BENLYSTA™

Belimumab

QUALITATIVE AND QUANTITATIVE COMPOSITION

Sterile lyophilized powder in a single use vial.

120 mg vial

Each vial contains a sufficient amount of belimumab to deliver 120 mg in 1.5 mL when reconstituted as recommended with sterile Water for Injection. After reconstitution, each mL of solution contains 80 mg belimumab.

400 mg vial

Each vial contains a sufficient amount of belimumab to deliver 400 mg in 5.0 mL when reconstituted as recommended with sterile Water for Injection. After reconstitution, each mL of solution contains 80 mg belimumab.

Belimumab is a recombinant, human, IgG1λ monoclonal antibody.

PHARMACEUTICAL FORM

Lyophilised powder for intravenous infusion.

CLINICAL PARTICULARS

Indications

BENLYSTA is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy (*see Clinical Studies*).

Dosage and Administration

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

Lyophilised powder for intravenous infusion

BENLYSTA is administered intravenously by infusion, and must be reconstituted and diluted prior to administration (*see Use and Handling*).

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

administered by a qualified healthcare professional trained to give infusion therapy. Administration of *BENLYSTA* may result in hypersensitivity reactions and infusion reactions. Therefore, *BENLYSTA* should be administered in an environment where resources for managing such reactions are immediately available.

BENLYSTA should be administered by a healthcare professional prepared to treat hypersensitivity reactions including anaphylaxis.

BENLYSTA should be infused over a 1-hour period.

BENLYSTA must not be administered as an intravenous push or bolus.

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 adverse reaction (*see Contraindications, Warnings and Precautions*).

Patients should be monitored during and for an appropriate period of time after administration of *BENLYSTA* (*see Warnings and Precautions, Adverse Reactions*).

There are no or insufficient data available on the effects of *BENLYSTA* in patients with severe active lupus nephritis or severe active central nervous system lupus.

The patient's condition should be evaluated continuously.

Premedication for intravenous infusion for patients with allergies

Premedication with an oral antihistamine, with or without an antipyretic, may be administered before the infusion of *BENLYSTA* (*see Warnings and Precautions, Clinical Studies*).

Adults

Lyophilised powder for intravenous infusion

The recommended dosage regimen is 10 mg/kg on Days 0, 14 and 28, and at 4-week intervals thereafter.

Children

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.

Special populations

Elderly (>65 years)

The efficacy and safety of *BENLYSTA* in the elderly has not been established. Data on patients >65 years are limited to <1.6% of the studied population. Therefore, the use of *BENLYSTA* in elderly patients is not recommended unless the benefits are expected to outweigh the risks. In case administration of *BENLYSTA* to elderly patients is deemed necessary, dose adjustment is not required (*see Pharmacokinetics - Special patient populations*).

Renal impairment

Belimumab has been studied in a limited number of SLE patients with renal impairment.

On the basis of the available information, dose adjustment is not required in patients with mild, moderate or severe renal impairment. Caution is however recommended in patients with severe renal impairment due to the lack of data (*see Pharmacokinetics - Special patient populations*).

Hepatic impairment

No specific studies with *BENLYSTA* have been conducted in patients with hepatic impairment. Patients with hepatic impairment are unlikely to require dose adjustment (*see Pharmacokinetics - Special patient populations*).

Contraindications

BENLYSTA is contraindicated in patients who have demonstrated anaphylaxis to *BENLYSTA*.

Warnings and Precautions

BENLYSTA has not been studied in the following patient groups, and is not recommended in:

- severe active central nervous system lupus
- severe active lupus nephritis
- HIV
- a history of, or current, hepatitis B or C
- hypogammaglobulinaemia (IgG <400 mg/dl) or IgA deficiency (IgA <10 mg/dl)
- a history of major organ transplant or hematopoietic stem /cell /marrow transplant or renal transplant.

Concomitant use with B-cell targeted therapy and cyclophosphamide

BENLYSTA has not been studied in combination with other B-cell targeted therapy or intravenous cyclophosphamide. Caution should be exercised if *BENLYSTA* is co-administered with other B-cell targeted therapy or cyclophosphamide.

Infusion reactions and hypersensitivity

Administration of *BENLYSTA* may result in hypersensitivity reactions and infusion 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. The risk of hypersensitivity reactions is greatest with the first two infusions; however the risk should be considered for every infusion administered. Patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk.

Premedication with an antihistamine, with or without an antipyretic, may be administered before the infusion of *BENLYSTA*. 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 approximately 0.9% of patients, and included anaphylactic reaction, bradycardia, hypotension, angioedema, and dyspnea. Infusion reactions occurred more frequently during the first two infusion days and tended to decrease with subsequent infusions.

Patients have been reported to develop symptoms of acute hypersensitivity several hours after the infusion has been administered. Recurrence of clinically significant reactions after initial appropriate treatment of symptoms has also been observed. Therefore, *BENLYSTA* should be administered in an environment where resources for managing such reactions are immediately available. Patients should remain under clinical supervision for a prolonged period of time (for several hours), following at least the first 2 infusions, taking into account the possibility of a late onset reaction. Patients should be advised that hypersensitivity reactions are possible on the day of, or the day after infusion, and be informed of potential signs and symptoms and the possibility of recurrence. Patients should be instructed to seek immediate medical attention if they experience any of these symptoms. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache, and facial oedema.

Risk of infections

The mechanism of action of *BENLYSTA* could increase the risk for the development of infections, including opportunistic infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant therapy, including *BENLYSTA* (*see Adverse Reactions*). Physicians should exercise caution when considering the use of *BENLYSTA* in patients with severe or chronic infections or a history of recurrent infection. Patients who develop an infection while undergoing treatment with *BENLYSTA* should be monitored closely, and consideration should be given to stopping immunosuppressant therapy. The risk of using *BENLYSTA* in patients with active or latent tuberculosis is unknown.

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 *BENLYSTA*. A diagnosis of PML should be considered in

any patient presenting with new-onset or deteriorating neurological signs and symptoms. The patient should be referred to a neurologist or other appropriate specialist for evaluation and if PML is confirmed, consideration should be given to stopping immunosuppressant therapy, including *BENLYSTA*.

Risk of malignancies

Immunomodulatory medicinal products, including belimumab, may increase the risk of malignancy. Caution should be exercised when considering belimumab therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancy. Patients with malignant neoplasm within the last 5 years have not been studied, with the exception of those with basal or squamous cell cancer of the skin, or cancer of the uterine cervix, that has been fully excised or adequately treated.

Immunisation

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 immunisations. However, in a study evaluating the response to a 23-valent pneumococcal vaccine, overall immune responses to the different serotypes were similar in SLE patients receiving belimumab compared with those not receiving treatment at the time of vaccination.

Limited data suggest that *BENLYSTA* does not significantly affect the ability to maintain a protective immune response to immunisations received prior to administration of *BENLYSTA*. There are insufficient data to draw conclusions regarding the ability of subjects receiving *BENLYSTA* to mount protective responses to vaccines.

Interactions

No drug interaction studies have been conducted with *BENLYSTA*.

In clinical trials of patients with SLE, concomitant administration of mycophenolate mofetil, azathioprine, hydroxychloroquine, methotrexate, non-steroidal anti-inflammatory medications, aspirin, and HMG CoA reductase inhibitors had no significant effect on belimumab exposures (*see Pharmacokinetics*).

Pregnancy and Lactation

Fertility

There are no data on the effects of *BENLYSTA* on human fertility. Effects on male and female fertility have not been evaluated in animal studies (*see Pre-clinical Safety Data*).

Pregnancy

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 be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

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.

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 Warning and Precautions*).

Lactation

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 cynomolgus monkeys, 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.

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 belimumab or from the underlying maternal condition.

Effects on Ability to Drive and Use Machines

There have been no studies to investigate the effect of *BENLYSTA* on driving performance or the ability to operate machinery. No detrimental effects on such activities are predicted from the pharmacology of *BENLYSTA*.

The clinical status of the patient and the safety profile of *BENLYSTA* should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills**.**

Adverse Reactions

Clinical Trial Data

The safety of *BENLYSTA* in patients with SLE has been evaluated in 3 placebo-controlled intravenous studies.

The data described below reflect exposure to *BENLYSTA* (10 mg/kg intravenously over a 1-hour period on Days 0, 14, 28, and then every 28 days up to 52 weeks) in 674 patients with SLE, including 472 exposed for up to 52 weeks. The safety data presented include data beyond Week 52 in some patients. Data from postmarketing reports are also included.

The majority of patients were also receiving one or more of the following concomitant treatments for SLE: corticosteroids, immunomodulatory agents, anti-malarials, non-steroidal anti-inflammatory drugs. Adverse reactions are listed below by MedDRA body system organ class and by frequency. The frequency categories used are:

Very common ≥ 1 in 10

Common ≥ 1 in 100 and < 1 in 10

Uncommon ≥ 1 in 1,000 and < 1 in 100

MedDRA SOC	**Very common:**	**Common:**	**Uncommon:**
Infections and infestations	Infections		
Immune System Disorders		Hypersensitivity reaction*****	Anaphylactic reaction Angioedema
Skin and Subcutaneous Tissue Disorders			Rash Urticaria
General Disorders and Administration Site Conditions		Pyrexia Infusion-related reaction*****	

*‘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 may not be possible to distinguish between hypersensitivity reactions and infusion reactions in all cases.

Hypersensitivity reactions: Clinically significant hypersensitivity reactions associated with *BENLYSTA* administered intravenously and requiring permanent treatment discontinuation were reported in 0.4% of patients. These reactions were generally observed on the day of the infusion, and patients with a history of multiple drug allergies or significant hypersensitivity reactions may be at increased risk. Delay in the onset of acute hypersensitivity reactions for several hours after the infusion, and recurrence of clinically significant reactions after initial resolution of symptoms following appropriate treatment, have been observed. Delayed-type, non-acute hypersensitivity reactions have also been observed and included symptoms such as rash, nausea, fatigue, myalgia, headache and facial oedema.

Infections: In the intravenous clinical studies, the overall incidence of infections was 70% in the group receiving belimumab and 67% in the group receiving placebo. Infections occurring in at least 3% of patients receiving belimumab and at least 1% more frequently than patients receiving placebo were nasopharyngitis, bronchitis, pharyngitis, cystitis and gastroenteritis viral. Serious infections occurred in 5% of patients receiving either belimumab or placebo; serious opportunistic infections accounted for <1% and 0% of these, respectively. Some infections were severe or fatal.

Leucopenia: The incidence of leucopenia reported as an adverse event was 4% in the group receiving *BENLYSTA* and 2% in the group receiving placebo.

Psychiatric disorders: Insomnia occurred in 7% of the group receiving *BENLYSTA* and 5% of the group receiving placebo. Depression was reported in 5% and 4% of the groups receiving *BENLYSTA* and placebo, respectively.

Gastrointestinal disorders: Obese patients (BMI >30 kg/m^2) treated with *BENLYSTA* reported higher rates of nausea**,** vomiting and diarrhoea relative to placebo, and compared with normal-weight patients (BMI ≥18.5 to ≤30 kg/m^2). None of these gastrointestinal events in obese patients were serious.

Overdose

There is limited clinical experience with overdosage of *BENLYSTA*. Adverse reactions reported in association with cases of overdose have been consistent with those expected for belimumab.

Two doses up to 20 mg/kg administered 21 days apart by intravenous infusion have been given to humans with no increase in incidence or severity of adverse reactions compared with doses of 1, 4 or 10 mg/kg.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Mechanism of Action

B-Lymphocyte Stimulator (BLyS, also referred to as BAFF and TNFSF13), a member of the tumour necrosis factor (TNF) ligand family, inhibits B-cell apoptosis and stimulates the differentiation of B cells into immunoglobulin-producing plasma cells. BLyS is overexpressed in patients with SLE. There is a strong association between SLE disease activity (as assessed by the Safety of Estrogen in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index [SELENA-SLEDAI]) and plasma BLyS levels.

Belimumab is a human IgG1λ monoclonal antibody that specifically binds to soluble human BLyS and inhibits its biological activity. Belimumab does not bind B cells directly, but by binding and neutralizing BLyS, belimumab inhibits the survival of B cells, including autoreactive B cells, and reduces the differentiation of B cells into immunoglobulin producing plasma cells.

Pharmacodynamic Effect

Intravenous infusion

Reductions in elevated levels of serum IgG and in anti-dsDNA antibodies were observed as early as Week 8 and continued to Week 52. In patients with hypergammaglobulinaemia at baseline, normalization of IgG levels was observed by Week 52 in 49% and 20% of patients receiving belimumab and placebo, respectively. In patients with anti-dsDNA antibodies at baseline, reductions in patients receiving belimumab were evident as early as Week 8, and by Week 52, 16% of patients treated with belimumab had converted to anti-dsDNA negative compared with 7% of the patients receiving placebo.

In patients with low complement levels at baseline, belimumab treatment resulted in increases in complement C3 and C4 which were seen as early as Week 4 and continued over time. By Week 52, levels of C3 and C4 had normalized in 38% and 44% of patients receiving belimumab compared with 17% and 19% of patients receiving placebo.

The target of belimumab, BLyS, is a critical cytokine for B-cell survival, differentiation, and proliferation. Belimumab significantly reduced circulating B cells, naïve, activated, plasma, 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. Memory cells increased initially and slowly declined toward baseline levels by Week 52.

In a long-term uncontrolled 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 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. Over the course of the study, the reported incidence of AEs generally remained stable or declined.

Immunogenicity

In the two Phase III studies with belimumab administered intravenously, 4 out of 563 (0.7%) patients in the 10 mg/kg group and 27 out of 559 (4.8%) patients in the 1 mg/kg group developed persistent anti-belimumab antibodies. The reported frequency for the 10 mg/kg group may underestimate the actual frequency due to lower assay sensitivity in the presence of high drug concentrations.

Neutralising antibodies were detected in 3 patients receiving belimumab 1 mg/kg intravenously. However, the presence of anti-belimumab antibodies was relatively uncommon in patients with belimumab administered intravenously, and no definitive conclusions can be drawn regarding the effect of immunogenicity on belimumab pharmacokinetics due to low numbers of anti-belimumab antibody positive subjects.

Pharmacokinetics

The intravenous pharmacokinetic parameters below are based on population parameter estimates from 563 patients who received belimumab 10 mg/kg intravenously in the two Phase III studies.

Absorption

Following intravenous administration, maximum serum concentrations (C_{max}) of belimumab were generally observed at, or shortly after, the end of the infusion. The C_{max} was 313 µg/mL at steady-state based on simulating the concentration time profile using the typical parameter values of the population pharmacokinetic model.

Distribution

Belimumab was distributed to tissues with an overall volume of distribution of approximately 5 L.

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.

Elimination

Following intravenous administration, serum belimumab concentrations declined in a bi-exponential manner, with a distribution half-life of 1.75 days and terminal half-life 19.4 days. The systemic clearance was 215 mL/day.

Drug interactions

Concomitant use of mycophenolate mofetil, azathioprine, and hydroxychloroquine did not substantially influence the pharmacokinetics of belimumab administered intravenously based on the results of the population pharmacokinetic analyses. Neither did a wide range of other co-medications (non-steroidal anti-inflammatory medications, aspirin, and HMG-CoA reductase inhibitors) significantly influence belimumab pharmacokinetics. Co-administration of steroids and ACE inhibitors resulted in a statistically significant increase of systemic clearance in the population pharmacokinetic analysis for intravenous administration. However, the steroid and ACE inhibitor effects for belimumab administered intravenously were not clinically meaningful as their magnitude was well within the range of normal variability of clearance.

Special Patient Groups

Elderly

Belimumab has been studied in a limited number of elderly patients. Age did not affect belimumab exposure in the intravenous population pharmacokinetic analysis. However, given the small number of subjects 65 years or older, an effect of age cannot be ruled out conclusively.

Children and adolescents

No pharmacokinetic data are available in paediatric patients.

Renal impairment

No formal studies were conducted to examine the effects of renal impairment on the pharmacokinetics of belimumab. During clinical development, belimumab administered intravenously was studied in a limited number of SLE patients with renal impairment (creatinine clearance <60 mL/min, including a small number with creatinine clearance <30 mL/min). Following belimumab administered intravenously, proteinuria ($\geq$ 2 g/day) increased belimumab clearance, and decreases in creatinine clearance decreased belimumab clearance. These effects were within the expected range of variability for belimumab administered intravenously. Therefore, no dose adjustment is recommended for patients with renal impairment.

Hepatic impairment

No formal studies were conducted to examine the effects of hepatic impairment on the pharmacokinetics of belimumab. IgG1 molecules such as belimumab are catabolised by widely distributed proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of belimumab.

Other patient characteristics

There was no significant effect of gender, race or ethnicity on the pharmacokinetics of belimumab administered intravenously. The effects of body size on belimumab exposure after intravenous administration are accounted for by weight normalized dosing.

Clinical Studies

Intravenous infusion

The efficacy of *BENLYSTA* administered intravenously was evaluated in two randomised, double-blind, placebo-controlled Phase III studies in 1,684 patients with a clinical diagnosis of SLE according to the American College of Rheumatology classification criteria. 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 SLE treatment regimen (standard of care) consisting of any of the following (alone or in combination): corticosteroids, anti-malarials, NSAIDs or other immunosuppressives. Patients were excluded from the study if they had ever received treatment with any B-cell targeted therapy, if they had received another biological 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 1 was a 76-week study and Study 2 was a 52-week study. Both studies had 52 week primary endpoints.

Study 1 (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 or American Indian, and 3% Asian. Background medications included corticosteroids (76%), immunosuppressives (56%), and anti-malarials (63%).

Study 2 (HGS1006-C1057) was conducted in South America, Eastern Europe, Asia, and Australia. The racial distribution was 38% Asian, 26% white/Caucasian, 32% Alaska native or American Indian, and 4% black/African American. Background medications included corticosteroids (96%), immunosuppressives (42%), and anti-malarials (67%).

Patient median age across both studies was 37 years (range: 18 to 73 years), and the majority (94%) were female. At screening, patients were stratified by disease severity based on their SELENA-SLEDAI score (≤ 9 vs ≥10), proteinuria level (<2 g per 24 hr vs ≥2 g per 24 hr), and race, 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 or 72 weeks.

The primary efficacy endpoint was a composite endpoint (SLE Responder Index) that defined response as meeting each of the following 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 score (PGA).

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 achieved at the expense of the patient's overall condition.

BENLYSTA produced significant improvements in the SLE Responder Index as well as in the individual component SELENA-SLEDAI score in both studies, see Table 1.

Table 1: Response Rate at Week 52

	Study 1		Study 2		Studies 1 and 2 Pooled	
Response	Placebo (n=275)	*BENLYSTA* 10mg/kg (n=273)	Placebo (n=287)	*BENLYSTA* 10mg/kg (n=290)	Placebo (n=562)	*BENLYSTA* 10mg/kg (n=563)

SLE Responder Index	33.8%	43.2% (P=0.021)	43.6%	57.6% (P=0.0006)	38.8%	50.6% (P<0.0001)
Components of SLE Responder Index						
Percent of patients with reduction in SELENA-SLEDAI ≥4	35.6%	46.9% (P=0.006)	46.0%	58.3% (P= 0.0024)	40.9%	52.8% (P<0.0001)
Percent of patients with no worsening by BILAG index	65.1%	69.2% (P=0.32)	73.2%	81.4% (P=0.018)	69.2%	75.5% (P=0.019)
Percent of patients with no worsening by PGA	62.9%	69.2% (P=0.13)	69.3%	79.7% (P=0.0048)	66.2%	74.6% (P=0.0017)

In a pooled analysis of the two studies, the percentage of patients receiving >7.5 mg/ day prednisone (or equivalent) at baseline whose average corticosteroid dose was reduced by at least 25% from baseline to a dose equivalent to prednisone ≤ 7.5 mg/day during Weeks 40 through 52, was 17.9% in the group receiving belimumab and 12.3% in the group receiving placebo (P=0.0451).

Flares in SLE were defined by the Modified SELENA-SLEDAI SLE Flare Index where the modification excludes severe flares that are triggered only by an increase of SELENA-SLEDAI score to > 12. The median time to the first flare was delayed in the pooled group receiving belimumab compared to the group receiving placebo (hazard ratio= 0.84, P=0.012). The risk of severe flares was also reduced by 36% over the 52 weeks of observation in the group receiving belimumab compared to the group receiving placebo (hazard ratio=0.64, P=0.0011).

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 2. Of these patients, 64.5% had SELENA-SLEDAI scores ≥ 10 at baseline.

Table 2: Patients with low complement and positive anti-dsDNA at baseline

Subgroup	**Anti-dsDNA positive AND low complement**	
Study 1 and Study 2 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=0.1510) 6.3
FACIT-fatigue score improvement from baseline at Week 52 (mean) Observed treatment difference vs placebo (mean difference)	1.80	4.07 (P=0.0039) 2.27
Study 1 only	**Placebo**	**Benlysta**

	(n=131)	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

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

Infusion-related reactions

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.

Pre-clinical Safety Data

Non-clinical data revealed no special hazard for humans based on studies of repeated dose toxicity and toxicity to reproduction.

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.

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.

As belimumab is a monoclonal antibody, no genotoxicity studies have been conducted. No carcinogenicity or fertility studies (male or female) have been performed.

PHARMACEUTICAL PARTICULARS

List of Excipients

Lyophilised powder for intravenous infusion

Citric acid monohydrate

Sodium citrate dihydrate

Sucrose

Polysorbate 80

Incompatibilities

BENLYSTA is not compatible with 5% dextrose.

BENLYSTA lyophilised powder for intravenous infusion must be prepared and administered only as directed, (*see Use and Handling*).

Shelf Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Unopened vials

Store at between 2°C and 8°C.

Do not freeze.

Protect from light. Store in the original carton until use.

Reconstituted solution for intravenous infusion

After reconstitution with Water for Injection, and dilution in 0.9% sodium chloride (normal saline), 0.45% sodium chloride (half normal saline), or Lactated Ringer's solution, the product is stable for up to 8 hours at 2°C to 8°C or at room temperature (19°C to 23°C). Protect from direct sunlight.

Nature and Contents of Container

Vials for intravenous infusion

5 mL Type 1 glass vial sealed with a latex-free siliconised rubber stopper and a flip-off seal containing 120 mg *BENLYSTA* as a lyophylised powder.

20 mL Type 1 glass vial sealed with a latex-free siliconised rubber stopper and a flip-off seal containing 400 mg *BENLYSTA* as a lyophylised powder.

The drug is supplied in a single use vial without a preservative.

Instructions for Use/Handling

Lyophilised powder for intravenous infusion

Reconstitution and dilution

BENLYSTA does not contain a preservative; therefore reconstitution and dilution must be carried out under aseptic conditions.

Allow 10-15 minutes for the vial to warm to room temperature.

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

The 120 mg single-use vial of *BENLYSTA* should be reconstituted with 1.5 mL of sterile Water for Injection to yield a final concentration of 80 mg/mL belimumab. The 400 mg single-use vial of *BENLYSTA* should be reconstituted with 4.8 mL of sterile Water for Injection to yield a final concentration of 80 mg/mL belimumab.

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.

If a mechanical reconstitution device is used to reconstitute *BENLYSTA* it should not exceed 500 rpm and the vial should be swirled for no longer than 30 minutes.

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.

The reconstituted product is diluted to 250 mL with 0.9% sodium chloride (normal saline), 0.45% sodium chloride (half normal saline) or Lactated Ringer's solution 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, half normal saline, or Lactated Ringer's solution, withdraw and discard a volume equal to the volume of the reconstituted *BENLYSTA* solution required for the patient's dose. Then add the required volume of the reconstituted *BENLYSTA* solution 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.

Inspect the *BENLYSTA* solution visually for particulate matter and discoloration prior to administration. Discard the solution if any particulate matter or discoloration is observed.

The reconstituted solution, if not used immediately, should be protected from direct sunlight and stored refrigerated at 2°C to 8°C. Solutions diluted in normal saline, half normal saline, or Lactated Ringer's solution may be stored at 2°C to 8°C or at room temperature (19°C to 23°C).

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

Administration

BENLYSTA should be infused over a 1 hour period.

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.

No incompatibilities between *BENLYSTA* and polyvinylchloride or polyolefin bags have been observed.

Not all presentations are available in every country.

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