PMDA's conclusion 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 and that belimumab has acceptable safety in view of its benefits. Benlysta (belimumab) is of clinical significance because it offers a new treatment option for patients with SLE. As for safety, infections including serious infection, PML, and neuropsychiatric events such as depression were

observed and serious adverse events such as tuberculosis, interstitial lung disease, and malignant tumor may occur. Therefore, patients should be closely monitored for adverse events during the treatment with belimumab and, in case of any adverse event, appropriate measure such as interruption of Benlysta, should be taken. In the post-marketing surveillance, the safety and efficacy of Benlysta should be further investigated in routine clinical practice, including long-term administration in patients including patients with severe SLE.

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

## 10. Other

Main endpoints used in the multi-regional phase III study were as shown below.

| Endpoint | Definition |
|---|---|
| SRI responders | Subjects who achieved all of the following measures at the time of assessment compared to baseline:<br>• ≥4 point reduction in SELENA SLEDAI score<br>• No worsening (increase of <0.3 points in PGA score) in PGA<br>• No new BILAG A organ domain score or 2 new BILAG B organ domain scores |
| SELENA SLEDAI score | This index is a modified version of the SLEDAI developed for a National Institutes 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).<br><br>The disease activity was assessed based on the sum (0-105 points) of the points of each of the following items corresponding to disease conditions of the patient in 10 days prior to the visit:<br>• CNS items (8 points for each item): Seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache<br>• Vascular items (8 points for each item): Cerebrovascular accident, vasculitis<br>• Musculoskeletal items (4 points for each item): Arthritis, myositis<br>• Renal items (4 points for each item): Urinary casts, hematuria, proteinuria, pyuria<br>• Mucocutaneous items (2 points for each item): Rash, alopecia, mucosal ulcer<br>• Cardiovascular and respiratory items (2 points for each item): Pleurisy, pericarditis<br>• Immunologic items (2 points for each item): Low complement, anti-dsDNA antibodies increased<br>• Hematologic items (including pyrexia) (1 point for each item): Pyrexia, thrombocytopenia, leukopenia<br><br>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]).<br><br>Increase in PGA score is correlated with the worsening of disease activity. At the final assessment, increase of ≥1 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). |
| BILAG (British Isles Lupus Assessment Group Index) | 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.<br><br>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).<br>**Organ system**<br>• General<br>• Mucocutaneous<br>• Neurological<br>• Musculoskeletal<br>• Cardiopulmonary vascular and respiratory<br>• Vasculitis<br>• Renal<br>• Hematology<br>**Treatment intensity (category)**<br>• Category A: Severe (requiring change of therapy)<br>• Category B: Moderate (reversible symptoms manageable by symptomatic therapy)<br>• Category C: Mild (stable symptoms)<br>• Category D: No current symptoms, but the system has previously been involved).<br>• Category E: No current or previous symptoms (the system has never been involved).<br>"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). |

| Endpoint | Definition |
|---|---|
| SLE flare | The patient is diagnosed with severe SLE flare if the SELENA SLEDAI score exceeded 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 in PGA score) is met.<br><br>The patient is diagnosed with mild-to-moderate SLE flare if SELENA SLEDAI score is ≥3 points, and if at least 1 of other criteria (emergence or worsening of SLE symptom, prednisone dose increase by <0.5 mg/kg/day, new addition of NSAID or hydroxychloroquine, PGA score increase by ≥1) is met. |

**Review Report (2)**

August 30, 2017

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | (a) Benlysta for I.V. Infusion 120 mg<br>Benlysta for I.V. Infusion 400 mg<br>(b) Benlysta for S.C. Injection 200 mg Autoinjector<br>Benlysta for S.C. Injection 200 mg Syringe |
| **Non-proprietary Name** | Belimumab (Genetical Recombination) |
| **Applicant** | GlaxoSmithKline K.K. |
| **Date of Application** | December 13, 2016 |

## 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 dosage and administration

The expert advisors at the Expert Discussion supported the PMDA's conclusion on the efficacy and dosage and administration of "Benlysta for I.V. Infusion 120 mg, Benlysta for I.V. Infusion 400 mg, Benlysta for S.C. Injection 200 mg Autoinjector, and Benlysta for S.C. Injection 200 mg Syringe" (hereinafter referred collectively to as Benlysta) described in the Review Report (1). Also, the following comments were raised:

- In clinical studies involving patients with systemic lupus erythematosus (SLE) showing diverse pathologies, the efficacy of belimumab in the treatment of SLE was evaluated using a combination of multiple indices including SELENA SLEDAI score. Thus, the conduct of such studies was understandable to a certain extent, and the studies have confirmed an improvement in autoimmune abnormality which constitute SLE.
- Studies on the lesion of individual organs are limited, and no results were obtained that clearly demonstrate the efficacy of belimumab for the treatment of lesions of any specific organ.

The data submitted showed the improvement in SRI response rate at Week 52 (the primary endpoint) and the steroid dose reduction and the suppression of the occurrence of SLE flare. Taking account of these results, PMDA has concluded that the efficacy of Benlysta in the treatment of SLE has been demonstrated. As for organ lesions, a tendency toward improvement in conditions of the musculoskeletal system, mucocutaneous system, etc., was observed in the belimumab group compared with the placebo group, suggesting that Benlysta is effective to a certain extent. However, patients with

severe lupus nephritis or central nervous system lupus (CNS lupus) were excluded from clinical studies. The organs presented by subjects were limited, resulting in scanty information available on the efficacy in the treatment of lesions of individual organs. Therefore, PMDA instructed the applicant to collect information on the efficacy of Benlysta in the treatment of the lesion of individual organs in the post-marketing surveillance, etc., and to communicate any new findings to healthcare professionals. The applicant agreed to the instruction.

### 1.2 Clinical positioning and indications

The following comments were raised at the Expert Discussion regarding the PMDA's conclusion on the clinical positioning and indication of belimumab described in the Review Report (1):

- Given the efficacy and safety data obtained in clinical studies and the treatment algorithm of systemic lupus erythematosus (SLE) in Japan, it is acceptable to indicate belimumab for the treatment of patients with SLE who have not responded adequately to conventional therapies, provided that the label specifies that belimumab should be used as an add-on treatment to conventional therapies in patients who have a high degree of disease activity despite standard treatment with anti-SLE drugs such as steroid and immunosuppressants.
- The clinical studies conducted did not investigate the efficacy or safety of belimumab in the treatment of lesions in the kidney or CNS, the key organ involvement of SLE. It is therefore not recommendable to use belimumab for the treatment of severe lupus nephritis or severe CNS lupus without careful consideration.
- Based on the results of the clinical studies, healthcare professionals should be informed that belimumab is used in only patients with SLE positive for autoantibodies such as antinuclear antibody and anti-dsDNA antibody.
- Given that patients with SLE have diverse clinical symptoms and serological findings, physicians should be provided with sufficient information to ensure that, based on a good understanding of the results of the clinical studies and of the efficacy and safety of belimumab, they determine the use of belimumab after carefully assessing its expected benefits that may be diverse depending on the conditions of individual patients.
- It is useful to provide healthcare professionals with information on the subpopulations who responded favorably to belimumab (those with high disease activity or low complement) in clinical studies.

PMDA's view:

Taking account of the comments raised by external experts in the Expert Discussion and the patients investigated in clinical studies, it is acceptable to position belimumab as one of treatment options for patients with SLE who have a high degree of disease activity despite the use of steroid and immunosuppressants. Therefore, the Indication and the Precautions for Indications statements should be established as shown below. In addition, taking account of the facts that clinical studies did not investigate severe lupus nephritis or severe CNS lupus and that patients with SLE have diverse clinical symptoms and serological findings, physicians highly experienced in the treatment of SLE should, based on a good understanding of the eligibility criteria for patients in clinical studies, rules for concomitant medications, patient characteristics, and efficacy and safety results including subgroup analysis, carefully determine the eligibility of individual patients with SLE for treatment with belimumab.

PMDA instructed the applicant to adequately communicate the above information to healthcare professionals using the package insert, etc. The applicant agreed to the instruction.

**Indication**

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

**Precautions for Indications**

- Belimumab should be used as an add-on treatment in patients with systemic lupus erythematosus (SLE) with a high degree of disease activity despite previous treatment with steroid and immunosuppressants.
- Belimumab should be used in patients with SLE who tested positive for autoantibodies such as antinuclear antibody and anti-dsDNA antibody.
- No clinical studies investigated the efficacy or safety of belimumab in patients with SLE with severe lupus nephritis or severe central nervous system lupus (see the "Clinical Studies" section).
- No clinical studies investigated the efficacy or safety of belimumab in combination with other biological products or cyclophosphamide intravenous injection products (see the "Clinical Studies" section).
- Physicians should identify patients eligible for treatment with belimumab based on a careful review of the content of the "Clinical Studies" section and a good understanding of the efficacy and safety of belimumab (see the "Clinical Studies" section).

### 1.3 Safety and risk management plan (draft)

The external experts of the Expert Discussion supported PMDA's conclusion on the safety of belimumab and post-marketing pharmacovigilance described in the Review Report (1). Also, the following comments were raised:

- In clinical studies, belimumab was administered as an add-on treatment to steroid and immunosuppressants. The studies may have failed to adequately assess the effect of concomitant drugs on the safety of belimumab alone. Such possibility should be considered.
- Given the mechanism of action of belimumab and the safety profile of other drugs in the same class that target B cells, the risk of severe infection including tuberculosis and opportunistic infection, malignant tumor, etc., is assumed. Also, taking account of the fact that death caused by infection such as sepsis and tuberculosis was reported in more than one patients only in the belimumab group, attention should be paid to serious infection including tuberculosis, reactivation of hepatitis B virus, and progressive multifocal leukoencephalopathy (PML).
- On the basis of the clinical study results, the package insert should contain information on the timing for treatment discontinuation in patients who have failed to achieve therapeutic effects such as reduction in disease activity after add-on therapy with belimumab.
- The long-term safety and efficacy of belimumab should be further investigated in the post-marketing surveillance covering all patients receiving belimumab.

On the basis of the results of the review in Section "7.R.6 Post-marketing investigations" and of the comments raised by the expert advisors at the Expert Discussion, PMDA has concluded that the current risk management plan (draft) for Benlysta should include the safety and efficacy specifications presented in Table 69, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 70.

**Table 69. Safety and efficacy specifications in the risk management plan (draft)**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| • Serious infection (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, and opportunistic infection)<br>• Serious hypersensitivity<br>• Progressive multifocal leukoencephalopathy (PML)<br>• Reactivation of hepatitis B virus | • Malignant tumor<br>• Interstitial pneumonia<br>• Immunogenicity<br>• Effect on immune response to vaccination<br>• Events related to depression and suicide/self-injury | • None |
| Efficacy specification | | |
| • Efficacy in routine clinical use | | |

**Table 70. Summary of additional pharmacovigilance activities and risk minimization activities included in the risk management plan (draft)**

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| • Early post-marketing phase vigilance<br>• Specified use-results survey (all-case)<br>• Post-marketing clinical studies[a)] | • Provision of information based on data from the early post-marketing phase vigilance.<br>• Preparation and distribution of materials for healthcare professionals.<br>• Preparation and distribution of materials on self-administration.<br>• Ensuring provision of information on proper use prior to delivery |

After the marketing approval of Benlysta, Study BEL114333 (ongoing) and Study BEL116027 (ongoing) will be switched to post-marketing clinical studies.

PMDA instructed the applicant to conduct a post-marketing surveillance, etc., to investigate these items.

The applicant's explanation about the main survey items:

As shown in Table 71, a specified use-results survey will be conducted with a 52-week follow-up period covering all patients receiving belimumab until data are collected from a certain number of patients receiving belimumab (target sample size, 600 patients). The survey intends to confirm the safety and efficacy of belimumab in routine clinical settings. Priority items of the survey consist of serious infection (including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, and opportunistic infection), serious hypersensitivity, PML, reactivation of hepatitis B virus, malignant tumor (including lymphoma), interstitial pneumonia, and events related to depression and suicide/self-injury. In addition, the incidences of serious infection, PML, malignant tumor, and adverse events leading to death will be followed up to the possible extent during the first 3 years after the start of treatment to further investigate the long-term safety, etc.

**Table 71. Outline of specified use-results survey (draft)**

| | |
|---|---|
| Objective | To investigate the long-term safety and efficacy of in routine clinical settings |
| Survey method | All-case surveillance |
| Population | Patients with SLE who have inadequately responded to conventional treatments |
| Follow-up period | 52 weeks (a 2-year surveillance will be conducted after the end of the observation period) |
| Planned sample size | 600 patients (evaluable for safety analysis) |
| Main survey items | • Priority items: Severe hypersensitivity, serious infection (including tuberculosis. pneumonia, Pneumocystis pneumonia, sepsis, and opportunistic infection), reactivation of hepatitis B virus, progressive multifocal leukoencephalopathy (PML), interstitial pneumonia, malignant tumor, and events related to depression and suicide/self-injury<br>• Patient characteristics (body weight, age, disease duration, disease activity, organ involvement, current or previous diseases, etc.)<br>• Previous therapies for SLE<br>• Status of belimumab treatment<br>• Concomitant drugs/therapies<br>• Steroid dose<br>• Adverse events<br>• Efficacy evaluation |

PMDA accepted the applicant's response. The applicant should publish information on the incidences of serious infection, PML, malignant tumor, etc., and other safety information in a timely manner using materials, on the applicant's website, or by other means, to ensure that such information is communicated to healthcare professionals and patients appropriately and promptly.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. 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. The following findings were noted during the inspection regarding Study BEL113750 (CTD 5.3.5.1 BEL113750) although they did not significantly affect the overall evaluation of the study. These were notified to the applicant (sponsor) as findings requiring corrective action.

**Findings requiring corrective action**

Applicant (sponsor)

- There were errors in the data analysis program for "BILAG," etc., used for the assessment of the primary efficacy endpoint, requiring a reanalysis.
- Some of the informed consent forms were signed with a false name, although the forms signed with the subject's own name were obtained eventually.
- Some of the case report forms (CRF) were not signed by the investigator of the study inspected, although Article 47, Paragraph 3 of the GCP specifies that the investigator should sign the CRF. Instead, they were signed by the investigator of the extension study BEL114333.

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

The new drug application data (CTD 5.3.5.1, BEL112341 [HGS1006-C1115]; CTD 5.3.5.1, BEL113750; CTD 5.3.5.2, BEL113750/BEL114333) 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 after modifying the proposed indication and dosage and administration as shown below, with the following conditions for approval. Since Benlysta is a drug with a new active ingredient, the re-examination period is 8 years. The drug product is classified as a biological product. The drug product and its drug substance are both classified as powerful drugs.

**Indication**

Benlysta for I.V. Infusion 120 mg
Benlysta for I.V. Infusion 400 mg

Treatment of patients with systemic lupus erythematosus <u>who have inadequately responded to conventional treatments</u>

(Underline denotes addition.)

Benlysta for S.C. Injection 200 mg Autoinjector
Benlysta for S.C. Injection 200 mg Syringe

Treatment of patients with systemic lupus erythematosus <u>who have inadequately responded to conventional treatments</u>

(Underline denotes addition.)

**Dosage and Administration**

Benlysta for I.V. Infusion 120 mg
Benlysta for I.V. Infusion 400 mg

The usual dosage for adults 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.

Benlysta for S.C. Injection 200 mg Autoinjector
Benlysta for S.C. Injection 200 mg Syringe

The usual dosage for adults is 200 mg of belimumab (genetical recombination) once weekly administered subcutaneously.

(Minor change in wording, with no change in the English translation)

**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 soon as possible, and thereby to take appropriate measures for the proper use of the product.