PRODUCT MONOGRAPH

Pr**BENLYSTA®**

belimumab

Lyophilized powder for intravenous infusion

120 mg in 5 mL vial
400 mg in 20 mL vial
(80 mg/mL after reconstitution)

Therapeutic Classification
Immunosuppressant

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4

Date of Approval:
September 8, 2016

Submission Control No: 193395

TABLE OF CONTENTS

PAGE

Pr**BENLYSTA®**

belimumab

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Nonmedicinal Ingredients
Intravenous Infusion	Lyophilized powder for intravenous infusion 120 mg in 5 mL vial 400 mg in 20 mL vial (80 mg/mL after reconstitution)	citric acid monohydrate, sodium citrate dihydrate, sucrose and polysorbate 80

DESCRIPTION

BENLYSTA® (belimumab) is a fully human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab has a molecular weight of approximately 147 kDa. Belimumab is produced by recombinant DNA technology in a mammalian cell expression system.

INDICATIONS AND CLINICAL USE

BENLYSTA® is indicated in addition to standard therapy for reducing disease activity in adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE).

The safety and efficacy of BENLYSTA® have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.

The efficacy of BENLYSTA® in patients of black African heritage has not been clearly established.

Geriatrics (> 65 years of age):

Although data are limited, dosage adjustment is not recommended in patients > 65 years of age (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Pediatrics:

Safety and efficacy have not been established in children.

CONTRAINDICATIONS

BENLYSTA® is contraindicated in patients who are hypersensitive to belimumab (e.g., have demonstrated anaphylaxis) or to any ingredient in the formulation or component of the container. For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Infusion/Hypersensitivity Reactions
Administration of BENLYSTA® may result in infusion and hypersensitivity reactions, which can be severe, and can be fatal. Serious infusion reactions and serious anaphylaxis/hypersensitivity have been observed uncommonly (*see* WARNINGS AND PRECAUTIONS, General - Infusion Reactions and Hypersensitivity**)**.

Severe Infections, including Progressive Multifocal Leukoencephalopathy (PML)
Severe infections, including PML have been reported in patients receiving BENLYSTA®, and other immune-modulating therapies for the treatment of SLE. Some cases were fatal (*see* WARNINGS AND PRECAUTIONS, Immune, and ADVERSE REACTIONS, Infections, and Post-Market Adverse Drug Reactions).

General

BENLYSTA® treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE.

Infusion Reactions and Hypersensitivity
BENLYSTA® should be administered in an appropriate setting by qualified healthcare providers trained to give infusion therapy and prepared to treat hypersensitivity, including anaphylaxis.

Administration of BENLYSTA® may result in infusion and hypersensitivity reactions, which can be severe, and can be fatal. In the event of a severe reaction, BENLYSTA® administration must be interrupted and appropriate medical therapy administered. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk (see ADVERSE REACTIONS).

Premedication with an oral antihistamine, with or without an antipyretic, may be administered before the infusion of belimumab (see DOSAGE AND ADMINSTRATION). There is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions. In clinical trials, serious infusion and hypersensitivity reactions affected less than 1% of patients, and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnea. Infusion reactions occurred more frequently on the first two infusion days and tended to decrease with subsequent infusions (see ADVERSE REACTIONS). Delay in the onset of acute hypersensitivity reactions and recurrence of clinically significant reactions after initial resolution of symptoms following appropriate treatment, have been observed. Monitor patients during and for an appropriate amount of time after administration of BENLYSTA® (see ADVERSE REACTIONS – Infusions Reactions and Hypersensitivity). Patients treated with BENLYSTA® should be made aware of these potential risks, the signs and symptoms of such reactions, and the importance of immediately seeking medical attention. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema.

The BENLYSTA® MONARCH PROGRAM has been established to facilitate the administration of BENLYSTA® The BENLYSTA® MONARCH PROGRAM infusion clinics are staffed by qualified healthcare professionals that have been trained in the administration of BENLYSTA® infusions. These clinics are available throughout Canada. Information about these clinics and the location of these clinics can be obtained by calling GSK Medical information at: 1-800-387-7374.

Immunization
Live vaccines should not be given for 30 days before, or concurrently with BENLYSTA® as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving BENLYSTA®.

Because of its mechanism of action, BENLYSTA® may interfere with the response to immunizations. The efficacy of concurrent vaccination in patients receiving BENLYSTA® is not known. Limited data suggest that BENLYSTA® does not significantly affect the ability to maintain a protective immune response to immunizations received prior to administration of BENLYSTA®.

Concomitant Use With Other Biologic Therapies or Intravenous Cyclophosphamide
BENLYSTA® has not been studied in combination with other biologic therapies, including B-cell targeted therapies, or intravenous cyclophosphamide. Therefore, use of BENLYSTA® is not recommended in combination with biologic therapies or intravenous cyclophosphamide.

Carcinogenesis and Mutagenesis

Risk of Malignancies
As with other immunomodulating agents, the mechanism of action of BENLYSTA® could increase the risk for the development of malignancies. The effect of treatment with BENLYSTA® on the development of malignancies is not known (see ADVERSE REACTIONS – Malignancies).

Immune

Infections
As with other immunomodulating agents, the mechanism of action of belimumab may increase the risk for the development of infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant therapy, including BENLYSTA® (see Adverse Reactions). Patients who develop an infection while undergoing treatment with belimumab should be monitored closely, and consideration should be given to stopping immunosuppressant therapy. Physicians should exercise caution when considering the use of BENLYSTA® in patients with severe or chronic infections.

Progressive multifocal leukoencephalopathy (PML)
Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. A diagnosis of PML should be considered in any patient presenting with new onset deficits or deterioration in cognition, speech or ocular functions, and/or motor and gait disturbances, and/or seizures. If PML is suspected it should be urgently investigated by a neurologist or other appropriate specialist, considering also CNS lupus in the differential diagnosis. Where appropriate, immunosuppressant medications including BENLYSTA® should be withheld until PML is excluded.

Neurologic
The safety and efficacy of BENLYSTA® have not been evaluated in patients with severe active central nervous system lupus.

Psychiatric
Depression, suicidality and suicides have been reported in BENLYSTA® studies. It is not known if BENLYSTA® treatment is associated with an increased risk for these events. Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts or other mood changes (see ADVERSE REACTIONS – Depression).

Renal

The safety and efficacy of BENLYSTA® have not been evaluated in patients with severe active lupus nephritis.

Sexual Function/Reproduction
See Pregnant Women *and* Nursing Women.

Deaths
There were more deaths reported with BENLYSTA® than with placebo during the controlled period of the clinical trials (see ADVERSE REACTIONS – Deaths).

Special Populations

Pediatrics: BENLYSTA® has not been studied in patients less than 18 years of age. There are no data on the safety and efficacy of BENLYSTA® in this age group.

Geriatrics (> 65 years of age): Although data are limited, dosage adjustment is not recommended in patients > 65 years of age (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions).

Pregnant Women: There are limited data on the use of BENLYSTA® in pregnant women. No formal studies have been conducted. Immunoglobulin G (IgG) antibodies, including belimumab, can cross the placenta. BENLYSTA® should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus.

If prevention of pregnancy is warranted, women of childbearing potential should use adequate contraception while using BENLYSTA® and for at least 4 months after the last BENLYSTA® treatment.

Animal studies did not indicate direct or indirect harmful effects with respect to maternal toxicity, pregnancy or embryofetal development except reductions in B-cells and IgM in infant monkeys exposed *in utero* (see TOXICOLOGY).

Monitor infants of treated mothers for B-cell reduction and depending upon the results, consider delaying infant vaccination with live viral vaccines. B-cell reduction in infants may also interfere with the response to immunisations (see WARNINGS AND PRECAUTIONS).

Pregnancy Registry: To monitor maternal-fetal outcomes of pregnant women exposed to BENLYSTA®, a pregnancy registry has been established. Healthcare professionals are encouraged to register patients and pregnant women are encouraged to enrol themselves by calling 1-877-681-6296.

Nursing Women:
The safety of BENLYSTA® for use during lactation has not been established. There are no data regarding the excretion of belimumab in human milk, or systemic absorption of belimumab after ingestion. Although belimumab was excreted into the milk of cynomolgous monkey, published literature suggests that human neonatal and infant consumption of breast milk does not result in clinically significant absorption of maternal IgG antibodies into circulation. There were treatment-related reductions in B-cells and IgM in infant monkeys exposed *in utero* which lasted 3-6 months post-partum (see TOXICOLOGY).

It is recommended that a decision should be made about BENLYSTA® therapy in breast-feeding mothers, taking into account the importance of breast-feeding to the infant and the importance of the drug to the mother, and any potential adverse effects on the breastfed child from BENLYSTA® or from the underlying maternal condition.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical trials have been conducted in SLE patients treated with BENLYSTA® plus standard of care. The most common serious adverse events were serious infections (6.0% and 5.2% in the groups receiving BENLYSTA® and placebo, respectively). Opportunistic infections were reported in two patients treated with BENLYSTA® and included disseminated CMV infection and Acinetobacter bacteremia. A third potential opportunistic infection (Acinetobacter iwoffii pneumonia) occurred on the first day of belimumab treatment and therefore a causal relationship is unlikely. No opportunistic infections were reported in the placebo group (see Infections).

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.*

The data described below reflect exposure to BENLYSTA® plus standard of care in 674 patients with SLE compared with 675 patients who received placebo plus standard of care in three controlled studies. Patients received BENLYSTA® in dosages of 10 mg/kg intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for 48 weeks. The population receiving BENLYSTA® was aged 18 to 71 years, 96% female,

and the race distribution was 50% white/Caucasian, 19% Asian, 19% Alaska native/American Indian, and 12% black/African American; 32% of subjects were Hispanic/Latino ethnicity.

The majority of patients were also receiving one or more of the following concomitant treatments for SLE: corticosteroids (83%), antimalarials (66%), immunosuppressives (49%), nonsteroidal anti-inflammatory drugs (NSAIDS, 34%), and angiotensin pathway antihypertensives (24%). More than half of the patients were receiving systemic corticosteroids at doses equivalent to > 7.5 mg/day of prednisone (54% of patients receiving BENLYSTA®10 mg/kg and 55% of patients receiving placebo).

The proportion of patients who discontinued treatment due to any adverse events during the three double-blind studies was 6.7% for patients receiving BENLYSTA®10 mg/kg and 7.1% for patients receiving placebo. The most common adverse events resulting in discontinuation of treatment (> 2 subjects in either treatment group) were lupus nephritis (0.9% BENLYSTA®and 1.2% placebo), infections (0.6% BENLYSTA® and 1.0% placebo), and infusion reactions (1% BENLYSTA®and 0.3% placebo).

Table 1 lists adverse events, regardless of causality, occurring in at least 1% of patients with SLE who received BENLYSTA® and at an incidence at least 1% greater than that observed with placebo in the three controlled studies.

Table 1 Incidence of Adverse Events Occurring in at Least 1% of Patients Treated with BENLYSTA® Plus Standard of Care and at Least 1% More Frequently Than in Patients Receiving Placebo Plus Standard of Care in Three Controlled SLE Studies

Preferred Term	BENLYSTA® 10 mg/kg + Standard of Care n= 674 (%)	Placebo + Standard of Care n= 675 (%)
Nausea	15	12
Diarrhea	12	9
Pyrexia	10	8
Nasopharyngitis	9	7
Bronchitis	9	5
Insomnia	7	5
Pain in extremity	6	4
Depression	5	4
Migraine	5	4
Pharyngitis	5	3
Cystitis	4	3
Leukopenia	4	2
Gastroenteritis viral	3	1
Hypokalemia	3	2
Dysuria	3	1
Neutropenia	3	1
Toothache	3	1
Pain	2	1
Infusion related reaction	2	1
Hypertensive Crisis	1	<1
Dysphonia	1	0

Deaths

There were more deaths reported with BENLYSTA® than with placebo during the controlled period of the clinical trials. Out of 2133 patients in 3 clinical trials, a total of 14 deaths occurred during the placebo-controlled, double-blind treatment periods: 3/675 (0.4%), 5/673 (0.7%), 0/111 (0%), and 6/674 (0.9%) deaths in the placebo, BENLYSTA® 1 mg/kg, BENLYSTA® 4 mg/kg, and BENLYSTA® 10 mg/kg groups, respectively. No single cause of death predominated. Etiologies included infection, cardiovascular disease, and suicide.

Infusion Reactions and Hypersensitivity

Hypersensitivity reactions and infusion-related reactions were observed in clinical trials. 'Hypersensitivity reaction' covers a group of terms, including anaphylaxis, and can manifest as a range of symptoms including hypotension, angioedema, urticaria or other rash, pruritus, and dyspnea. 'Infusion-related reaction' covers a group of terms and can manifest as a range of symptoms including bradycardia, myalgia, headache, rash,

urticaria, pyrexia, hypotension, hypertension, dizziness, and arthralgia. Due to overlap in signs and symptoms, it is not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases.

The incidence of infusion reactions, including hypersensitivity reactions, was 17% and 15% in the groups receiving BENLYSTA® 10 mg/kg and placebo, respectively. The most common infusion reactions (≥ 1% of patients receiving BENLYSTA® 10 mg/kg) were headache, nausea, infusion-related reaction (not specified), arthralgia, hypotension, hypertension, and pyrexia. Dermatologic manifestations were reported in 1.8% of patients receiving BENLYSTA® and 1.5% of patients receiving placebo and included events such as urticaria, other rashes, and pruritus. Severe and/or serious infusion or hypersensitivity reactions were reported in 1.2% and 0.6% of subjects receiving BENLYSTA® 10 mg/kg and placebo, respectively, and 1% and 0.3% of subjects receiving BENLYSTA® 10 mg/kg and placebo, respectively, had reactions that lead to discontinuation of treatment. Infusion reactions were generally observed on the day of the infusion, and occurred more frequently with the first two infusions and tended to decrease with subsequent infusions. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema. Patients with a history of multiple drug allergies or significant hypersensitivity reactions may be at increased risk. Serious and/or severe hypersensitivity reactions included drug hypersensitivity (not specified), anaphylactic reaction, and angioedema (see WARNINGS AND PRECAUTIONS).

There is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions. Over 15,000 belimumab infusions were administered in the Phase III clinical studies, with approximately 800 belimumab infusions administered to patients who had been premedicated with an antihistamine and antipyretic at the investigator's discretion. In these trials, subjects with a history of allergies were more likely to have been premedicated (22%) than subjects without a history of allergies (9%). The proportion of infusions with infusion reactions was numerically greater for premedicated infusions than non-premedicated infusions (3% vs 2%, respectively). However, the incidence of serious and/or severe infusion reactions was 0.1% for non-premedicated infusions while none occurred with premedicated infusions.

Infections

Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including BENLYSTA®. Physicians should exercise caution when considering the use of BENLYSTA® in patients with chronic infections. Patients receiving any therapy for chronic infection should not begin therapy with BENLYSTA®. Consider interrupting BENLYSTA® therapy in patients who develop a new infection while undergoing treatment with BENLYSTA® and monitor these patients closely.

In the controlled clinical trials, the overall incidence of infections was 71% in patients treated with BENLYSTA® compared with 67% in patients who received placebo. The most frequent infections (>5% of patients receiving BENLYSTA®) were upper respiratory tract infection, urinary tract infection, nasopharyngitis, sinusitis, bronchitis,

and influenza. Serious infections occurred in 6.0% of patients treated with BENLYSTA® and in 5.2% of patients who received placebo. Some infections were severe or fatal. The most frequent serious infections included pneumonia, urinary tract infection, cellulitis and bronchitis. Infections leading to discontinuation of treatment occurred in 0.7% of patients receiving BENLYSTA® and 1.0% of patients receiving placebo. Infections resulting in death occurred in 0.3% (4/1458) of patients treated with BENLYSTA® and in 0.1% (1/675) of patients receiving placebo.

Malignancies
The effect of treatment with BENLYSTA® on the development of malignancies is not known. In the controlled clinical trials, malignancies (including non-melanoma skin cancers) were reported in 0.4% of patients receiving BENLYSTA® and 0.4% of patients receiving placebo. In the controlled clinical trials, malignancies, excluding non-melanoma skin cancers, were observed in 0.2% (3/1458) and 0.3% (2/675) of patients receiving BENLYSTA® and placebo, respectively. As with other immunomodulating agents, the mechanism of action of BENLYSTA® could increase the risk for the development of malignancies.

Immunogenicity
In the two controlled Phase III clinical studies, anti-belimumab antibodies were detected in 4 of 563 (0.7%) patients receiving BENLYSTA® 10 mg/kg and in 27 of 559 (4.8%) patients receiving BENLYSTA® 1 mg/kg. The reported frequency for the group receiving 10 mg/kg may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentrations. Neutralizing antibodies were detected in three patients receiving BENLYSTA® 1 mg/kg. Three patients with anti-belimumab antibodies experienced mild infusion reactions of nausea, erythematous rash, pruritus, eyelid edema, headache, and dyspnea; none of the reactions were serious. The clinical relevance of the presence of anti-belimumab antibodies is not known.

The data reflect the percentage of patients whose test results were positive for antibodies to belimumab in specific assays. The observed incidence of antibody positivity in an assay is highly dependent on several factors, including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to belimumab with the incidence of antibodies to other products may be misleading.

Depression
In the controlled clinical trials, psychiatric events were reported more frequently with BENLYSTA® (16%) than with placebo (12%), primarily depression-related events (6.3% BENLYSTA® and 4.7% placebo), insomnia (6.0% BENLYSTA® and 5.3% placebo), and anxiety (3.9% BENLYSTA® and 2.8% placebo). Serious psychiatric events were reported in 0.8% of patients receiving BENLYSTA® (0.6% and 1.2% with 1 and 10 mg/kg, respectively) and 0.4% of patients receiving placebo. Serious depression was reported in 0.4% (6/1458) of patients receiving BENLYSTA® and 0.1% (1/675) of patients receiving placebo. Two suicides (0.1%) were reported in patients receiving BENLYSTA®. The majority of patients who reported serious depression or suicidal

behaviour had a history of depression or other serious psychiatric disorders and most were receiving psychoactive medications. It is unknown if BENLYSTA® treatment is associated with increased risk for these events.

Abnormal Laboratory Findings
See ADVERSE REACTIONS – Immunogenicity.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

The uncommon adverse reactions are related to infusion reactions, which include: anaphylactic reactions, angioedema, rash, and urticaria.

See CLINICAL TRIAL ADVERSE REACTIONS- Infusion Reactions and Hypersensitivity

Post-Market Adverse Drug Reactions

The following adverse reactions have been identified during post approval use of BENLYSTA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Fatal anaphylaxis (see WARNINGS AND PRECAUTIONS – Infusion Reactions and Hypersensitivity).

Fatal progressive multifocal leukoencephalopathy (see WARNINGS AND PRECAUTIONS – Immune).

DRUG INTERACTIONS

Overview

Formal drug interaction studies have not been performed with BENLYSTA®. Co-administration of steroids and ACE inhibitors increased mean clearance of BENLYSTA® in clinical trials, although still within normal ranges.

DOSAGE AND ADMINISTRATION

Discontinuation of treatment with BENLYSTA® should be considered if there is no improvement in disease control after 6 months of treatment.

Dosing Considerations

BENLYSTA® is for intravenous infusion and must be reconstituted and diluted prior to administration (see Preparation of Solutions). **Do not administer as an intravenous push or bolus.**

Premedication Recommendations
Premedication with an oral antihistamine, with or without an antipyretic, may be administered before the infusion of belimumab (see WARNINGS AND PRECAUTIONS).

Recommended Dose and Dosage Adjustment

The recommended dosage regimen is 10 mg/kg at 2-week intervals for the first three doses and at 4-week intervals thereafter. BENLYSTA® should be infused over a 1-hour period. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life threatening infusion reaction (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS).

Missed Dose

If a dose is missed or the patient is unable to attend appointment for one of the infusions, the missed dose should be administered as soon as possible.

Administration

BENLYSTA® should be administered in an appropriate setting by qualified healthcare providers trained to give infusion therapy and prepared to treat hypersensitivity, including anaphylaxis. Monitor patients during and for an appropriate amount of time after administration of BENLYSTA® (See WARNINGS AND PRECAUTIONS).

The intravenous infusion of the diluted solution of BENLYSTA® should be administered over a period of 1 hour.

It is recommended that a 21-25 gauge needle be used when piercing the vial stopper for reconstitution and dilution.

BENLYSTA® should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of BENLYSTA® with other agents.

Reconstitution:

Vial Size	Volume of Diluent to be Added to Vial	Nominal Concentration per mL Upon Reconstitution	Approximate Available Volume Upon Final Dilution
120 mg as lyophilized powder in 5 mL vial	1.5 mL Sterile Water for Injection, USP	80 mg/mL*	250 mL*
400 mg as lyophilized powder in 20 mL vial	4.8 mL Sterile Water for Injection, USP		

*The reconstituted solution must be further diluted to 250 mL in 0.9% Sodium Chloride Injection, USP (normal saline).

Preparation of Solutions

BENLYSTA® is provided as a lyophilized powder in a single-use vial for intravenous infusion after reconstitution and dilution. BENLYSTA® does not contain a preservative; therefore reconstitution and dilution must be carried out under aseptic conditions as follows:

1. Allow 10 to 15 minutes for the vial to warm to room temperature.
2. Reconstitute the BENLYSTA® powder with Sterile Water for Injection, USP (sterile water), as follows. The reconstituted solution will contain a concentration of 80 mg/mL belimumab.
    - Reconstitute 120 mg in 5 mL vial with 1.5 mL sterile water.
    - Reconstitute 400 mg in 20 mL vial with 4.8 mL sterile water.
3. The stream of sterile water should be directed toward the side of the vial to minimize foaming. Gently swirl the vial for 60 seconds. Allow the vial to sit at room temperature during reconstitution, gently swirling the vial for 60 seconds every 5 minutes until the powder is dissolved. **DO NOT SHAKE.** Reconstitution is typically complete within 10 to 15 minutes after the sterile water has been added, but it may take up to 30 minutes. Protect the reconstituted solution from direct sunlight.
4. If a mechanical reconstitution device (swirler) is used to reconstitute BENLYSTA®, it should not exceed 500 rpm and the vial swirled for no longer than 30 minutes.
5. Once reconstitution is complete, the solution should be opalescent and colourless to pale yellow, and without particles. Small air bubbles, however, are expected and acceptable.
6. Dilute the reconstituted product to 250 mL in 0.9% Sodium Chloride Injection, USP (normal saline) for IV infusion. 5% Dextrose IV solutions are incompatible with BENLYSTA® and should not be used. From a 250-mL infusion bag or bottle of normal saline, withdraw and discard a volume equal to the volume of the reconstituted solution of BENLYSTA® required for the patient's dose. Then add the required volume of the reconstituted solution of BENLYSTA® into the infusion bag or bottle. Gently invert the bag or bottle to mix the solution. Any

unused solution in the vials must be discarded.

7. Inspect the solution of BENLYSTA® visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard the solution if any particulate matter or discoloration is observed.
8. The reconstituted solution of BENLYSTA®, if not used immediately, should be stored protected from direct sunlight and refrigerated at 2° to 8°C. Solutions of BENLYSTA® diluted in normal saline may be stored at 2° to 8°C or room temperature. The total time from reconstitution of BENLYSTA® to completion of infusion should not exceed 8 hours.
9. No incompatibilities between BENLYSTA® and polyvinylchloride or polyolefin bags have been observed.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

There is limited experience with overdosage of BENLYSTA®. Adverse reactions reported in association with cases of overdose have been consistent with those expected for BENLYSTA®. Two doses of up to 20 mg/kg have been given 21 days apart by intravenous infusion to humans with no increase in incidence or severity of adverse reactions compared with doses of 1, 4, or 10 mg/kg.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Belimumab is a B Lymphocyte Stimulator (BLyS)-specific inhibitor that blocks the binding of soluble BLyS, a B-cell survival factor, to its receptor on B-cells. Belimumab does not bind B-cells directly, but by binding BLyS, belimumab inhibits the survival of B-cells, including autoreactive B-cells, and reduces the differentiation of B-cells into immunoglobulin producing plasma cells.

Pharmacodynamics

In the controlled clinical studies, treatment with BENLYSTA® reduced circulating CD19+, CD20+, naïve, and activated B-cells, plasma cells, plasmacytoid cells, and the SLE B-cell subset at Week 52. Reductions in naïve, plasma and short lived plasma cells as well as the SLE B-cell subset were observed as early as Week 8 and were sustained to Week 52. Memory cells increased initially and slowly declined toward baseline levels by Week 52. The clinical relevance of these effects has not been established.

Treatment with BENLYSTA® also led to reductions in IgG and anti-dsDNA, and increases in complement (C3 and C4). These changes were observed as early as Week 8 and were sustained through Week 52. The clinical relevance of these effects has not been established.

In a long-term extension study, B cells (including naïve, activated, plasma cells and the SLE B cell subset) and IgG levels were followed for more than 7 years. A substantial and sustained decrease in various B cell subsets was observed. A reduction in IgG levels was also observed. The impact of long-term B cell decrease on efficacy and safety has not been determined (see DETAILED PHARMACOLOGY).

Pharmacokinetics

The pharmacokinetic parameters displayed in Table 2 are based on population parameter estimates which are specific to patients who received belimumab 1 mg/kg or 10 mg/kg in the two phase 3 studies (see CLINICAL TRIALS and DETAILED PHARMACOLOGY).

Table 2 Population Pharmacokinetic Parameters in Patients with SLE After Intravenous Infusion of BENLYSTA® 1mg/kg and 10 mg/kg[a]

Pharmacokinetic Parameter	BENLYSTA® 1 mg/kg[b] (n =559)	BENLYSTA® 10 mg/kg (n = 563)
Peak concentration (C_{max}, µg/mL)	30.1	313
Area under the curve ($AUC_{0-\infty}$, day●µg/mL)	308	3,083
Distribution half-life ($t_{½}$, days)	1.14	1.75
Terminal half-life ($t_{½}$, days)	12.5	19.4
Systemic clearance (CL, mL/day)	215	215
Volume of distribution (V_{ss}, L)	3.70	5.29

[a] Intravenous infusions were administered at 2-week intervals for the first 3 doses and at 4-week intervals thereafter.

[b] The 1 mg/kg dose is not recommended

Absorption: Belimumab was administered by an intravenous infusion over 1 hour in the phase 3 studies, and maximum serum concentrations were reached shortly after the completion of infusion. The C_{max} was 30.1 µg/mL and 313 µg/mL for 1 mg/kg and 10 mg/kg doses, respectively. $AUC_{0-\infty}$ was 308 µg·day/mL and 3083 µg·day/mL for 1 mg/kg and 10 mg/kg doses, respectively.

Distribution: Belimumab, as a macromolecule, is expected to distribute to plasma and intracellular compartments and have limited distribution to tissues. Consistent with PK parameters from other monoclonal antibodies, the volume of distribution of belimumab at steady-state was 3.7-5.3 L (56-80 mL/kg based on median body weight of the population [66.3 kg]).

Metabolism: Belimumab is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by widely distributed proteolytic enzymes. Classical biotransformation studies have not been conducted.

Excretion: Serum belimumab concentrations declined in a bi-exponential manner. In general, renal elimination is relatively unimportant for monoclonal antibodies, since their large size prevents efficient filtration through the intact glomerulus. Accordingly, no studies of renal elimination of belimumab were performed. Although increases in creatinine clearance and proteinuria (>2 g/day) increased belimumab clearance, these effects were within the expected range of variability. The effect of renal disease on elimination of belimumab is otherwise unknown.

Special Populations and Conditions

The following information is based on the population pharmacokinetic analysis.

Pediatrics: No pharmacokinetic data are available in pediatric patients.

Geriatrics: Belimumab has been studied in a limited number of elderly patients. Within the overall SLE study population, age did not affect belimumab exposure in the population pharmacokinetic analysis. However, given the small number of subjects 65 years or older (1.4%), an effect of age cannot be ruled out conclusively.

Gender: Gender did not significantly influence belimumab pharmacokinetics in the largely (94%) female study population.

Race: Race did not significantly influence belimumab pharmacokinetics. The racial distribution was 53% white/Caucasian, 16% Asian, 16% Alaska native/American Indian, and 14% black/African American.

Hepatic Insufficiency: No formal studies were conducted to examine the effects of hepatic impairment on the pharmacokinetics of belimumab. Belimumab has not been studied in patients with severe hepatic impairment. Baseline ALT and AST levels did not significantly influence belimumab pharmacokinetics.

Renal Insufficiency: No formal studies were conducted to examine the effects of renal impairment on the pharmacokinetics of belimumab. During clinical development, belimumab was studied in a limited number of SLE patients with renal impairment (261 subjects with moderate renal impairment, creatinine clearance ≥30 and <60 mL/min; 14 subjects with severe renal impairment, creatinine clearance ≥15 and <30 mL/min). Although increases in creatinine clearance and proteinuria (> 2 g/day) increased belimumab clearance, these effects were within the expected range of variability. The effect of renal disease on elimination of belimumab is otherwise unknown.

STORAGE AND STABILITY

Store vials of BENLYSTA® refrigerated between 2° to 8°C. Vials should be protected from direct sunlight and stored in the original carton until use. Do not freeze. Avoid exposure to heat. Do not use beyond the expiration date.

Reconstituted solution
After reconstitution with sterile Water for Injection, the reconstituted solution, if not used immediately, should be protected from direct sunlight, and stored refrigerated at 2° to 8°C.

Reconstituted and diluted solution for infusion
Solutions of BENLYSTA® diluted in normal saline may be stored at 2° to 8°C or room temperature.

The total time from reconstitution of BENLYSTA® to completion of infusion should not exceed 8 hours.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Forms

BENLYSTA® is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for reconstitution, dilution, and intravenous infusion. Each 5 mL vial delivers 120 mg of belimumab. Each 20 mL vial delivers 400 mg of belimumab.

Composition

Upon reconstitution with Sterile Water for Injection, USP (see DOSAGE AND ADMINISTRATION, Preparation of Solutions), each single-use vial delivers 80 mg/mL belimumab in 0.16 mg/mL citric acid, 0.4 mg/mL polysorbate 80, 2.7 mg/mL sodium citrate, and 80 mg/mL sucrose, with a pH of 6.5.

Packaging

BENLYSTA® is supplied in single-use glass vials with a latex free, siliconised rubber stopper and a flip-off aluminium seal, as follows:

- 120 mg belimumab in a 5-mL single-use vial
- 400 mg belimumab in a 20-mL single-use vial

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

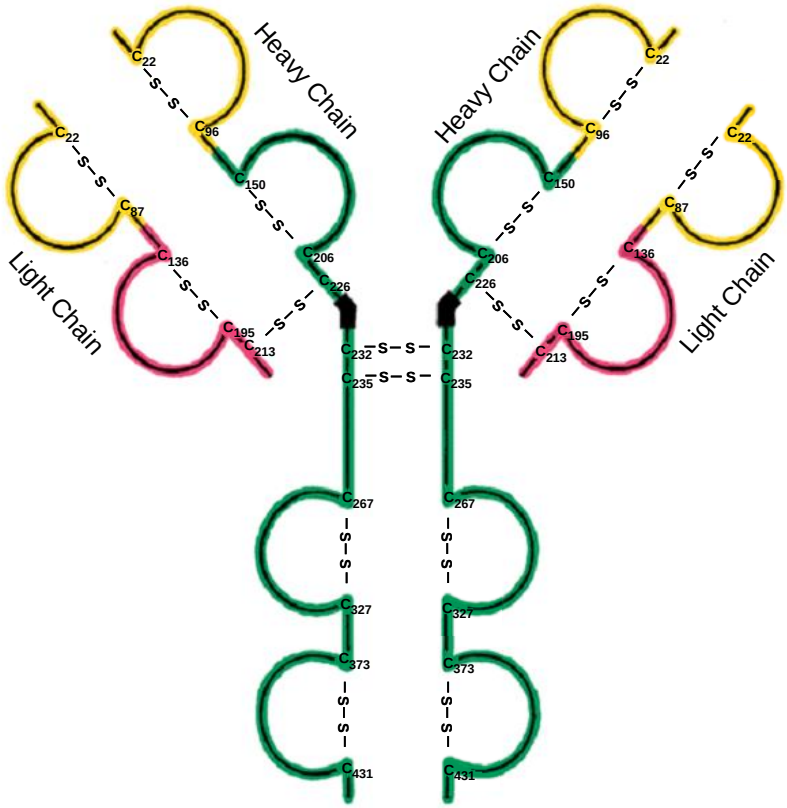
Drug Substance

Proper name: belimumab

Chemical name: immunoglobulin G1, anti-(human cytokine BAFF) (human monoclonal LymphoStat-B heavy chain) disulfide with human monoclonal LymphoStat-B light-chain, dimer

Molecular formula and molecular mass: Belimumab has a molecular formula of $C_{6358}H_{9904}N_{1728}O_{2010}S_{44}$ prior to post-translational modifications and disulfide bond formation. It contains 1332 amino acid residues and has an approximate molecular weight of 147 kilodaltons.

Structural formula: Belimumab is a fully human $IgG_1\lambda$ immunoglobulin and consists of two heavy chains of 452 amino acids and two light chains of 214 amino acids.



Physicochemical properties: Belimumab bulk drug substance is an opalescent, colorless to pale yellow solution with a concentration of approximately 105 mg/mL and an osmolality of approximately 333 mOsm/kg in a formulation buffer of pH 6.5.

Product Characteristics
Belimumab is produced by mammalian cells (NS0 mouse myeloma) in serum-free cell culture production medium. Belimumab is secreted into cell culture medium during cell culture production, recovered from the medium and purified using a series of chromatographic and filtration steps.

BENLYSTA® consists of a sterile, lyophilized formulation in single-use vials to be reconstituted with sterile Water for Injection (WFI not supplied) for intravenous infusion. Upon reconstitution with sterile WFI, each vial contains 80 mg/mL solution of belimumab with formulation buffer (0.16 mg/mL citric acid, 2.7 mg/mL sodium citrate, 80 mg/mL sucrose, 0.4 mg/mL polysorbate 80, pH 6.5) in either 120 mg (5 mL) or 400 mg (20 mL) single-use vials.

CLINICAL TRIALS

The safety and efficacy of BENLYSTA® were evaluated in three randomized, double-blind, placebo-controlled studies including 2133 patients with SLE according to the American College of Rheumatology criteria (Study 1, 2, and 3; see Table 3); those patients with severe active lupus nephritis and severe active CNS lupus were excluded. Patients were stable on a standard of care SLE treatment regimen including any of the following (alone or in combination): corticosteroids, antimalarials, NSAIDS, and immunosuppressives. Use of other biologics and intravenous cyclophosphamide were not permitted.

Table 3 Summary of Patient Demographics for Clinical Trials in Patients with SLE

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age ± SD (Range)	Gender
Study 1 (LBSL02)	Dose ranging, multicentre, double-blind, parallel-group, placebo-controlled, randomized study	*Treatment period* (52 weeks): Belimumab (IV) 1 mg/kg 4 mg/kg 10 mg/kg or placebo; IV *Extension period* (24 weeks): Placebo to 10 mg/kg 1 to 1 mg/kg 1 to 10 mg/kg 4 to 4 mg/kg 4 to 10 mg/kg 10 to 10 mg/kg (every 28 days)	*Treatment period* N=114 N=111 N=111 N=113 *Extension period* N=88 N=19 N=65 N=24 N=64 N=85	42.2±11.2 (20-75)	Female: 419 (93.3%)
Study 2 (HGS1006-C1056)*	Multicentre, double-blind, placebo-controlled, randomized study	Belimumab 1 mg/kg or 10 mg/kg, or placebo; IV; primary endpoint assessed at 52 weeks, trial continued to 76 weeks	1 mg/kg: N=271 10 mg/kg: N=273 Placebo: N=275	40.2 ± 11.5 (18-73)	Female: 764 (93.3%)
Study 2 Extension (BEL112233 / HGS1006-C1066)	Multi-centre, open-label continuation trial	Belimumab 1mg/kg and/or 10 mg/kg IV (every 28 days); for up to 2908 days (median 2167 days)	N=268 1mg/kg and/or 10mg/kg	43 ± 11.33 (21-72)	Female: 250 (93%)
Study 3 (HGS1006-C1057)*	Multicentre, double-blind, placebo-controlled, randomized study	52 weeks	1 mg/kg: N=288 10 mg/kg: N=290 Placebo: N=287	35.5 ± 11.1 (18-71)	Female: 821 (94.9%)

*HGS1006-C1056 and HGS1006-C1057 are also referred to as BLISS-76 and BLISS-52, respectively

Study 1: BENLYSTA® 1 mg/kg, 4 mg/kg, 10 mg/kg
Study 1 enrolled 499 patients and evaluated doses of 1, 4, and 10 mg/kg BENLYSTA® plus standard of care compared with placebo plus standard of care over 52 weeks in patients with SLE. Patients had to have a SELENA-SLEDAI score >4 at baseline and a history of autoantibodies (anti-nuclear antibody (ANA) and/or anti-double-stranded DNA (anti-dsDNA), but 28% of the population was autoantibody negative at baseline. The co-primary endpoints were percent change in SELENA-SLEDAI score at week 24 and time to first flare over 52 weeks. No significant differences between any of the BENLYSTA® groups and the placebo group were observed. Exploratory analysis of this study identified a group of patients (72%), who were autoantibody positive, and in whom BENLYSTA® appeared to offer benefit. The results of this study informed the design of studies 2 and 3 and led to the selection of a target population and indication that is limited to autoantibody-positive SLE patients.

Studies 2 and 3: BENLYSTA® 1 mg/kg, and 10 mg/kg
Eligible patients had active SLE disease, defined as a SELENA-SLEDAI score ≥6 and positive anti-nuclear antibody (ANA or anti-dsDNA) test results (ANA titre ≥1:80 and/or a positive anti-dsDNA [≥30 units/mL]) at screening. Patients were on a stable standard of care SLE treatment regimen consisting of any of the following (alone or in combination): corticosteroids, antimalarials, NSAIDs, and/or immunosuppressives. In the studies, patients were not required to be treated with each of these drugs; the choice of agent or agents was based on clinical judgment. Patients were excluded from the study if they had ever received treatment with any B-cell targeted agent; if they had received another biologic investigational agent in the previous year; or if they had a positive response to testing for HIV antibody, hepatitis B surface antigen, or hepatitis C antibody. The two studies were similar in design except that Study 2 was a 76-week study and Study 3 was a 52-week study, but in both studies the primary efficacy endpoint was determined at 52 weeks. 268 subjects from Study 2 entered an open label extension study for a median of 2167 days, receiving a median of 67 (± 26.4) BENLYSTA® infusions.

Study 2 (HGS1006-C1056) was conducted primarily in North America and Western Europe. The racial distribution was 70% white/Caucasian, 14% black/African American, 13% Alaska native/American Indian, and 3% Asian; 21% of subjects were of Hispanic/Latino ethnicity.

Study 3 (HGS1006-C1057) was conducted in South America, Eastern Europe, Asia, and Australia. The racial distribution was 38% Asian, 26% white/Caucasian, 32% Alaska native/American Indian, and 4% black/African American; 49% of subjects were of Hispanic/Latino ethnicity.

The concurrent SLE medications allowed were controlled with provision for adjustments early in the trial and protocol outlined restrictions or prohibitions after specified study visits for each category of medication. This provision permitted subjects an opportunity to have their disease activity managed with medication adjustments optimized while minimizing unnecessary subject requests for withdrawal for lack of efficacy or mild disease flares.

Patient mean age across both studies was 38 years (range: 18 to 73 years), and the majority (94%) were female. Baseline concomitant medications included corticosteroids (Study 2:76%, Study 3: 96%), immunosuppressives (Study 2: 56%, Study 3: 42%; including azathioprine, methotrexate and mycophenolate), and antimalarials (Study 2: 63%, Study 3: 67%). Most patients (>70%) were receiving 2 or more classes of SLE medications.

In Study 2 and Study 3, more than 50% of patients had 3 or more active organ systems at baseline. The most common active organ systems at baseline based on SELENA SLEDAI were mucocutaneous (82% in both studies); immunology (Study 2: 74%, Study 3: 85%); and musculoskeletal (Study 2: 73%, Study 3: 59%). Less than 16% of patients had some degree of renal activity and less than 7% of patients had activity in the vascular, cardio-respiratory, or CNS systems.

At screening, patients were stratified by disease severity based on their SELENA-SLEDAI score (≤9 vs ≥10), proteinuria level (<2 g/24 hr vs ≥2 g/24 hr), and race (African or Indigenous-American descent versus other), and then randomly assigned to receive BENLYSTA® 1 mg/kg, BENLYSTA® 10 mg/kg, or placebo in addition to standard of care. The patients were administered study medication intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days for 48 weeks in Study 3 and for 72 weeks in Study 2.

The primary efficacy endpoint was a composite endpoint (SLE Responder Index) that defined response as meeting each of the following clinically relevant criteria at Week 52 compared with baseline:

- ≥4-point reduction in the SELENA-SLEDAI score, and
- no new British Isles Lupus Assessment Group (BILAG) A organ domain score or 2 new BILAG B organ domain scores, and
- no worsening (<0.30-point increase) in Physician's Global Assessment (PGA) score.

The SLE Responder Index uses the SELENA-SLEDAI score as an objective measure of reduction in global disease activity; the BILAG index to ensure no significant worsening in any specific organ system; and the PGA to ensure that improvements in disease activity are not accompanied by worsening of the subject's condition overall.

In both studies 2 and 3, the proportion of SLE patients achieving an SRI response, as defined for the primary endpoint, was significantly higher in the BENLYSTA® 10 mg/kg group than in the placebo group. The effect on the SRI was not consistently significantly different for the BENLYSTA® 1 mg/kg group relative to placebo in both trials. The 1 mg/kg dose is not recommended. The trends in comparisons between the treatment groups for the rates of response for the individual components of the endpoint were generally consistent with that of the SRI (Table 4). At week 76 in Study 2, the SRI response rate with BENLYSTA® 10 mg/kg was not significantly different from that of placebo (39% and 32%, respectively).

The reduction in disease activity seen in the SRI was related primarily to improvement in the most commonly involved organ systems namely, mucocutaneous, musculoskeletal, and immunology.

Table 4 Clinical Response Rate in Patients with SLE After 52 Weeks of Treatment

	Study 2			Study 3		
Response[1]	**Placebo + Standard of Care (n = 275)**	**BENLYSTA 1 mg/kg + Standard of Care[2] (n = 271)**	**BENLYSTA 10 mg/kg + Standard of Care (n = 273)**	**Placebo + Standard of Care (n = 287)**	**BENLYSTA 1 mg/kg + Standard of Care[2] (n = 288)**	**BENLYSTA 10 mg/kg + Standard of Care (n = 290)**
SLE Responder Index	34%	41% (p = 0.104)	43% (p = 0.021)	44%	51% (p = 0.013)	58% (p < 0.001)
Odds Ratio (95% CI) vs. placebo		1.3 (0.9, 1.9)	1.5 (1.1, 2.2)		1.6 (1.1, 2.2)	1.8 (1.3, 2.6)
Components of SLE Responder Index						
Percent of patients with reduction in SELENA-SLEDAI ≥4	36%	43%	47%	46%	53%	58%
Percent of patients with no worsening by BILAG index	65%	75%	69%	73%	79%	81%
Percent of patients with no worsening by PGA	63%	73%	69%	69%	79%	80%

[1]Patients dropping out of the study early or experiencing certain increases in background medication were considered as failures in these analyses. In both studies, a higher proportion of placebo patients were considered as failures for this reason as compared to the BENLYSTA groups.
[2]The 1 mg/kg dose is not recommended.

There were too few males or patients over 65 years of age enrolled in the controlled clinical trials to draw meaningful conclusions about the effects of gender or age, on clinical outcomes.

Effect in Black/African Patients
Exploratory subgroup analyses of SRI response rate in patients of black race were performed. In Study 2 and Study 3 combined, the SRI response rate in black patients (N=148) in the BENLYSTA® groups was less than that in the placebo group (22/50 or 44% for placebo, 15/48 or 31% for BENLYSTA® 1 mg/kg, and 18/50 or 36% for BENLYSTA® 10 mg/kg). In Study 1, black patients (N=106) in the BENLYSTA®

groups did not appear to have a different response than the rest of the study population. Although no definitive conclusions can be drawn from these subgroup analyses, caution should be used when considering BENLYSTA® treatment in SLE patients of black African heritage since efficacy has not been clearly established.

Effect on Concomitant Steroid Treatment
In Study 2 and Study 3, 46% and 69% of patients, respectively, were receiving prednisone at doses > 7.5 mg/day at baseline. The proportion of patients able to reduce their average prednisone dose by at least 25% to ≤7.5 mg/day during Weeks 40 through 52 was not consistently significantly different for BENLYSTA® relative to placebo in both studies. In Study 2, 17% of patients receiving BENLYSTA® 10 mg/kg and 19% of patients receiving BENLYSTA® 1 mg/kg achieved this level of steroid reduction compared with 13% of patients receiving placebo. In Study 3, 19%, 21%, and 12% of patients receiving BENLYSTA® 10 mg/kg, BENLYSTA® 1 mg/kg, and placebo, respectively, achieved this level of steroid reduction.

Effect on Severe SLE Flares
The probability of experiencing a severe SLE flare, as defined by a modification of the SELENA Trial flare criteria which excluded severe flares triggered only by an increase of the SELENA-SLEDAI score to >12, was calculated for both Studies 2 and 3. The proportion of patients having at least 1 severe flare over 52 weeks was not consistently significantly different for BENLYSTA® relative to placebo in both studies. In Study 2, 18% of patients receiving BENLYSTA® 10 mg/kg and 16% of patients receiving BENLYSTA® 1 mg/kg had a severe flare compared with 24% of patients receiving placebo. In Study 3, 14%, 18%, and 23% of patients receiving BENLYSTA® 10 mg/kg, BENLYSTA® 1 mg/kg and placebo, respectively, had a severe flare.

Univariate and multivariate analysis of the primary endpoint in pre-specified subgroups demonstrated that the greatest benefit was observed in patients with higher disease activity including patients with SELENA SLEDAI scores ≥ 10, patients requiring steroids to control their disease, and patients with low complement levels.

Post-hoc analysis has identified high responding subgroups such as those patients with low complement and positive anti-dsDNA at baseline, see Table 5. Of these patients, 64.5% had SELENA SLEDAI scores ≥ 10 at baseline.

Table 5 Patients with low complement and positive anti-dsDNA at baseline

Subgroup	**Anti-dsDNA positive AND low complement**	
BLISS-76 and BLISS-52 pooled data	**Placebo (n=287)**	**BENLYSTA® 10 mg/kg (n=305)**
SRI response rate at Week 52 (%) Observed treatment difference vs placebo (%)	31.7	51.5 (p<0.0001) 19.8
SRI response rate (excluding complement and anti-dsDNA changes) at Week 52 (%) Observed treatment difference vs placebo (%)	28.9	46.2 (p<0.0001) 17.3
Severe flares over 52 weeks Patients experiencing a severe flare (%) Observed treatment difference vs placebo (%) Time to severe flare [Hazard ratio (95% CI)]	29.6	19.0 10.6 0.61 (0.44, 0.85) (p=0.0038)
Prednisone reduction by ≥25% from baseline to ≤7.5 mg/day during Weeks 40 through 52* (%) Observed treatment difference vs placebo (%)	(n=173) 12.1	(n=195) 18.5 (p=0.0964) 6.3
FACIT-fatigue score improvement from baseline at Week-52 (mean) Observed treatment difference vs placebo (mean difference)	1.99	4.21(p=0.0048) 2.21
BLISS-76 Study only	**Placebo (n=131)**	**BENLYSTA® 10 mg/kg (n=134)**
SRI response rate at Week-76 (%) Observed treatment difference vs placebo (%)	27.5	39.6 (p=0.0160) 12.1

* Among patients with baseline prednisone dose >7.5 mg/day

DETAILED PHARMACOLOGY

B Lymphocyte Stimulator (BLyS)

Belimumab specifically binds to soluble B Lymphocyte Stimulator (BLyS) protein and blocks the binding of soluble BLyS to its receptors expressed on B cells. Administration of recombinant human BLyS in mice results in increased representation of splenic B lymphocytes and elevated immunoglobulin (Ig) concentrations, specifically IgA, IgG and IgM. Mice transgenic for BLyS develop autoimmune phenotypes including elevated anti-dsDNA (double stranded DNA) antibody titers, proteinuria, and glomerulonephritis. Similarly, BLyS levels have been shown to be elevated in the serum of patients with autoimmune diseases such as systemic lupus erythematosus (SLE).

Pharmacodynamics

Belimumab has been shown to bind soluble BLyS with an approximate 250 pM affinity but does not recognize membrane-bound BLyS. Moreover, belimumab binds cynomolgus monkey and human BLyS with nearly identical affinities, and has similar pharmacologic effects in monkeys and humans.

In repeat-dose toxicology studies in the cynomolgus monkey, reduction of B cells was the primary pharmacologic effect of belimumab. In monkeys, reductions in B cells were observed in lymphoid tissues by Week 4 and in peripheral blood B cells by Week 13 of treatment. Recovery in peripheral B lymphocytes was generally observed to begin approximately 13 weeks after the cessation of treatment and was nearly complete or complete by 32 or 52 weeks (see Table 10).

In a long-term extension clinical trial following Study 2 (see Table 3), B cells (including naïve, activated, plasma cells and the SLE B cell subset) and IgG levels were followed for more than 7 years with ongoing treatment. A substantial and sustained decrease in various B cell subsets was observed leading to median reductions of 87% in naive B cells, 67% in memory B cells, 99% in activated B cells, and 92% in plasma cells after more than 7 years of treatment. After about 7 years, a 28% median reduction in IgG levels was observed with 1.6% of subjects experiencing a decrease in IgG levels to below 400 mg/dL. The impact of long-term B cell decrease on efficacy and safety has not been determined.

Safety Pharmacology

Belimumab has demonstrated high specificity for its target. No binding of belimumab was detected in any human or cynolgus monkey tissue tested in a GLP tissue cross reactivity study. Safety pharmacology endpoints were included in the 4 week and 6 month toxicology studies in cynomolgus monkeys, as well as neurobehavioural assessments in infants in the monkey maternal, fetal and neonatal reproductive toxicology study. No belimumab related adverse effects were noted on cardiovascular or renal endpoints at doses up to 50 mg/kg. Although no formal assessments of effects on central nervous or respiratory systems were undertaken, no treatment-related changes in these parameters were noted in the repeat dose toxicology studies at doses up to 50 mg/kg and no neurobehavioral changes were noted in infant monkeys in a reproductive toxicology study (see Table 10).

Pharmacokinetics

Nonclinical

The nonclinical studies demonstrated that belimumab PK were dose proportional over the 5-150 mg/kg range of doses tested and remained consistent after multiple IV doses. Mean steady-state volumes of distribution (V_{ss}) in monkeys ranged from 66-126 mL/kg, which is less than the extracellular fluid volume (~170-210 mL/kg including plasma), indicating that belimumab localizes primarily in the plasma compartment and the interstitial fluid spaces of more permeable tissues. Similar results were observed in the PK study conducted in SLE subjects. CL values in humans and monkeys were similar, ranging from 5.5-7.2 mL/day/kg in monkeys compared to 5.6-7.3 mL/kg/day in humans. These CL values are much lower than the glomerular filtration rate (~3000 mL/kg/day), indicating little clearance of belimumab by renal routes. In monkeys, the terminal half-life of belimumab ranged from 7-16 days which was similar to the 8.5-14 day-terminal half-life observed in subjects with SLE. Overall, the PK of belimumab was characteristic of that expected for a human monoclonal antibody.

Belimumab PK was also assessed in a reproductive toxicology study in cynomolgus monkeys, which demonstrated belimumab exposure was as expected based on studies in non-pregnant monkeys.

Clinical

The pharmacokinetics of BENLYSTA® administered intravenously in SLE patients were evaluated in four studies. The pharmacokinetics (PK) of belimumab after single or double dose (spaced 21 days apart) in humans was characterized in the Phase 1 study LBSL01 using serial sampling. Subsequent Phase 2 (LBSL02) and Phase 3 studies (HGS1006-C1056, HGS1006-C1057) also included evaluation of belimumab serum concentrations using a sparse sampling approach. In the phase 1 and 2 studies, BENLYSTA® was infused over a 2-hour period. In the phase 3 studies, the commercial formulation was infused over a 1-hour period and the data from these studies is therefore considered relevant to the recommended dosage and administration (See Part I – DOSAGE and ADMINISTRATION). Table 6, Table 7, Figure 1 and Figure 2 summarize the PK parameters obtained by compartmental analysis in study LBSL01 for single and double dose cohorts, respectively. Table 8 summarizes the peak and trough concentrations observed in the Phase 2 and Phase 3 studies.

Table 6 **Mean (± SD) PK parameters following a single IV dose of belimumab at 1, 4, 10 and 20 mg/kg given as a 2-hour infusion, in the phase 1 study**

	Cohort 1 1 mg/kg (n = 7)	Cohort 2 4 mg/kg (n = 7)	Cohort 3 10 mg/kg (n = 7)	Cohort 4 20 mg/kg (n = 6)
C_{max} (µg/mL)	22.3 ± 4.2	81.2 ± 24.6	192.4 ± 34.9	523.9 ± 293.7
$AUC_{0-\infty}$ (day•µg/mL)	156 ± 46	629 ± 258	1510 ± 315	3384 ± 1424
$t_{1/2,\alpha}$ (day)	0.96 ± 0.61	1.49 ± 0.76	1.84 ± 0.89	1.27 ± 0.43
$t_{1/2,\beta}$ (day)	8.46 ± 2.21	9.88 ± 2.18	10.63 ± 2.89	11.34 ± 3.02
V_1 (mL/kg)	44.90 ± 7.12	52.69 ± 18.59	52.91 ± 10.20	53.17 ± 40.89
V_{ss} (mL/kg)	73.29 ± 13.64	82.33 ± 22.31	86.30 ± 16.77	111.67 ± 95.72
CL (mL/day/kg)	7.15 ± 3.18	7.20 ± 2.48	6.90 ± 1.57	7.33 ± 4.38
MRT (day)	11.13 ± 3.08	12.18 ± 3.22	13.03 ± 3.59	14.01 ± 4.17

Abbreviations: C_{max}, maximum serum drug concentration; $AUC_{0-\infty}$, area under the serum drug concentration-time curve from time 0 to infinite time; $t_{1/2,\alpha}$, half-life for the distribution phase; $t_{1/2,\beta}$, elimination half-life for the terminal phase; V_1, volume of distribution for the central compartment; V_{ss}, volume of distribution at steady-state; CL, clearance; MRT, mean residence time. Parameters obtained through compartmental analysis.

Figure 1 **Mean (± SD) serum concentrations in subjects administered a single dose of belimumab at 1, 4, 10 or 20 mg/kg intravenously by a 2-hour infusion**

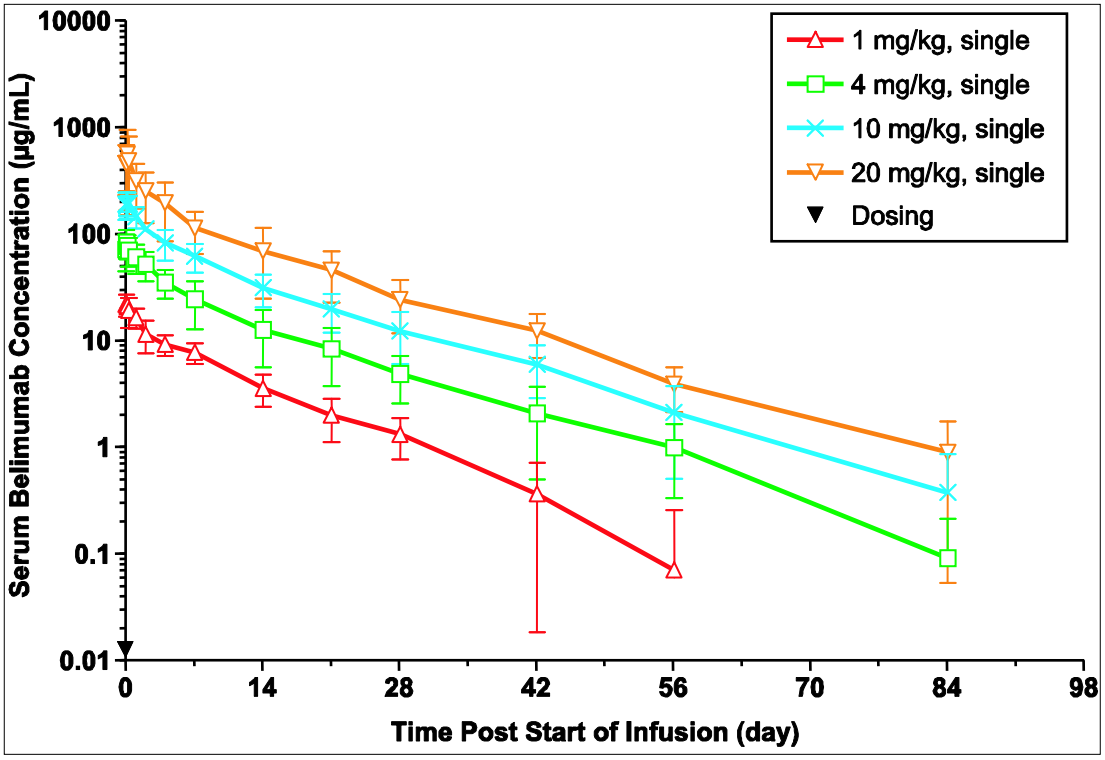


Table 7 **Mean (± SD) PK parameters following 2 IV doses of belimumab at 1, 4, 10 and 20 mg/kg given as a 2-hour infusion, 21 days apart, in the phase 1 study**

	Cohort 5 1 mg/kg (n = 6)	Cohort 6 4 mg/kg (n = 7)	Cohort 7 10 mg/kg (n = 7)	Cohort 8 20 mg/kg (n = 6)
C_{max} (µg/mL)	20.6 ± 3.0	105.4 ± 28.0	240.7 ± 41.7	368.1 ± 93.5
$AUC_{0-\infty}$ (day•µg/mL)	148 ± 30	729 ± 145	1849 ± 355	3221 ± 781
$t_{1/2,\alpha}$ (day)	1.87 ± 0.99	1.23 ± 0.65	1.03 ± 0.48	2.21 ± 1.84
$t_{1/2,\beta}$ (day)	9.67 ± 1.33	9.91 ± 2.99	9.64 ± 2.20	14.13 ± 5.31
V_1 (mL/kg)	48.95 ± 8.26	39.61 ± 11.00	41.83 ± 7.63	56.60 ± 15.02
V_{ss} (mL/kg)	76.45 ± 19.64	69.82 ± 22.72	69.21 ± 13.59	102.11 ± 30.40
CL (mL/day/kg)	7.00 ± 1.38	5.68 ± 1.11	5.57 ± 1.02	6.52 ± 1.54
MRT (day)	10.97 ± 1.86	12.47 ± 4.07	12.65 ± 2.66	16.06 ± 4.15

Abbreviations: C_{max}, maximum serum drug concentration; $AUC_{0-\infty}$, area under the serum drug concentration-time curve from time 0 to infinite time; $t_{1/2,\alpha}$, half-life for the distribution phase; $t_{1/2,\beta}$, elimination half-life for the terminal phase; V_1, volume of distribution for the central compartment; V_{ss}, volume of distribution at steady-state; CL, clearance; MRT, mean residence time. Parameters obtained through compartmental analysis.

Figure 2 **Mean (± SD) serum concentrations in subjects administered 2 doses of belimumab at 1, 4, 10 or 20 mg/kg intravenously by a 2-hour infusion, 21 days apart**

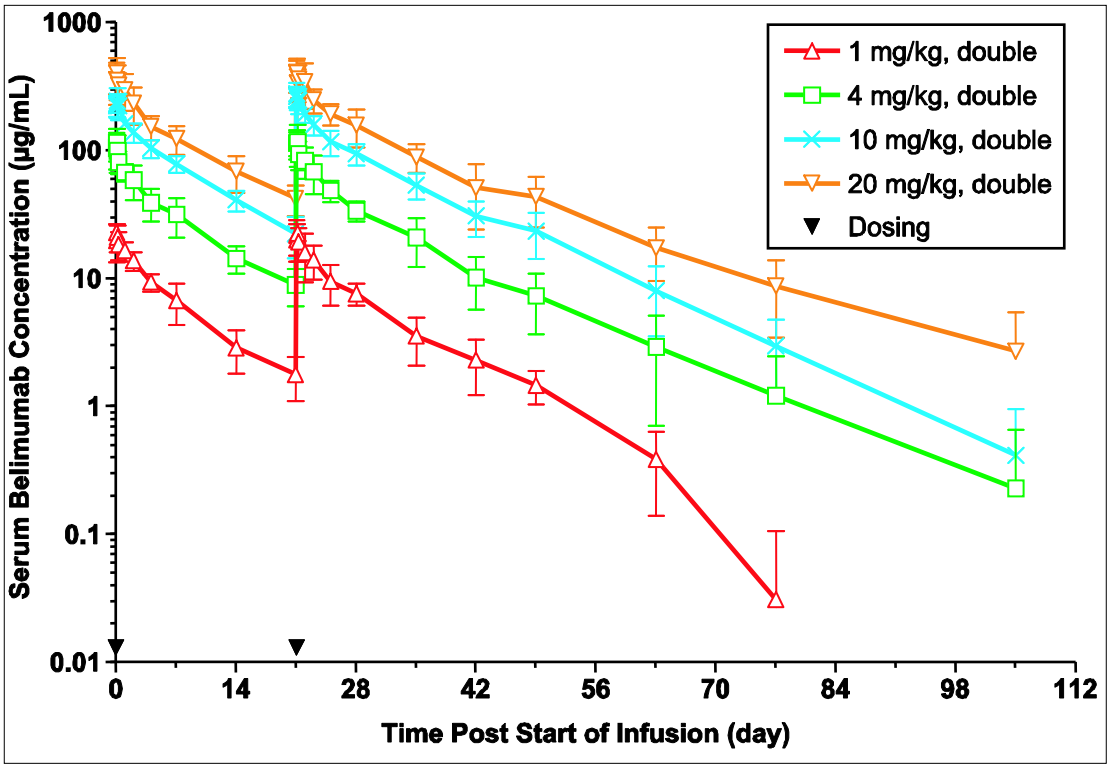


Table 8 **Mean observed peak and trough belimumab concentrations from Phase 2 and Phase 3 studies in SLE (%CV, number of subjects shown in parentheses)**

	Dose Group	
PK Parameter	**1 mg/kg**	**10 mg/kg**
Day 14 peak concentration (µg/mL)		
Phase 2 (LBSL02)	27.2 (35.0%, N=106)	246 (30.5%, N=103)
Phase 3 (C1056)	32.6 (38.0%, N=222)	335 (38.4%, N=221)
Phase 3 (C1057)	32.9 (63.5%, N=256)	342 (31.3%, N=265)
Steady-State peak concentration (µg/mL)		
Phase 2 (LBSL02)	NA	NA
Phase 3 (C1056)	30.0 (36.8%, N=207)	335 (36.6%, N=205)
Phase 3 (C1057)	31.5 (111.5%, N=248)	333 (33.3%, N=253)
Day 56 trough concentration (µg/mL)		
Phase 2 (LBSL02)	2.45 (73.9%, N=74)	34.9 (95.4%, N=83)
Phase 3 (C1056)	6.27 (91.0%, N=204)	70.07 (74.5%, N=196)
Phase 3 (C1057)	4.72 (86.8%, N=231)	56.0 (70.4%, N=228)
Steady-State trough concentration (µg/mL)		
Phase 2 (LBSL02)	2.26 (78.1%, N=84)	29.3 (57.3%, N=87)
Phase 3 (C1056)	5.47 (71.2%, N=189)	72.0 (59.4%, N=199)
Phase 3 (C1057)	3.75 (80.3%, N=186)	54.8 (52.4%, N=187)

Abbreviations: NA, not assessed; CV, coefficient of variation (ratio of standard deviation to mean)

In the population PK analysis including data from these four studies and a total of 1603 subjects, belimumab PK were well described with a linear 2-compartment model with clearance from the central compartment (see Table 2 for population parameters).

The individual PK parameters for subjects receiving 10 mg/kg in the phase 3 studies were estimated as part of the population PK analysis and are summarized in Table 9.

Table 9 Summary of individual Belimumab PK parameters (N = 563) for Phase 3 studies

PK Parameters	Geom. Mean (%CV, Range)
CL (mL/day)	232 (34.4%, 68.82-622.64)
C_{min} (µg/mL)	46.1 (63.9%, 3.86-222)
C_{max} (µg/mL)	311 (21.3%, 173-573)
$AUC_{0-\infty}$ (day·µg/mL)	2811 (38.7%, 954-8627)
$t_{1/2,\alpha}$ (days)	1.68 (12.9%, 0.75-2.57)
$t_{1/2,\beta}$ (days)	18.0 (28.1%, 6.3-39.6)
V_{ss} (mL)	5216 (12.5%, 2163-8653)

Abbreviations: CV, coefficient of variation (ratio of untransformed standard deviation and geometric mean); CL, systemic clearance; C_{min}, minimum serum drug concentration; C_{max}, maximum serum drug concentration; $AUC_{0-\infty}$, area under the serum drug time-concentration curve from time 0 to infinite time; $t_{1/2,\alpha}$, distribution half-life (α phase); $t_{1/2,\beta}$, terminal half-life (β phase); V_{ss}, volume of distribution at steady-state.

TOXICOLOGY

Nonclinical data revealed no special hazard for humans based on studies of repeat dose toxicity and reproductive toxicology.

Intravenous and subcutaneous administration to monkeys resulted in the expected reduction in number of peripheral and lymphoid tissue B-cell counts with no associated toxicological findings (see Table 10).

Reproductive studies have been performed in pregnant cynomolgus monkeys receiving belimumab 150 mg/kg by intravenous infusion (approximately 9 times the anticipated maximum human clinical exposure) every 2 weeks for up to 21 weeks, and belimumab treatment was not associated with direct or indirect harmful effects with respect to maternal toxicity, developmental toxicity, or teratogenicity. Treatment-related findings were limited to the expected reversible reduction of B-cells in both dams and infants and reversible reduction of IgM in infant monkeys. B-cell numbers recovered after the cessation of belimumab treatment by about 1 year post-partum in adult monkeys and by 3 months of life in infant monkeys; IgM levels in infants exposed to belimumab in utero recovered by 6 months of age (see Table 10).

No genotoxicity studies were conducted. BENLYSTA® is a monoclonal antibody and is not expected to interact directly with DNA or other chromosomal material.

No carcinogenicity studies have been conducted with BENLYSTA®. A traditional rodent carcinogenicity study cannot be conducted due to rapid formation of anti-drug-antibodies to both BENLYSTA® and an anti-mouse BLyS homologue in rodents. A study in BLyS knockout mice for pre-neoplastic changes would not be a representative model as mice deficient in BLyS, or the main BLyS receptor B3, have severely depleted numbers of

peripheral B cells while BENLYSTA® treatment in humans reduces peripheral B cell populations by 50% but does not deplete them. No proliferative and or pre-neoplastic changes were reported in the 6 month repeat dose study with BENLYSTA® in monkeys.

No standard fertility studies have been conducted with BENLYSTA®. It is recognized that a standard fertility study in monkeys (the only relevant species) is not practical to conduct. However, potential for effects on male and female fertility were assessed by evaluation of the reproductive tract (organ weights and histopathological evaluation) in the 6 month repeat dose study in male and female cynomolgus monkeys receiving BENLYSTA® and revealed no gross or microscopic findings to suggest any effects of BENLYSTA® on the reproductive system.

Table 10 Summary of Toxicology Findings with BENLYSTA®

Study ID	Species/ Dose/(mg/kg)/ Route	Study Design	Findings / Conclusion
Short Term Repeat Dose Studies			
Dose Finding Toxicity Study of BENLYSTA Administered by Intravenous (IV) Injection to Non-Pregnant Female Cynomolgus Monkeys	Cynomolgus monkey Doses: 121 mg/kg, 97 mg/kg, 125 mg/kg Route: IV (bolus)	3 females only; duration of study: 15 days; Day 1: 121 mg/kg; Day 4: 97 mg/kg; Day 15: 125 mg/kg	There were no findings indicative of an adverse effect of BENLYSTA. The NOAEL is >125mg/kg.
A 4 Week Repeat Dose Toxicity Study of BENLYSTA Administered by Intravenous Injection to Cynomolgus Monkeys, with a 4 Week Recovery Period	Cynomolgus monkey Doses: 0 (vehicle control), 5, 15, 50 mg/kg Dosing: Weekly Route: IV (bolus)	5/sex/dose group 3/sex/group necropsied 4 weeks after treatment; remaining 2/sex/group necropsied after 4 weeks of treatment followed by 4 weeks of recovery period	**In all BENLYSTA-treated dose groups:** A reduction of B cells in spleen and/or mesenteric lymph node, the expected pharmacological effect of treatment with BENLYSTA, was noted. There was no significant difference in the absolute numbers of peripheral blood mononuclear cell (PBMC) populations (total lymphocytes, B lymphocyte subsets, T lymphocyte subsets or monocytes) at the end of treatment or at the end of the recovery phase. An increase in T cells was observed and is considered to be secondary to the decreases in B lymphocyte populations. Minimal to mild thyroid follicular epithelial degeneration was noted in 1 out of 10 and 5 out of 10 BENLYSTA-treated monkeys at 5 and 50 mg/kg, respectively. A possible treatment relationship could not be excluded; however, similar findings were not observed in the 6 month repeat dose study. **At 50 mg/kg BENLYSTA dose group:** Splenic abscess (1 out of 10) and necrotizing granuloma (1 out of 10) were noted. These findings may have been associated with infection, and possible treatment relationship could not be excluded. In the subsequent 6 month repeat dose study, similar findings were not observed, confirming the view that the observations in the 4 week study were not treatment-related. The NOAEL is >50 mg/kg.

Long Term Repeat Dose Study			
A 6 Month Toxicity Study of BENLYSTA Administered Bi-Weekly by Intravenous Injection to Cynomolgus Monkeys, with an 8 Month Recovery Period	Cynomolgus monkey Doses: 0 (vehicle control), 5, 15, 50 mg/kg Dosing: Every 14 days Route: IV (bolus)	6/sex at 0 mg/kg and 8/sex/dose group at all BENLYSTA treatment groups; 2/sex/group at 0 mg/kg and 3/sex/group at all BENLYSTA dose groups necropsied 13 weeks after treatment initiation; 2/sex/group at 0 mg/kg and 3/sex/group at all BENLYSTA dose groups necropsied 26 weeks after treatment intiation; 2/sex/group at 0 mg/kg and 3/sex/group at all BENLYSTA dose groups necropsied after 26 weeks of treatment followed by 8 month (Week 60) recovery period	**In all BENLYSTA-treated dose groups:** A reduction of B cells in spleen and/or mesenteric lymph node (MLN), the expected pharmacological effect of treatment with BENLYSTA, was noted at Weeks 13 and 26. The B lymphocyte reductions in the spleen and MLN resolved by the end of the recovery period. Also, a reduction in peripheral blood B cells was noted after 13 weeks of treatment in the 15 and 50 mg/kg groups and in all groups by Week 26. The reduction in B cells persisted into the recovery period through Week 39 followed by a trend for recovery of peripheral blood B lymphocytes back to baseline levels at Week 45, which continued through to the end of the recovery period. Consistent with the pharmacologic effect of BENLYSTA, there was a reduction in spleen weights at Week 26. In addition, at Week 13, microscopic changes attributed to BENLYSTA administration consisted of decreased lymphoid follicle size and/or number in the spleen. A reduction in the size and/or number of lymphoid follicles in the spleen and mesenteric lymph node was also evident in the BENLYSTA-treated animals at Week 26. These effects correlated with decreases in splenic and MLN B lymphocytes at Weeks 13 and 26, as well as reduced splenic weights at Week 26. These changes, as well as splenic mesenteric B lymphocyte reductions, resolved by the end of the recovery period. The NOAEL is >50 mg/kg.

Reproductive and Developmental Toxicity Studies			
Maternal, Fetal and Neonatal Toxicity Study of BENLYSTA Administered Bi-Weekly by Intravenous (Bolus) Injection to Pregnant Cynomolgus Monkeys, Including a One Year Postnatal Evaluation	Cynomolgus monkey Doses: 0 (vehicle control), 5, 150 mg/kg Dosing: within 2 days of confirmed pregnancy by ultrasound [Gestation Day 20 (GD20) to GD22], on GD34 and every 14 days throughout pregnancy (GD150) Route: IV (bolus)	0 (vehicle control) mg/kg: Total 21 females of which 11 females were C-sectioned at GD150, and 10 females were followed out to 1 year postpartum 5 mg/kg: Total 25 females of which 13 females were C-sectioned at GD150, and 12 females were followed out to 1 year postpartum 150 mg/kg: Total 20 females of which 9 females were C-sectioned at GD150, and 11 females were followed out to 1 year postpartum	**In all BENLYSTA-treated dose groups:** No maternal toxicity and no adverse effects on embryofetal development or teratogenicity were noted. As expected, there were decreases in total and mature B lymphocytes in maternal peripheral blood during dosing and in fetal lymphoid tissues. Recovery of the total and mature B lymphocytes was observed in maternal blood and in infant blood and tissues after the cessation of dosing. Infant serum immunoglobulin M (IgM) levels were decreased in the first 3 months of life but recovered to control levels by 6 months after birth. In addition, it was confirmed that BENLYSTA, like other antibodies of the immunoglobulin G1 (IgG1) subclass, is able to cross the placenta and can be secreted into milk. After cessation of dosing and clearance of BENLYSTA and just prior to (or concomitant with) B cell recovery, BLyS levels, which pre-dose were very low in adult females, transiently increased in both mothers and infants prior to returning to baseline levels. There were a total of 12 fetal losses (12 out of 66 or 18.2%); overall incidence of fetal losses and stillbirths was 3 out of 21 (14.3%) in the 0 (vehicle control), 6 out of 25 (24.0%) at 5 mg/kg dose and 3 out of 20 (15.0%) at the 150 mg/kg dose of BENLYSTA. There were a total of 3 neonatal deaths (3 out of 43 or 7.0%); overall incidence was 0 out of 10 in the 0 (vehicle control), 2 out of 12 (16.7%) at 5 mg/kg dose and 1 out of 11 (9.0%) at the 150 mg/kg dose of BENLYSTA. No BENLYSTA-related adverse effects were seen on embryofetal development in fetuses examined following C-section (GD150) or in the aborted or stillborn fetuses. No abnormalities were noted in the 3 neonates lost within the first few weeks, confirming that the deaths were not related to BENLYSTA treatment. Reproductive failure through abortions and stillbirths in early and late pregnancy and neonatal losses within the first few weeks is significant and common among non-human primates. The number of fetal losses / stillbirths and neonatal / infant deaths in this study are consistent with historical data in cynomolgus monkeys of 17.8% and 21.9%, respectively (Hendrie et al. 1996; Small 1982; Gardin 1989; Hird 1975). The NOAEL is >150 mg/kg.
Other Studies – Safety Pharmacology			
			Stand-alone safety pharmacology studies were not undertaken with BENLYSTA. Instead, safety pharmacology end points were assessed as part of the 4 week and 6 month repeat dose studies. No BENLYSTA-related adverse effects were noted on cardiovascular or renal end points at doses up to 50 mg/kg. Although no formal assessments of effects on central nervous or respiratory systems were undertaken, no treatment-related changes in these parameters were noted in the repeat dose toxicology studies at doses up to 50 mg/kg, and no neurobehavioral changes were noted in infant monkeys in a reproductive toxicology study at doses up to 150 mg/kg.

Other Studies - Local Tolerance			
Subcutaneous (SC) Local Tolerance Study with BENLYSTA in Cynomolgus Monkeys	Cynomolgus monkey Doses: 25 mg/kg sucrose lyophilized formulation (06-B) or 25 mg/kg liquid formulation (06-C) Dosing: Single or repeated (Days 1, 3, 5, 7) Route: SC	3/sex/group Single or repeat SC dosing to evaluate local injection site irritation	Single or repeated SC administration of either the lyophilized (06-B) or liquid formulations (06-C) of BENLYSTA at 25 mg/kg in cynomolgus monkeys resulted in minimum dermal irritation and microscopic findings that were not attributed to BENLYSTA. NOAEL is >25 mg/kg.
Other Studies - Immunogenicity			
22 Week Subcutaneous Injection Immunogenicity and Toxicokinetic Study with BENLYSTA in Cynomolgus Monkeys	Cynomolgus monkey Doses: 0 (vehicle control); 1 mg/kg twice per week; 1 mg/kg four times per week Route: SC	5/sex/group SC injections of BENLYSTA for 13 weeks followed by a 9 week recovery period	SC injection of BENLYSTA for 13 weeks followed by a 9 week recovery period was well tolerated. There were no BENLYSTA-related effects on clinical signs, body weight or food consumption. BENLYSTA significantly reduced the number of peripheral blood B cells (CD20+) in both dose groups (expected pharmacological effect). NOAEL is >1 mg/kg.
Other Studies - Tissue Cross Reactivity			
Cross Reactivity of BENLYSTA with Human and Cynomolgus Monkey Tissues Ex Vivo	Human tissue, monkey tissue and cultured cells 2 to 10 μg/mL and 50 to 225 μg/mL	In vitro	No specific staining was observed when anti-BENLYSTA antibody was applied to any human tissue at any of the 4 concentrations tested. There was no staining of thyroid tissue from the 2 cynomolgus monkeys at any of the 4 concentrations tested. There was strong positive staining of zymogen granules in the pancreatic acinar cells from 1 of 4 cynomolgus monkeys and light positive staining of the cervical epithelium from 1 of 3 cynomolgus monkeys. There was no other specific staining of any cynomolgus monkey tissues.

REFERENCES

1. Bernatsky S, Boivin JF, Joseph L, et al. An international cohort study of cancer in systemic lupus erythematosus. Arthritis & Rheum. 2005;52(5):1481-1490.
2. Davies B, Morris T. Physiological parameters in laboratory animals and humans. Pharm Res 1993;10(7):1093-5.
3. Furie RA, Petri MA, Wallace DJ. Novel Evidence-Based Systemic Lupus Erythematosus Responder Index. Arthritis & Rheum. 2009;61(9):1143–1151
4. Gross JA, Johnston J, Mudri S, et al. TACI and BCMA are receptors for a TNF homologue implicated in B cell autoimmune disease. Nature 2000;404:995-9.
5. Levine, RR. How drugs reach their site of action: distribution. In: Pharmacology: Drug actions and reactions. 4th Ed. Boston, MA: Little, Brown, and Co. 1990:107-13.
6. MacKay F, Woodcock SA, Lawton P, et al. Mice transgenic for BAFF develop lymphocytic disorders along with autoimmune manifestations. J Exp Med 1999;190(11):1697-710.
7. Moore PA, Belvedere O, Orr A, et al. BLyS: member of the tumor necrosis family and B lymphocyte stimulator. Science 1999;285(5425):260-3.
8. Navarra SV, Guzmán RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377(9767):721-31.
9. Schaer GL, Fink MP, Chernow B, et al. Renal hemodynamics and prostaglandin E2 excretion in a nonhuman primate model of septic shock. Crit Care Med 1990;18(1):52-9.
10. Petri M, Stohl W, Chatham W, et al. Association of plasma B lymphocyte stimulator levels and disease activity in systemic lupus erythematosus. Arthritis & Rheum. 2008; 58(8):2453-2459.
11. Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharm and Therapeutics 2008; 84(5):548-58.
12. Zhang J, Roschke V, Baker K, et al. Cutting edge: a role for B lymphocyte stimulator in systemic lupus erythematosus. J Immunol 2001;166(1):6-10.

PART III: CONSUMER INFORMATION

BENLYSTA®
(belimumab)
Lyophilized powder for intravenous infusion

This leaflet is part III of a three-part "Product Monograph" published when BENLYSTA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about BENLYSTA®. Contact your healthcare provider if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

BENLYSTA® (ben-LIST-ah) is a prescription drug used to treat adults with lupus (systemic lupus erythematosus, also called SLE), who are also receiving other medicines for lupus.

BENLYSTA® is not approved for use in children less than 18 years old.

It is not known if BENLYSTA® is safe and effective in people with severe active lupus nephritis or severe active central nervous system lupus. It is not known if BENLYSTA® is effective in people of black ethnicity.

What it does:

BENLYSTA® contains *belimumab* which belongs to a group of drugs called *monoclonal antibodies*.

SLE is a disease of the immune system (the body system that fights infection). People with active lupus often have high levels of a protein called BLyS in their blood. BLyS plays a role in the functioning of white blood cells called B cells. The abnormal activity of B cells in lupus may lead to damage affecting multiple organ systems. BENLYSTA® binds to BLyS and limits the activity of BLyS. When given together with other drugs for lupus, BENLYSTA® decreased lupus disease activity more than the other drugs alone.

When it should not be used:

Do not take BENLYSTA® if:

- You have an allergic reaction (hypersensitivity) to BENLYSTA® (also known as belimumab)
- You have an allergic reaction to any ingredient in BENLYSTA® (See the section *What the non-medicinal ingredients are).*

What the medicinal ingredient is:

belimumab

What the nonmedicinal ingredients are:

citric acid monohydrate, sodium citrate dihydrate, sucrose and polysorbate 80

What dosage forms it comes in:

BENLYSTA® is supplied as a white to off-white powder, in a glass vial with a latex-free, siliconised rubber stopper and a flip-off aluminium seal. Each 5 ml vial contains 120 mg of BENLYSTA®. Each 20 ml vial contains 400 mg of BENLYSTA®.

The powder will be reconstituted and diluted into a solution by your healthcare provider and be given to you by intravenous infusion (through a needle placed in your vein).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Allergic and Infusion Reactions
BENLYSTA® can cause a reaction to the infusion or an allergic (hypersensitivity) reaction. Occasionally, these reactions can be severe, and can cause death. They are more likely to happen on the day of treatment, but can happen later. Call your healthcare provider right away if you get any of the symptoms listed in the SIDE EFFECTS, Allergic and Infusion Reactions section.

Severe infections
Patients receiving BENLYSTA® may have a higher chance of getting infections. Some infections may be serious and can uncommonly cause death. Call your healthcare provider right away if you feel sick or get any of the symptoms listed in the SIDE EFFECTS, Infection, section.

Progressive multifocal leukoencephalopathy (PML)
PMLis a serious brain condition that has been reported in patients receiving BENLYSTA® and other drugs that weaken the immune system. Death has occurred. The signs and symptoms of PML may include but are not limited to: memory loss, trouble thinking, confusion, problems with vision, difficulty with swallowing, talking, walking, or seizures. Call your healthcare provider right away if you

have any new or worsening experiences of the above symptoms. See SIDE EFFECTS, PML below.

Please also see the SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM table below.

BEFORE you receive BENLYSTA®, tell your healthcare provider about all of your medical conditions, including if you:

- Have had an allergic reaction (hypersensitivity) to other drugs or shots/injections. You may be given medicines to help prevent reactions before you are given BENLYSTA®.
- Have a current or long term infection or if you often get infections. Your healthcare provider will decide if you can be given BENLYSTA®.
- Have been diagnosed with cancer.
- Have memory loss, trouble thinking, difficulty with talking or walking, loss of vision, or similar problems.
- Have had mental health problems such as depression or thoughts of suicide.
- Have recently received a vaccination (within the last 30 days) or if you think you may need a vaccination. If you are receiving BENLYSTA®, you should not take live vaccines.
- Are pregnant, think you could be pregnant, or are planning to become pregnant. The effects of BENLYSTA® on pregnant women are not known. You and your healthcare provider need to consider the risks and benefits of taking BENLYSTA® while you are pregnant. Follow your healthcare provider's advice aboutcontraception if you are treated with BENLYSTA® and for at least 4 months after the last dose.
  A registry for pregnant women exposed to BENLYSTA® has been established. The purpose of this registry is to check the health of the pregnant mother and child. Patients are asked to call the registry themselves or have their healthcare provider contact the registry for them by calling 1-877-681-6296.
  Are nursing. It is likely that BENLYSTA® can pass into human breast milk. You and your healthcare provider should decide if you will take BENLYSTA® while breastfeeding.

  If you have a baby while receiving BENLYSTA®, tell your baby's healthcare provider, because your baby's vaccination schedule may be changed.

INTERACTIONS WITH THIS MEDICATION

Tell your healthcare provider about all the drugs you take, including prescription and non-prescription drugs, vitamins, and herbs. Keep a list of all your drugs and show it to your healthcare provider when you get a new prescription.

It is very important to tell your healthcare provider if you are taking intravenous cyclophosphamide, biologic drugs or monoclonal antibodies that may affect your immune system. BENLYSTA® was not studied together with intravenous cyclophosphamide, other drugs called monoclonal antibodies or biologics.

PROPER USE OF THIS MEDICATION

Usual dose:

- Your healthcare provider will decide on the correct dose of BENLYSTA®depending on your body weight. The usual dose is 10 mg for each kilogram (kg) of your body weight.
- You will be given BENLYSTA® by your healthcare provider through a needle placed in a vein (intravenously or IV). It takes about 1 hour to give you the full dose of drug.
- You will receive the first 3 doses of BENLYSTA® once every 2 weeks. After this, you will receive BENLYSTA®once every 4 weeks.
- Your healthcare provider may decide to give you an antihistamine and a drug to treat fever before you receive BENLYSTA®. A healthcare provider will watch you closely during and following the infusion. You will be treated if you have any reaction.

Overdose:

In case of drug overdose, contact a regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:

If you miss your appointment to receive BENLYSTA®, ask your healthcare provider when to schedule your next dose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Common side effects of BENLYSTA®include:

- nausea
- diarrhea
- fever
- stuffy or runny nose
- sore throat
- bronchitis

- trouble sleeping
- pain in legs or arms
- depression
- headache
- vomiting
- stomach pain
- bladder or kidney infections or painful urination
- toothache
- pain
- sudden high blood pressure
- speech difficulties
- changes in lab tests including: decreased white blood cell count (leucopenia/neutropenia), low potassium (hypokalemia)

Allergic and infusion reactions: BENLYSTA® can cause a reaction to the infusion or an allergic (hypersensitivity) reaction. These can affect 1 to 10 users in 100. Occasionally, these reactions can be severe, and can cause death. They are more likely to happen on the day of treatment, but can happen later, even 5-10 days after a dose of medication (or before or after that time). Symptoms of a reaction to the infusion and hypersensitivity are similar, and can include breathing difficulties or shortness of breath, wheezing, tongue, throat or face swelling, itching, rash, fever, low blood pressure (can cause light-headedness when you stand up), high blood pressure, slow heart beat, muscle pain, joint pain, dizziness, nausea, fatigue, and headache. Tell your healthcare provider if you have any of these signs or symptoms. Please refer to the table below for more information.

Infection: BENLYSTA® is a drug that affects your immune system. Patients receiving BENLYSTA® may have a higher chance of getting sick or getting infections including chest infection, kidney infection, infection of nose and throat, bowel infection etc. These can affect more than 1 in 10 users. Some infections may be serious and can uncommonly cause death. Call your healthcare provider right away if you feel sick or get any of the following symptoms, which may be early signs of a serious infection:

- fever
- feeling very tired
- cough, breathing problems
- flu-like symptoms
- warm, red, or painful skin
- diarrhea, vomiting
- burning sensation while passing urine

You should not start taking BENLYSTA® if you have an infection unless your healthcare provider says it is okay.

Progressive Multifocal Leukoencephalopathy (PML): Progressive multifocal leukoencephalopathy **(**PML) is a serious and life threatening brain condition. Your chance of getting PML may be higher if you are treated with medicines that weaken your immune system, including BENLYSTA®. Call your healthcare provider right away if you have memory loss, trouble thinking, confusion, difficulty with talking, swallowing, or walking, loss of vision, seizures, or similar problems that have lasted over several days. If you had these symptoms before treatment with BENLYSTA®, tell your healthcare provider immediately about any changes in these symptoms. It is advisable that your healthcare provider refer you to a neurologist or an appropriate specialist.

Cancer: BENLYSTA® may decrease your immunity. Medicines that affect the immune system may also increase your risk of certain cancers.

Heart Problems: Symptoms of heart problems when receiving BENLYSTA® can include:

- chest discomfort or pain
- shortness of breath
- cold sweats
- nausea
- dizziness

Mental health problems and suicide: Symptoms of mental health problems when receiving BENLYSTA® can include:

- thoughts of suicide or dying;
- thoughts of hurting yourself or others;
- attempting to commit suicide or acting on other dangerous impulses;
- trouble sleeping (insomnia)
- new or worse anxiety;
- new or worse depression;
- other unusual changes in your behaviour or mood.

Tell your healthcare provider if these feelings change or get worse when using BENLYSTA®.

Patients receiving BENLYSTA®can have serious side effects. Some of these side effects may cause death. It is not known if BENLYSTA® causes these serious side effects. Tell your healthcare provider immediately if you have any of the symptoms listed below.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk to your healthcare provider immediately
Rare	**Progressive multifocal leukoencephalopathy (PML).** Signs and symptoms may include new: • memory loss, trouble thinking, confusion, difficulty talking, swallowing or walking, loss of vision, seizures.	✓
Uncommon	**Severe allergic and infusion reactions.** Signs and symptoms may include: • severe allergic reactions, sometimes with swelling of face or mouth causing difficulty in breathing • swelling of the face, lips and tongue • rash, possibly with itchy raised bumps or hives • low blood pressure (can cause light-headedness when you stand up) • slow heart beat • difficulty breathing, shortness of breath	✓
Very Common	**Infections.** Symptoms may include: • fever • chills • pain or burning with urination or urinating often • bloody diarrhea • coughing up mucus	✓

This is not a complete list of side effects. For any unexpected effects while taking BENLYSTA®, contact your healthcare provider.

HOW TO STORE IT

Store vials of BENLYSTA® refrigerated between 2° to 8°C. Vials should be protected from direct light and stored in the original carton until use. Do not freeze. Avoid exposure to heat.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect
Call toll-free at 1-866-234-2345
Complete a Canada Vigilance Reporting Form and:
- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at:

http://www.gsk.ca or by contacting the sponsor,

GlaxoSmithKline Inc.
7333 Mississauga Road
Mississauga, Ontario
L5N 6L4
1-800-387-7374

This leaflet was prepared by GlaxoSmithKline Inc.

Last revised: August 31, 2016