Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Belimumab

Proprietary Product Name: Benlysta

Sponsor: GlaxoSmithKline Australia

October 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to product submission

Submission details

Type of Submission	New Biological Entity
Initial Decision:	Rejected
Final Decision:	Approved
Date of Initial Decision:	17 February 2012
Date of Final Decision:	6 July 2012
Active ingredient(s):	Belimumab
Product Name(s):	Benlysta
Sponsor's Name and Address:	GlaxoSmithKline Australia Pty Ltd PO Box 168, Boronia VIC 3155
Dose form(s):	Lyophilized powder for intravenous infusion in sterile single-use vials, stored light. Two configurations of the FDP are available to accommodate dosing bas
Strength(s):	400 mg/vial 5mL deliverable configuration 120 mg/vial 1.5mL deliverable configuration
Container(s):	Glass flint tubing vial with rubber stopper
Pack size(s):	1 vial
Approved Therapeutic use:	Benlysta is indicated as add-on therapy for reducing disease activity in adult patients with active, autoantibody-positive systemic lupus erythematosus (SL with a high degree of disease activity (e.g. ANA titre ≥ 1:80 and/or anti-dsDNA titre ≥30 IU/mL) despite standard therapy. The safety and efficacy of Benlysta have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.
Route(s) of administration:	Intravenous (IV).
ARTG Numbers:	173078 and 173077

Product background

This AusPAR describes the application by GlaxoSmithKline Australia Pty Ltd to register a powder for IV infusion containing belimumab, a new, fully human immunoglobulin (IgG1λ) monoclonal antibody. Belimumab was designed to specifically neutralise soluble B

lymphocyte stimulator (BLyS) protein, which is one of several members of the TNF family of ligands involved in B lymphocyte homeostasis. A main role of BLyS is to promote the survival of B lymphocytes, mainly of the immature, naïve subtype, possibly by inhibiting apoptosis. By reducing elevated levels of BLyS found in patients with SLE it is expected belimumab will prevent the development and survival of B cell populations, resulting ultimately in reduced levels of autoreactive B cells and immunoglobulin producing plasma cells that mediate much of the pathology observed in the autoimmune disorder.

The sponsor's initially proposed the following indication for belimumab:

> *"Benlysta® is indicated for the reducing disease activity in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) who are receiving standard therapy".*

It is proposed to be administered as a 10 mg/kg intravenous (IV) infusion every 2 weeks for the first 3 doses and monthly thereafter.

Belimumab represents a new class of therapeutic agents. No new therapy has been scientifically validated and approved for the treatment of SLE for more than 50 years.

Regulatory status

The product has gained marketing approval in the USA (9 March 2011), Canada (6 July 2011) and the European Union (EU) (13 July 2011) for the treatment of SLE. A marketing application was approved in Switzerland on 13 June 2012.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

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

The molecular formula of belimumab is C6358H9904N1728O2010S44, which is the amino acid sequence of belimumab prior to post translational modifications and disulfide bond formation.

The three post-translational modifications are N-linked glycosylation on the CH2 domain of the heavy chain at asparagine 303 (**N**303ST), the conversion of the N-terminal glutamine residue of the heavy chain **Q** into pyroglutamate and **K** the loss of C-terminal lysine residue of the heavy chain. There are 452 amino acid residues in the heavy chain and 214 amino acid residues in the light chain. Belimumab contains 2 heavy and 2 light chains (1332 amino acid residues). Belimumab contains 32 cysteine residues (10 in the 2 light chains and 22 in the 2 heavy chains), all of which participate in 4 inter-chain disulfide bonds and 12 intra-chain disulfide bonds for a total of 16 disulfide bonds. Disulfide linkages in belimumab are identical to the native wild-type human IgG1 antibody.

Carbohydrates in the N-linked glycosylation are core-fucosylated, bi-antennary, complex-type oligosaccharides, typical of IgG1 antibodies produced from NS0 cell lines.

The primary structure of belimumab was well characterised with respect to its amino acid composition, monosaccharide composition, terminal sequences, complete sequence verification, disulfide linkages and post-translation modifications, including glycosylation and attached glycan structures. Edman degradation was used to verify N-terminal and internal sequences. The overall integrity of the primary structure was assessed by mass spectrometry and peptide mapping. The secondary and tertiary structures of belimumab were evaluated using far-ultra violet (UV) circular dichroism (CD), Fourier transform infrared spectroscopy (FTIR), UV spectroscopy and fluorescence spectroscopy. The evaluation of these structures showed the characteristics of beta sheets and buried tryptophan residues, in agreement with the published IgG1 structures. The thermal stability was assessed using differential scanning calorimetry (DSC).

The approximate molecular weight is 147.0 kDa.

Drug product

The proposed commercial final drug product is a lyophilized formulation to be reconstituted with sterile Water for Injection (WFI) to a final concentration of 80 mg/ml. Two configurations of the lyophilized product are available to accommodate dosing based on patient weight: 120 mg in a 5 mL vial and 400 mg in a 20 mL vial. The proposed patient population for belimumab is adults with active, autoantibody-positive, systemic lupus erythematosus who are receiving standard therapy. The proposed treatment regimen is 10 mg/kg administered as an intravenous infusion at 2 week intervals for the first 3 doses and at 4 week intervals thereafter.

The belimumab final drug product for intravenous (IV) use has utilised 2 formulations during its clinical history. Belimumab in formulation buffer 06-A was used in Phase I and II clinical studies while formulation buffer 06-B was used for Phase III clinical studies and is the commercial product formulation.

The drug product comprises lyophilized 80 mg/mL belimumab in citrate, sucrose, polysorbate 80, pH 6.5. Formulation development for the Phase III and commercial drug product consisted of a buffer and pH screen, bulking agent/cryo-protectant/lyo-protectant screen and a polysorbate 80 concentration screen.

The physicochemical and biological properties of belimumab BDS and reconstituted drug product have been analysed. Since the drug substance and reconstituted drug product solutions differ only in the concentration of belimumab , the properties of the reconstituted drug product are similar to those of the drug substance.

Specifications

The proposed acceptance criteria for belimumab fixed dose product (FDP) are based on TGA adopted EU guideline[1] and were derived from statistical analysis of release testing results for lots manufactured at the commercial site and scale, as well as stability data generated at recommended (2-8°C with protection from light) and accelerated storage conditions. In addition, clinical experience and analytical method performance were also considered.

[1]ICH Topic 6 B. Note for Guidance on specifications: Test procedures and acceptance criteria for biotechnological/biological products. http://www.tga.gov.au/pdf/euguide/ich036596en.pdf

With respect to the proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product, appropriate validation data have been submitted in support of the test procedures.

Some changes were made to the proposed commercial specifications from the previous versions used to release Phase III clinical material.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The available data indicate that belimumab is stable in the vial after reconstitution for up to 8 hours when stored at 2-8°C. Belimumab is also stable over an 8 hour period at ambient conditions when diluted with normal saline in polyvinylchloride and polyolefin IV bags. If not used immediately the reconstituted belimumab solution should be stored refrigerated at 2-8°C. The total time from reconstitution of belimumab to completion of infusion should not exceed 8 hours. The product is not photostable. The proposed shelf life is 3 years when stored at 2-8°C.

Bioavailability

Biopharmaceutic data are not required for this product.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA. The evaluation report(s) are attached.

Issues of concern

A number of deficiencies and other issues requiring resolution before the product could be recommended for approval were identified during the evaluation and have been referred to the applicant for comment or resolution.

The following have yet to be addressed to the satisfaction of the evaluator:

1. The relative potency acceptance criteria for FDP appear to be quite wide. This raises questions about the protein concentration and purity of the final antibody preparation. *The sponsor has agreed to follow the advice of the evaluator and use the narrower limits determined from manufacturing batch release data.*

2. On 28 July 2011 TGA Good Manufacturing Practice (GMP) clearance had not been obtained for all manufacturing sites. It was anticipated that clearance would be obtained by 1 August 2011. On 1 August it was reported that Active Pharmaceutical Ingredient (API) manufacture was not covered by any of the clearance applications submitted by the sponsor.[2]

[2] Sponsor comment: "This issue has now been resolved."

III. Nonclinical findings

Introduction

Background and nonclinical evidence for efficacy

Belimumab is the first drug proposed for registration that targets a TNF ligand involved in B cell homeostasis. B lymphocyte stimulator (BLyS) protein was identified relatively recently (1999), by the group who subsequently developed belimumab as an antibody to the active (soluble) form of BLyS (also known by several other names, including B cell Activating Factor belonging to the TNF Family (BAFF)). While studies have shown that BLyS promotes the survival of (mainly) naive B cells, the role of and interactions between BLyS and other ligands involved in B cell homeostasis, including APRIL (A Proliferation inducing ligand) and TWEAK (TNF-like weak inducer of apoptosis) are not completely understood.[3]

In published *in vivo* studies, BLyS was found to form heterotrimers with a splice variant of itself as well as with APRIL but, as mentioned above, the roles of these and the potential effects of belimumab on their activity is not understood and these aspects were not considered for this application. Overall, the nonclinical pharmacology information on the role and function of BLyS was somewhat limited but it appears that research into the area of B cell homeostasis including the role of BLyS and other TNF ligands is on-going.

Evidence for the involvement of BLyS in systemic lupus erythematosus (SLE) is mainly based on published findings that mice over-expressing BLyS develop an autoimmune phenotype; and that BLyS levels are elevated in patients with SLE, which are thought to result in increased levels of B cells (including abnormal B cells) and of B-cell-derived antigens. It is expected that a reduction in the population of immature B cells by belimumab will reduce the down-stream B cell populations and therefore the levels of abnormal B cells and antigens derived from these.

There were no nonclinical studies that directly investigated the efficacy of belimumab in models of SLE. However, a reduction in lymphoid tissue B cells and to a lesser extent in peripheral blood B lymphocytes was found in normal monkeys and mice given belimumab. These effects were relatively mild and complete or near complete depletion of B cells was not observed in any of the nonclinical studies even at belimumab serum concentrations markedly (more than 1000-fold) in excess of the *in vitro* IC_{50} at BLyS. There was also no or only minor inhibition of circulating immunoglobulin levels in the nonclinical program with belimumab.

A possible reason for the relatively weak-moderate pharmacological effects of belimumab in the nonclinical studies could be because BLyS alone has only a minor role in B cell homeostasis in normal animals. As noted above, the role of other mediators in B cell homeostasis and the possible consequences of BLyS inhibition on these was not explored for this application. In addition, nonclinical studies in animals with elevated BLyS and/or B cell levels were not conducted.

The effect of belimumab on endogenous BLyS levels was explored only after treatment ceased in the post-partum phase of a study in pregnant monkeys. These were close to or below the assay limit of detection (LOD 0.023 ng/mL) at baseline and during the time when exposure to belimumab was high, and showed a transient overshoot (up to about 1

[3] Review by Bossen C and Schneider P. 2006. BAFF, APRIL and their receptors: structure, function and signalling Review Semin Immunol, 18(5): 263-75).

ng/mL before returning to baseline levels) when belimumab was no longer detectable in serum. The investigators noted that free BLyS would only be expected to be measurable once belimumab was no longer present in circulation and prior to complete repopulation of B cells bearing BLyS receptors. A similar pattern has reportedly been observed in patients with SLE treated with the B cell depleting agent rituximab. As mentioned above, the nonclinical program did not include studies in animals with elevated BLyS levels and there were therefore no studies addressing the effect on previously elevated BLyS levels and B cell numbers once treatment with belimumab ceased. There were also no investigations of specific B cell subsets that survived belimumab treatment.

In monkeys with normal BLyS levels and normal B lymphocyte counts, the inhibitory effect of belimumab on lymphoid tissue and on peripheral lymphocyte counts was slowly reversible once treatment ceased and there was some evidence that BLyS levels returned to normal once lymphocyte numbers re-established. Belimumab induced depression of B lymphocytes was slow to develop (observed after 3 months but not 4 weeks of treatment at a given dose) and did not increase with increasing dose across 5-50 mg/kg IV, despite serum drug concentrations increasing with dose. The belimumab-BLyS time and dose response curve was not sufficiently explored in non-clinical studies to allow comment on this aspect.

Specificity of action. Secondary and safety pharmacology studies

Conventional secondary and safety pharmacology studies were not conducted to investigate the potential range of target organs for belimumab. These were not wholly warranted because belimumab was specifically engineered to bind to and neutralise BLyS and is not expected to interact with other molecules. Belimumab binds with high affinity to the soluble but not the membrane-bound form of BLyS, which is reportedly expressed as a membrane-bound protein on cells of myeloid origin including normal monocytes, macrophages, dendritic cells and bone marrow stromal cells and is released as an active soluble form following proteolytic cleavage. Distribution studies submitted for this application provided some reassurance that BLyS binding sites are limited to tissues with cells of B cell lineage. A tissue cross-reactivity study showing no off-target binding sites for belimumab also suggested that its actions are likely to be restricted to cells in which BLyS and its receptors are expressed. Relatively limited findings in the toxicity studies in monkeys (up to 6 months) also provide some reassurance that long-term inhibition of BLyS does not substantially disrupt physiological systems other than those associated with B lymphocytes.

Studies were not conducted to determine if belimumab affects the capacity to mount a normal humoral response. However, impairment of primary responses to antigens would be expected given that the targeted effect of belimumab is on immature B lymphocytes.

Species relevance for nonclinical studies with belimumab

In addition to defining the interactions between belimumab and BLyS and/or BLyS receptors, the primary pharmacology studies established the cynomolgus monkey as a relevant species in which to conduct nonclinical studies. Similarities between cynomolgus monkey and humans were demonstrated in terms of:

- Homology (98%) in the amino acid sequence of BLyS (including 100% homology at the receptor binding site) from either species;
- Similar BLyS distribution pattern (limited to B cells and lymphoid tissues);
- Similar belimumab binding affinity for BLyS from either species

- Similar potency of BLyS derived from either species (assessed in mouse splenocyte expansion assay)
- Similar belimumab pharmacokinetics profile between humans and monkeys

Belimumab was only weakly immunogenic in monkeys, with the majority of animals remaining adequately exposed to belimumab for the duration of the studies (see table on exposure comparisons, below).

Belimumab was tested for up to 6 months in a single non primate species (cynomolgus monkeys) but it was fatal after 1 or 2 doses in mice, rats, guinea pigs and rabbits, presumably because of extreme hypersensitivity to the human protein. This justifiably rules these species out as suitable models for toxicity tests of belimumab. The hypersensitivity response was dose-dependent in mice (which also developed a strong anti-belimumab antibody response), and was associated with activation of complement in guinea pigs. The use of one species is acceptable for this application (see below under 'Toxicity studies')

No other studies investigated the effect of belimumab on elements of the immune system other than B lymphocytes but it is recognised that such studies are more appropriately performed with belimumab in humans than in animals. It is noted that precautionary information relating to hypersensitivity reactions in humans is given in the Benlysta PI.

Pharmacokinetics

Pharmacokinetic parameters for belimumab were typical for a large protein. It has a long half life and small volume of distribution (suggesting localisation mainly in the plasma compartment and the interstitial fluid spaces of more permeable tissues) and would be expected to undergo metabolism via proteolysis rather than usual metabolic processes. Its clearance rate is lower than the glomerular filtration rate, suggesting little clearance by the renal route. Basic parameters after a single or multiple doses are similar in monkeys and humans, as shown below in Table 1.

Table 1. Basic PK parameters in monkeys and humans

	Cynomolgus monkey	Human
Cl (mL/kg/day)	5.5-7.2	5.6-7.3
Vss (mL/kg)	67-126 mL/kg	69-112 mL/kg
$t_{½}$ (days)	7.1-16	8.5-14

CL=Clearance; Vss=Volume of distribution at steady state; $t_{1/2}$=half-life

Toxicology

The potential toxicity profile of belimumab was investigated in two studies in cynomolgus monkeys. The dosing regimen (weekly or fortnightly), route of administration (short IV infusion), duration (up to 6 months) and exposure levels (up to 12 times the expected human area under the plasma concentration time curve (AUC), see Table 2 below) adequately mimicked or exaggerated conditions under which belimumab is proposed to

be used in humans. While the duration of human treatment with belimumab has not been specified, 6 month studies in monkeys are usually acceptable for toxicity tests of drugs proposed for chronic use in humans. Doses of 5, 50 and 150 mg/kg/dose were used for both the 4 week and the 3-6 month monkey study, which provided information on whether increased duration of dosing was association with the development of new toxicities and/or exacerbation of toxicities that developed over a shorter period. Both studies included recovery periods, with the duration (up to 8 months after treatment in the 6 month study ceased) adequately covering the time taken for belimumab to become undetectable once treatment ceased.

Estimated exposure levels in monkeys during the toxicity studies and a comparison of expected human exposure to belimumab are tabulated below.

Table 2. Exposure comparisons between monkeys and humans (ratios)

Monkey studies of 4 weeks or 6 months duration	Doses (mg/kg/dose)	*C_{max} (µg/mL)	*$AUC_{0\text{-}24\ h}$ (µg.day/dose)	Exposure ratio** C_{max}	Exposure ratio** AUC
	5	153	2868	0.5	1
	15	472	9459	1.5	3
	50	1713	37145	5.5	12

C_{max}=peak plasma concentration; $AUC_{0\text{-}24\ h}$ = the area under the concentration-time curve calculated by linear trapezoidal rule from time zero to 24 h. *Values are actual data obtained in the 4 week study and are likely to be representative of exposure in the 6 month study.

**Based on a human C_{max} value of 313 µg/mL and AUC value of 3083 µg.day/mL, obtained from the sponsor's Clinical Overview, steady state IV dosing 10 mg/kg during a 28 day interval).

Despite serum concentrations substantially exceeding the 50% inhibitory concentration (IC_{50}) for BLyS or for BLyS-BLyS receptor binding (up to 97 nM), belimumab had relatively mild effects in monkeys and the use of higher doses was probably possible. Nonetheless, exposure level at the highest dose is adequately in excess of that expected in humans and therefore effects at this dose level provide some indication of potential activity beyond doses that are just pharmacologically effective. The comparable half life of belimumab in cynomolgus monkeys and humans and the more frequent dosing interval used in the monkey studies ensured exposure in animals was continuous during the non-dosing periods, with levels likely to have remained greater than those in humans during the non-dosing period.

The effects of belimumab in monkeys were mostly consistent with its pharmacological activity, with the main observed effects being B lymphocyte inhibition and lymphoid depletion. The tissue inflammatory infiltrate profile in treated monkeys appeared to be much more extensive and severe than in controls and individual treated monkeys appeared to have greater susceptibility to bacterial infection. While it was impossible to quantitate these effects and associate them conclusively with treatment because of the small numbers of animals, an effect of belimumab is plausible given its desired effect is to inhibit elements of immunity.

Findings of thyroid gland degeneration and renal tubular regeneration and mesangial thickening in individual treated monkeys may have been related to treatment but again it was impossible to make definitive conclusions given the small number of animals. It is

anticipated that such effects can be monitored clinically and would not preclude registration.

Histopathology investigations of IV injection sites in monkeys suggested potential for localised, reversible irritation and tissue damage.

Carcinogenicity and genotoxicity

Nonclinical studies to address potential carcinogenicity with large proteins, particularly human-derived, are usually not feasible and genotoxic activity with such molecules is not anticipated. As with other agents that target the immune system, there is a possibility that belimumab might cause tumours as a result of its effects on the immune system. This possibility was not explored in animal studies and it is not essential that such studies be conducted, particularly given the lack of a suitable animal model in which valid studies can be done. However, the theoretical risk of carcinogenicity should be considered.

Reproductive toxicity

A study investigating the potential effect of belimumab on embryofetal and postnatal development in cynomolgus monkeys was justifiably conducted on the basis that women of child-bearing potential constitute a large portion of the SLE patient population. However, specific studies were not done to investigate the effects of belimumab on fertility, including implantation, on the basis of:

- a lack of evidence for belimumab binding to reproductive tissues;
- a lack of effect on oestrus cycles in female monkeys in the repeat dose toxicity studies (although this was not monitored formally); and
- a lack of effect on male and female reproductive tissues in the repeat dose toxicity studies in monkeys.

These observations provide indirect but cumulative support against a potential effect of belimumab on fertility. While a role for BLyS in fertility has not been investigated, studies to date have not identified a plausible mechanism that might reasonably be expected to affect fertility if BLyS is inhibited. Therefore, the lack of male and female fertility studies with belimumab was accepted.

The embryofetal and peri/post natal development study of belimumab in monkeys was comprehensive in that the treatment period covered early and late organogenesis and parturition and exposure remained substantial in mothers and infants for at least 3 months after dosing ceased. A summary of exposure in monkeys during the study and when compared with human exposure is shown in Table 3 below.

Table 3. Plasma exposure in monkeys in embryofetal and peri/post natal development study

	5 mg/kg/dose		150 mg/kg/dose	
	Week 1-17	**x Human***	**Week 1-17**	**x Human***
C_{max} (µg/mL)	142-192	45-61%	5017-5241	1.6-1.7
AUC (µg.day/mL)	674-1041	2-3	19567-27441	6-9

Based on a human C_{max} value of 313 µg/mL and AUC value of 3083 µg.day/mL obtained from the sponsor's Clinical Overview.

Belimumab was detected in fetuses from treated mothers at levels at least 4 times lower based on umbilical cord serum levels. While belimumab was found in milk, it is not certain that infants would be exposed during breast feeding because the protein is likely to be metabolised to smaller peptides before absorption in the gut.

Fetuses from mothers of either group showed reduced levels of B cells in the spleen and lymph nodes. The consequences of this for fetal and neonatal immune function could not be properly investigated given the controlled environment in which monkeys are kept but an increase in susceptibility to infection must be assumed. The effect on lymphoid tissues was reversible and was correlated with reductions in belimumab levels and increases in BLyS levels in the neonates.

An important finding of note in this study was a higher incidence of neonatal deaths in both belimumab treated groups (1 each on post-natal Days 7 and 11 at the low dose, 1 on post-natal Day 1, 1 still birth and 1 fetal death *in utero* close to term at the high dose; total of 5 neonatal deaths from 20 treated mothers that carried to term) when compared with controls (0/10). A cause of death was not determined for any of the neonates.

The sponsor suggested that the neonatal deaths were not related to treatment based on an analysis of all fetal/neonatal deaths from both the pre and postnatal parts of this study. From this analysis, the overall number of fetal/neonatal losses in the combined controls (3/21 or 14.3%) and in the belimumab groups combined (9/45or 20%) was reportedly consistent with historical control data for cynomolgus monkeys (17.8%)[4]. The sponsor further suggested that the overall incidence of low dose postnatal deaths (2 of 27 infants, or 7.4%) was consistent with historical control data for macaques (10-12%)[5,6].

The denominator of 27 (above) used by the sponsor takes into account the number of neonates from all groups in the monkey study. If the controls and treated groups are taken separately, mortality was 0/9 neonates in the control group and 3/18 neonates (or 17%) in the belimumab groups combined (approxiamtely21% if a stillbirth is included). Given the concurrent (0%) and historical control incidences (10-12%) for monkey neonatal deaths is much lower than the incidence for belimumab treated groups, a possible effect of maternal belimumab treatment either on parturition or on early neonatal survival cannot be ruled in or out. It is noted that the draft PI recommends against the use of belimumab in

[4] Hendrie TA *et al.* 1996. Frequency of prenatal loss in a macaque breeding colony. *Am J Primatol.* 40:41-53
[5] Gardin JF *et al* 1989. Maternal factors affecting reproduction in a breeding colony of cynomolgus macaques. *Lab Animal Sci*. 39:205-212.
[6] Hird DW *et al* 1975. Infant mortality in macaca mulatta: neonatal and post-neonatal mortality at the California Primate Research Center, 1968-1972. *J Med Primatol*. 4:8-22

pregnancy and a Use in pregnancy Category C is proposed, both of which were considered appropriate.

Overall comments

The nonclinical testing program has provided basic information on the pharmacological effects of belimumab and on its potential toxicity at exposure levels exceeding those expected in humans. No findings preclude the registration of belimumab however, the limitations of the nonclinical program include: lack of knowledge on the effects of belimumab in situations where BLyS or B lymphocytes are elevated; lack of studies in animal models of the proposed indication; lack of interaction studies with other treatments that might have been used for SLE; lack of studies in an altered immunological milieu; lack of studies assessing normal immune function during treatment. These deficiencies were not considered critical and/or could be addressed clinically if warranted.

Use in children

No relevant nonclinical data were provided.

Nonclinical summary and conclusions

- Limited nonclinical studies were conducted with belimumab; however, the nonclinical data package is typical of that submitted for humanised antibodies where conventional studies in multiple species are either not appropriate or not required. The quality and extent of the documentation adequately complied with current regulatory standards and guidelines relevant to belimumab.
- Pharmacology studies were limited and did not include studies in animal models of SLE or with elevated BLyS levels and there were no studies on the impact of treatment on the ability to mount a normal immune response. The precise role of BLyS in concert with other ligands involved in B lymphocyte homeostasis is not fully understood at this time and was not investigated in the context of this application.
- An acceptable range of pivotal toxicity studies with belimumab was conducted in one species, the cynomolgus monkey, which was adequately confirmed as a relevant human model in terms of responding to belimumab without overt immune toxicity associated with administration of a humanised molecule, and in terms of pharmacokinetics. Formulations used in Phase II and Phase III clinical trials, with excipient profile similar or identical to that proposed for registration were used for all nonclinical studies. “Bioequivalence” between these two formulations in terms of similar AUC and C_{max} values was demonstrated in monkeys.
- The effects of soluble BLyS (the active form) are mediated *via* 3 membrane-bound receptors: BR3, TACI and BCMA, which are expressed to varying degrees on human peripheral blood naïve, antigen-activated, plasma and/or memory B cells. BR3 is considered to be the main receptor for BLyS since mice deficient in either BLyS or BR3 have a profound loss of immature and later stage B cell populations. *In vitro*, BLyS expression was identified in human lymphoid tissues (spleen, lymph node, bone marrow) and peripheral blood mononuclear cells (PBMC) but not in T cells, macrophages, NK cells, granulocytes or non-lymphoid tissues and cells. BLyS-induced proliferation of B cells (in the presence of a B cell co-stimulator) was demonstrated *in vitro* for human tonsillar cells (by 100% at 10 ng/mL) and splenocytes from mouse or cynomolgus monkey (also at ng/mL BLyS concentrations). Increases in splenic B cell

counts and immunoglobulin (IgA) production *in vivo* were also demonstrated with BLyS administered IV (0.3 mg/kg) to mice.

- Pharmacology studies adequately characterise the interaction between belimumab and BLyS in vitro and supported the rationale for treatment in so far as a role for BLyS in SLE has been confirmed elsewhere. The antibody showed high affinity (KD 250-350 pM), slowly reversible binding to the soluble but not the membrane-bound form of BLyS from humans or cynomolgus monkeys. Belimumab inhibited the binding of human BLyS to each of its three receptors (IC50 52-97 nM) in a human B cell line (IM9 cells) and it inhibited BLyS-induced in vitro proliferation of human primary B cells (IC50 8.8 ng/mL) and mouse splenocytes (IC50 0.06 nM, 30-100 ng/mL in another assay).
- In in vivo studies, belimumab (≥ 0.15 mg/kg IV) given concomitantly with exogenous BLyS offset BLyS-associated increases in splenic B cell counts and IgA levels in mice; while in a toxicology studies in monkeys belimumab was associated with reduced (by up to 70%) peripheral blood CD20+ (total B cells) and CD20+/CD21+ (mature B cells) counts from 3 months after fortnightly IV dosing with 5, 15 and 50 mg/kg. Depression of peripheral B lymphocytes appeared to plateau rather than increase with dose, and recovery was slow, with some animals continuing to show low B cell numbers, along with detectable serum belimumab levels, 8 months after dosing had ceased. Depression of peripheral B lymphocytes was not seen after 4 weekly injections at the same doses used in the 3-6 month study.
- The effect of belimumab on endogenous serum BLyS concentrations was determined only during the postnatal period (postpartum Day 1-365) in monkeys given belimumab (5 or 150 mg/kg IV) every 2 weeks during gestation. In controls aniimals, BLyS levels were below or close to the assay limit of detection (LOD, 0.023 ng/mL) at all times. In treated monkeys BLyS levels were close to or below the LOD up until Day 28 (low dose) or 91 (high dose) after dosing, at which time an overshoot (up to 4-7 times higher than baseline levels) was observed. BLyS levels had gradually returned to baseline by Day 182 (LD) or 273 (HD) in most animals. A similar pattern, including BLyS level over-shoot, was observed in infants from treated mothers.

  The study investigators noted that free BLyS would only be expected to be measurable once belimumab was no longer present in circulation and prior to complete repopulation of B cells bearing BLyS receptors. The above pattern was generally consistent with this scenario for individual cases.
- Conventional secondary and safety pharmacology studies were not conducted with belimumab, however, the weight of evidence from pharmacology and toxicity studies suggests little potential for direct effects outside the immune system: a study with belimumab in a wide range of tissues from humans or cynomolgus monkeys showed no evidence for cross reactivity with off-target tissues; specific monitoring in toxicology studies in monkeys showed no evidence for effects on the cardiovascular system; and findings in toxicity studies could in most cases be explained in terms of the inhibitory effect of belimumab on BLyS and subsequent B lymphocyte depression. Therefore, the absence of specific safety pharmacology studies with belimumab was acceptable.
- The capacity to mount effective immunological responses to antigens or pathogens during treatment with belimumab was not investigated. Two published studies using alternative methods to inhibit BLyS showed that primary and secondary immune responses were unaffected in monkeys. In mice, the secondary (memory) response to

a T-cell dependent antigen was unaffected by BLyS inhibition but the primary immune response (and levels of naïve B cells) was reduced markedly.

- Serum pharmacokinetics after IV administration of belimumab were adequately characterised in cynomolgus monkeys and were similar to the kinetic profile observed for belimumab in humans. After a single IV dose in monkeys, belimumab showed limited distribution (steady state volume of distribution 66-108 mL/kg), slow clearance (5.6-6.7 mL/kg/day) and long terminal half life (6-14 days). Kinetics were independent of dose over the range 5-150 mg/kg and there were no gender differences. Accumulation in exposure (about 2 fold) with repeated (weekly or fortnightly) dosing was consistent with the drug's long half life.

  Belimumab was weakly immunogenic in cynomolgus monkeys: of the 124 monkeys used in the nonclinical program only 12 developed antibodies and reduced serum levels (suggesting the antibodies were neutralising) was found in only 6 of these.

- Conventional studies of the distribution, metabolism and excretion of belimumab were not conducted in animals and this was considered acceptable. There were no nonclinical interaction studies.

- Pivotal toxicology studies with belimumab comprised a 4 week study with weekly dosing and a 3-6 month study with dosing every 2 weeks, both in male and female cynomolgus monkeys given belimumab 5, 15 and 50 mg/kg by slow bolus IV injection. Exposure (AUC) to belimumab in monkeys adequately matched or exceeded (by up to approximately 12 fold) that expected in humans.

- Comprehensive in-life investigations in both studies were unremarkable, with the exception of depressed peripheral B cell counts, as described above in the 3-6 month study. At necropsy, slowly reversible lymphoid depletion was found in lymphoid tissues (spleen, lymph nodes and gut) at all doses in both the 4 week and 3-6 month studies. Flow cytometry showed relative increases in B subtypes and decreases in T cell subtypes in the spleen, with the effect on T cells attributed to decreases in B cells. Injection site reactions were observed but these were not severe.

- An increased incidence and severity of inflammatory infiltrates in multiple tissues was observed in treated monkeys and development or exacerbation of atypical bacterial infection was seen in 2 monkeys in the 4 week study.

- Findings that may have been related to treatment comprised thyroid enlargement and follicular epithelial degeneration at 50 mg/kg in the 4 week (but not 6 month) study, and renal tubular epithelial regeneration and mesangial thickening of the renal glomerulus at 15 and 50 mg/kg in the 3-6 month study.

- There was no or negligible effect on serum IgA, IgG or IgM levels and no effect on total lymphocytes, T lymphocytes, monocytes or other peripheral blood subtypes other than B lymphocytes as mentioned above.

- Nonclinical studies investigating genotoxicity or carcinogenicity are usually not conducted with human monoclonal antibodies and none was conducted with belimumab. However, there is a theoretical risk of malignancy with most immunomodulators and this should be considered with belimumab.

- An embryofetal and postnatal development study was performed in pregnant cynomolgus monkeys given IV belimumab 5 or 150 mg/kg every 2 weeks from early organogenesis (gestation day (GD) 20) until Caesarean section on GD 150 or just prior to parturition (GD 160).

- Belimumab crossed the placenta (expected for an IgG1 antibody) and was found at concentrations about 4 fold lower in umbilical cord serum and 32-36 fold lower in amniotic fluid when compared with maternal serum concentrations. There was also evidence that belimumab is excreted via milk during lactation. Belimumab remained detectable in infant serum until postnatal Day 91 (at the low dose) or 182 (at the high dose) at levels similar to or lower than corresponding levels in maternal serum. BLyS levels after treatment ceased were determined in this study, as described above.
- Fetuses delivered from treated mothers at GD 150 showed depression of B cells in the lymph nodes and spleens but similar effects were not found in 1 year old infants. Infants from treated mothers tended to have lower B cell counts in peripheral blood, higher IgG and lower IgM levels than controls during the early postnatal period but there were no group differences from 6 months of age.
- Mortality of infants at term or early in the post-natal period was greater in the belimumab groups (approximately 20%) than in concurrent controls (0) or historical controls (10-12%). Cause of death could not be established for any neonate and a possible effect of maternal treatment with belimumab cannot be ruled in or out.
- Treatment with belimumab had no effect on in-life maternal parameters and there was no evidence for adverse effects on embryofetal development or infant overt physical, neurological and physiological development for up to 1 year after birth.
- The effects of belimumab on male or female fertility including implantation, were not investigated. There was no evidence for adverse histopathology in reproductive tissues assessed in the 4 week and 3-6 month repeat dose toxicity studies.
- Nonclinical studies using the subcutaneous (SC) route of administration comprised a pharmacokinetics study showing relatively high (79%) bioavailability; a local tolerance study with dosing every 2 days for a total of 6 doses, which showed potential for irritation with repeated dosing; and an immunogenicity study with dosing at 1 mg/kg twice/week or 4 times/week for 13 weeks that showed low potential for an immunogenic response (only 1 of 10 monkeys developed (low levels of) anti-belimumab antibodies).

Conclusions and recommendations

- Belimumab was shown to inhibit soluble BLyS, a B cell survival factor, in vitro; it offset exogenous BLyS-induced proliferation of mouse B slenocytes in vivo; and was associated with slow-onset, moderate and prolonged depression of peripheral B lymphocytes in monkeys in vivo. The effect of belimumab on endogenous BLyS levels was investigated only after treatment ceased in a reproductive toxicity study in monkeys, where an overshoot of baseline levels occurred once serum belimumab levels dropped.
- There were no studies of efficacy in animal (mouse) models of SLE; and a dose-response curve for the effect of belimumab on B lymphocytes was not established in animals. Therefore, demonstration of efficacy will depend on clinical data.
- Toxicology studies were limited to one species (monkeys) due to practical constraints. Belimumab exposure multiples (AUC, Cmax) and treatment duration (up to 6 months) were adequate. There were few findings other than partial depression of B cell numbers, which reversed gradually after the cessation of treatment. Antibody responses against belimumab were relatively low and no anaphylaxis type reactions occurred in monkeys,

- IgG levels remained normal in the toxicity studies but no studies examined primary immune responses to infection.
- Equivocal findings of thyroid gland enlargement and follicular epithelial degeneration, renal tubular epithelial regeneration and mesangial thickening of the renal glomerulus may warrant specific consideration in post market studies should belimumab be approved for registration.
- No carcinogenicity studies were conducted due to practical limitations. Carcinogenic potential will require on-going clinical surveillance.
- Reproductive toxicity studies showed transfer of belimumab to the fetus and depression of B cell numbers as well as altered immunoglobulin levels in the offspring. Treated mothers had a higher incidence of early neonatal deaths and a possible association with belimumab treatment cannot be ruled out.
- Belimumab is not recommended for use in pregnancy; Pregnancy category C is suggested for this drug.

Toxicological assessment of belimumab was adequate and revealed no findings that would preclude the registration of this drug.

IV. Clinical findings

Introduction

The belimumab clinical development program for SLE consists of 4 controlled studies.

A single Phase I multicentre, double blind, dose escalation study (**LBSL-01**) in which 70 adult subjects with SLE in the USA received 1 of 4 weight-tiered doses (1, 4, 10, 20 mg/kg) of belimumab or placebo, as either a single infusion or 2 infusions (21 days apart). This study was used to inform the dose selection for the subsequent Phase II dose ranging efficacy study.

The Phase I study was designed to evaluate safety, tolerability and pharmacokinetic (PK)/pharmacodynamic (PD) parameters and did supply efficacy information for this submission.

A single Phase II trial (**LBSL-02**) conducted in 449 adult subjects (476 randomised) with active SLE in the USA and Canada. In this study, belimumab was given at doses of 1, 4 and 10 mg/kg (or placebo) in combination with the standard of care treatment for 48 weeks. The final efficacy assessment was performed at 52 weeks. An extension period was included in this trial whereby subjects could continue to receive belimumab therapy for an additional 24 weeks. For the extension phase of the trial, placebo plus standard of care subjects could subsequently receive belimumab at 10 mg/kg, while subjects who previously receiving 1 and 4 mg/kg of belimumab could remain on that dose or switch to 10 mg/kg. Furthermore, patients could optionally continue to receive treatment with belimumab 10 mg/kg in the continuation phase if they had responded to this treatment in the double blind treatment phase.

The results of **LBSL-02** were used to inform the design of the Phase III program including the selection of an appropriate patient population and the primary efficacy endpoint. However, no clear dose response was observed in the Phase II trial but the sponsor claims that there was a trend towards improved efficacy with the 10 mg/kg dose, so that belimumab doses of 1 mg/kg and 10 mg/kg were evaluated in the Phase III studies. The

failure to demonstrate a clear dose response relationship with belimumab is a significant deficiency of the clinical trial program and the sponsor has only assessed a limited dose range between 1 and 10 mg/kg. The results from **LBSL-02** were not included in the integrated discussion of efficacy results across studies or in the pooled analyses (such as those performed to evaluate subgroups and secondary endpoints) because there are major differences in study design including subject population, primary endpoint and concomitant medication controls between the Phase II and III studies.

Two Phase III randomised, double blind, placebo controlled, repeat dose studies have been conducted in subjects with clinically active, autoantibody positive SLE (**HGS1006-C1056** and **HGS1006-C1057**, henceforth referred to as **C1056** and **C1057**, respectively).

Study **C1056** involved 819 treated adult subjects (826 randomised) with active, autoantibody positive SLE recruited within North America, Central America and Europe. Belimumab was administered at doses of 1 and 10 mg/kg (versus placebo) in combination with standard of care for 72 weeks. The primary efficacy endpoint was assessed at Week 52 and efficacy was further evaluated through to 76 weeks. This study is also referred to as the BLISS-76 study in certain communications and publications. After completing this study, subjects could optionally receive belimumab treatment in continuation studies; either HGS1006-C1066 [**C1066**] for US subjects or HGS1006-C1074 [**C1074**] for non-US subjects.

Study **C1057** involved 865 treated adult subjects (867 randomised) with active, autoantibody positive SLE from the Asia-Pacific region, South America and Eastern Europe. Again, belimumab was administered at doses of 1 and 10 mg/kg (versus placebo) in combination with s but for a slighter shorter but clinically meaningful period of 48 weeks. The primary efficacy endpoint was assessed at Week 52. This study is also referred to as the BLISS-52 study in publications. After completing this study, subjects could optionally receive continued belimumab therapy in the open-label extension Study **C1074**.

The open-label extension studies are ongoing and are intended to provide the option of continued therapy to subjects who are responding and to collect long term safety data with belimumab. However, the lack of a parallel control group to the open-label extension studies limits the ability to draw conclusions regarding efficacy.

The Phase II and III studies in patients with SLE are well controlled and adequate in design to gauge the risk: benefit of belimumab in treating adult subjects with active SLE. In particular, the method of analyses was pre-specified in the protocols and the statistical plans. Furthermore, the Phase III studies were well powered and the primary endpoint was statistically controlled for multiple comparisons. For all of the trials, the control group also received standard medical care so any benefit of belimumab is demonstrated over and above the standard of care. For the Phase III studies, the standard of care was more flexible in the first 6 months but medication restrictions were required thereafter. The patients recruited into the Phase III trials were well defined as having significantly active SLE and were generally positive for antibodies against either Anti-nuclear antibody (ANA) or double stranded DNA antibody (dsDNA). As SLE is a heterogeneous condition, this limits the generalisability of the results to the wider population of SLE patients that may be cared for in Australia. The target population identified for the Phase III trials consisted of adult subjects with a clinical diagnosis of SLE according to the American College of Rheumatology (ACR) criteria, who had currently active SLE disease defined as a Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) Systemic Lupus Erythematosus Disease Activity index (SLEDAI) score ≥ 6 at screening and who were positive for autoantibodies, defined as ANA (titre ≥ 1:80) and/or anti-dsDNA (≥ 30 IU/mL) at 2 time points prior to randomisation. These inclusion criteria were based on data from

the Phase II trial (**LBSL-02**) that identified these subjects as those who responded most favourably to treatment with belimumab relative to placebo plus standard of care.

Prior to the commencement of the Phase III studies, the sponsor discussed and agreed with health regulatory authorities in the USA and Europe about the design of the trials, appropriateness of the primary efficacy endpoint and the subject population to be recruited. The primary efficacy endpoint for the Phase III trials was a sponsor developed composite measure, referred to as the SLE Responder Index (SRI). Although novel in nature, the endpoint appears to be soundly based on evidence and clinical practice experience. It is additionally supported by the data from the Phase II trial (**LBSL-02**) and is also consistent with the FDA draft guidance for the development of drugs for SLE (March 2005). Furthermore, it was agreed with FDA and European Medicines Agency (EMA) at scientific advice meetings prior to the commencement of the Phase III studies, as well as via a Special Protocol Assessment (SPA) agreement with FDA. The SRI has 3 equally weighted measures which includes an objective measure of the reduction in global disease activity (a reduction in the SELENA SLEDAI score of ≥ 4 points), and 2 measures to ensure that the improvement in disease activity is not offset by a worsening of the subject's condition overall (no worsening [defined as a < 0.3 increase] in the Physician's Global Assessment [PGA]), or a worsening in any specific organ system (no new BILAG A or 2 new B flares). To confirm the robustness of the primary endpoint evaluation, the sponsor also assesses each efficacy endpoint individually.

GCP aspects

All studies in the belimumab clinical development program were conducted in accordance with the principles of Good Clinical Practice (GCP) and compliance with ethical requirements was met. Protocol deviations involved < 10% of subjects in the 4 SLE clinical trials, were clearly articulated and were equally distributed among the active and control treatment groups.

Pharmacokinetics

Introduction

The PK of intravenous belimumab was assessed in 412 subjects in two Phase I studies (one in subjects with SLE [HGS1006-**LBSL-01**] and one in healthy subjects [HGS1006-**C1058**]), one Phase II [HGS1006-**BSL-02**] and two Phase III studies in subjects with SLE [HGS1006-**C1056** and HGS1006-**C1057**]. The submission also includes PK data produced in subjects with rheumatoid arthritis (RA) and after SC injection of belimumab but these will not be discussed in this report.

A complete PK data profile was collected from subjects involved in Phase I studies (**LBSL-01** and **C1058**) and a sparse sampling approach to PK assessment was used in the subsequent Phase II and III studies. Table 4 outlines the main PK parameters for belimumab at the 10 mg/kg dose (which is the sponsor requested dose for approval) obtained from the Phase III trials in subjects with SLE.

Table 4. Summary of Population PK Parameters

PK parameter	
Distribution half-life	1.8 days
Elimination half-life	19.4 days
Clearance	215 mL/day (3.2 mL/kg/day)
Steady-State Volume of Distribution	5.3 L (80 mL/kg)

Validated assays were used to determine drug concentrations and appropriate methods were used in the PK analysis.

Single dose PK study in healthy subjects

The objectives of Study [**C1058**] were to obtain the full PK data for both IV administered belimumab (M13/06-C, liquid formulation) and the SC injection (M16/06-C, liquid formulation) and to estimate that absolute bioavailability of subcutaneous administration. The PK data was obtained from 17 healthy subjects after the IV administration of 100 mg of belimumab. Subjects ranged in age from 18 to 63 years (mean 38.5 years). Most (72%) were of Caucasian ethnicity, with most of remainder subjects being either of Hispanic or Latino origin. There was approximately equal gender allocation (9 females and 8 males).

The results demonstrated that belimumab administered by IV infusion has biphasic kinetics with a volume of distribution close to that of the volume of plasma (36 mL/kg) and a steady state volume of distribution of approximately one quarter of the extracellular volume (63 mL/kg). This indicates that belimumab localises primarily to the plasma and to the more permeable tissues of the interstitial fluid compartment. The mean C_{max} and area under the plasma concentration time curve from time zero to infinity (AUC_{∞}) were 36.7 µg/mL and 413 day.µg/mL, respectively. The mean clearance was 3.3 mL/kg/day and the elimination half-life was 13.5 days.

Subsequent PK studies have identified moderate differences in some of the main pharmacokinetic parameters in healthy subjects compared to those subjects with SLE (see section *Single and multiple doses PK in subjects with SLE* below), particularly with respect to clearance (which was 2 fold lower than in the Phase I study of subjects with SLE [**LBSL-01**]), elimination half-life (which was about 2/3 of the half-life found in [**LBSL-01**) and a slightly smaller volume of distribution. The reasons for these differences have not been fully elucidated but are unlikely to be clinically relevant given that belimumab therapy will not be administered to healthy subjects outside of PK studies.

Single and multiple doses PK in subjects with SLE

Study **LBSL-01** was a Phase I trial performed in subjects with SLE. There were a total of 70 subjects in 8 different cohorts; 57 of which received IV belimumab and 13 were given placebo infusions. Belimumab was administered as either a single or double dose (21 days apart) in escalating doses of 1, 4, 10, and 20 mg/kg (involving 7, 7, 7 and 6 subjects,

respectively). Overall, 93% of the subjects were female; with 44% of subjects being White, 53% Black/African-American and 4% Asian. Subject ages ranged from 22 to 80 years.

Similar to the profile seen in healthy subjects, belimumab initially distributes to the plasma space (mean central compartment [V1] of 45 to 53 mL/kg, distribution half-life ($t_{1/2},\alpha$) of 1.0 to 1.8 days), before further distribution to the more permeable tissues of the interstitial fluid compartment (mean steady-state volume of distribution [Vss] of 73 to 112 mL/kg, mean terminal elimination half-life [$t_{1/2},\beta$] of 8.5 to 11.3 days). Clearance (CL) of belimumab after a single IV dose (6.9 – 7.3 mL/kg/day) was a small fraction of normal the glomerular filtration rate, indicating that renal clearance is unlikely to be a major contributor. Over the dose ranges studied, there was a dose proportional rise in C_{max} and AUC_{∞}.

A total of 26 subjects received a second dose of belimumab at Day 21 (6, 7, 7 and 6 subjects received 1, 4, 10, or 20 mg/kg, respectively). There were no clinically or statistically significant differences in PK parameters after a second dose of IV belimumab given 21 days after this initial dose. There was a 9% drug accumulation based on maximum serum drug concentration (C_{max}) following the second dose. This is an expected result given the known rates of elimination and is unlikely to have any clinical consequence.

Dose-ranging PK studies in subjects with SLE

LBSL-02 was a Phase II dose ranging study that evaluated the safety, tolerability and efficacy of belimumab in subjects with SLE. Subjects received belimumab via IV infusion on Days 0, 14, 28 and then every 28 days for the remainder of 52 weeks. There was an optional 24 week extension whereby subjects received belimumab at 1, 4, or 10 mg/kg. In total, 338 subjects received belimumab in doses of 1, 4, or 10 mg/kg (113, 114, or 111 subjects respectively; 111 received placebo). In the analysis, 331 subjects were considered evaluable for PK data in the initial 52 week trial and 345 subjects were considered evaluable in the 24 week extension. The PK data obtained is summarised in Table 5.

Table 5. Mean Peak and Trough Belimumab Concentrations in Phase II and III Studies

PK Parameter	Dose Group 1 mg/kg	4 mg/kg	10 mg/kg
Day 14 peak concentration (µg/mL)			
Phase 2 (LBSL02)	27.2	104	246
Phase 3 (C1056)	32.5	-	332
Phase 3 (C1057)	32.9	-	342
Steady-State peak concentration (µg/mL)			
Phase 2 (LBSL02)	NA	NA	NA
Phase 3 (C1056)	30.0	-	336
Phase 3 (C1057)	31.5	-	333
Day 56 trough concentration (µg/mL)			
Phase 2 (LBSL02)	2.45	12.3	34.9
Phase 3 (C1056)	6.25	-	69.5
Phase 3 (C1057)	4.72	-	56.0
Steady-State trough concentration (µg/mL)			
Phase 2 (LBSL02)	2.26	11.4	29.3
Phase 3 (C1056)	5.53	-	70.9
Phase 3 (C1057)	3.75	-	54.8

NA: not assessed.

PK data was also obtained from the two Phase III efficacy trials (**C1056** and **C1057**). Both of these trials were multi centre, randomised, double blind, placebo controlled trials of 76 weeks and 52 weeks, respectively. Belimumab (1 or 10 mg/kg) or placebo were administered by IV infusion in the same regimen utilised in **LBSL-02**. In both Phase III studies, serum belimumab measurements were collected:

- Prior to the first dose of belimumab or placebo on Day 0
- Between 0-4 hours following the completion of the second infusion on Day 14 (Week 2) and eighth infusion on Day 168 (Week 24)
- Prior to dosing on Day 56 (Week 8) and Day 364 (Week 52, C1056)

If subjects were participating in the open label extension studies, samples were to be obtained prior to the subjects' first dose on the continuation protocol. This was on Day 364 (Week 52) for subjects involved in Study **C1057** and Day 532 (Week 76) for patients recruited into Study **C1056**. In total, 1132 subjects received belimumab in the extension phases and 1112 subjects (538 in Study **C1056** and 574 in Study **C1057**) were considered to have data evaluable for PK interpretation. The results are summarised in Table 5.

Overall, serum belimumab peak and trough exposures were approximately dose proportional across the 1 to 10 mg/kg doses in the Phase II and III studies. Steady-state levels were achieved in the first month of the study following the loading doses on Days 0 and 14 and steady-state was reached and maintained for all dose groups in the Phase II and 3 studies. The mean peak and trough serum belimumab concentrations observed in the Phase III studies were higher (peak, 20% to 37%; trough, 1.8 to 2.2 fold) than those in the Phase II study. The reason for this difference is unclear but is not likely to be clinically relevant. The PK differences among studies are discussed further in Population PK section.

Population pharmacokinetics

Introduction

A non linear, mixed effects model describing the PK of belimumab was developed. Initially, a base model was developed using exploratory data analysis (particularly, compartmental behaviour, inter-individual and residual variability and other model factors). An extensive set of patient characteristics were evaluated for their effect as covariates on PK parameters. A total of 1512 females and 91 males were used to evaluate population PK (POPPK). Ages of subjects ranged from 18 to 80 years and weights from 36 to 165 kg. Ethnicities of subjects included White/Caucasian (53%, 856), Asian (16%, 249), Alaska Native or American Indian (16%, 258) and Black/African American (14%, 227). Covariate factors assessed included age, gender, race/ethnicity, body size, laboratory assessments reflecting hepatic function and renal function, concomitant medications, disease state and immunogenicity status. POPPK analysis included data obtained after single or multiple doses over a range of 1 to 20 mg/kg.

POPPK estimates

Belimumab PK was well described with a linear 2 compartment model with clearance from the central compartment. Following IV administration of belimumab, the distribution half-life ($t_{1/2\alpha}$) was 1.1 and 1.8 days, respectively, for the 1 and 10 mg/kg doses. The terminal elimination half-life ($t_{1/2,\beta}$) was 12.5 and 19.4 days, respectively, for the 1 and 10 mg/kg doses. The volume of distribution at steady-state was 3.7 and 5.3 L (56 and 80 mL/kg based on median weight of 66.3 kg), respectively, for the 1 and 10 mg/kg doses. The central clearance was 215 mL/day (3.2 mL/day/kg based on median weight of 66.3 kg). These results are consistent with PK results from other IgG1 monoclonal antibodies.

Effect of weight

Weight appears to be the most influential covariate identified in the POPPK studies. It was positively correlated with both clearance and the distribution phase volume of distribution (V1). At the fifth and ninety-fifth percentiles of weight, there was a 15% decrease and 30% increase, respectively in CL. V1 was decreased by 31% at the fifth percentile for weight and increased by 82% at the 95th percentile. The effects on V1 were partially counteracted by an inverse correlation with body mass index (BMI). However, the weight-based dosing regimen has attempted to address these PK differences. Table 6 outlines the PK parameters identified for each quartile of body weight for the 10 mg/kg dose. Overall belimumab exposure at steady-state, as described by C_{max}, AUC and trough plasma levels (C_{min}) is slightly lower in subjects with a weight < 54kg and slightly higher if weight is ≥ 75kg compared with the subjects in the interquartile range. This demonstrates that the weight based dose adjustment slightly under compensates at lower body weight and slightly over compensates at higher body weight. These differences are small (in the order of 9-25% at the extremes) and are not of clinical significance.

Table 6. Belimumab PK parameters by Quartiles of Body Weight (at 10 mg/kg dose)

Secondary Parameters	< 54 kg Geometric Mean	≥ 54 kg to < 63 kg Geometric Mean	≥ 63 kg to < 75 kg Geometric Mean	≥ 75 kg Geometric Mean
C_{max} (µg/mL)[1]	274	302	314	360
$AUC_{0-\infty}$ (day•µg/mL)	2357	2739	2819	3419
C_{min} (µg/mL)[1]	39.5	46.4	45.4	54.4
$t_{1/2,\alpha}$ (days)	1.53	1.62	1.71	1.87
$t_{1/2,\beta}$ (days)	18.5	18.7	17.6	17.2
V_{ss} (mL)	4816	5009	5307	5785
CL (mL/day)	209	214	243	269

Abbreviations: C_{max}, maximum serum drug concentration; C_{min}, minimum serum drug concentration; $AUC_{0-\infty}$, area under the serum drug time-concentration curve from time 0 to infinite time; $t_{1/2,\alpha}$, half-life for the 1st phase; $t_{1/2,\beta}$, elimination half-life for the 2nd (terminal) phase; V_{ss}, volume of distribution at steady-state, CL, central clearance.

[1] C_{min} and C_{max} simulated at steady-state using population PK parameters and including dose effect on V_2 for 1 mg/kg dosing and assuming a 28 day dosing interval.

There was a statistically significant effect on POPPK from baseline haemogloblin and white blood cell count but these differences are not pharmacokinetically (defined as a change beyond -20% or +25% for the central 90% range of covariate values) or clinically relevant.

Effect of age

There was no statistically significant impact of age on belimumab PK. However, although there was a wide range of subject ages (18 to 80 years), the majority of subjects were 45 years or younger (70%, 1122) with only a small proportion of patients being aged 65 years or older (1.4%, 22). Given this, an impact of age cannot be conclusively excluded.

Effect of impaired renal function

Belimumab has been studied in only a small number of subjects with SLE and renal impairment; 261 subjects with moderate renal impairment (creatinine clearance 30-60 mL/min), 14 subjects with severe renal impairment (creatinine clearance 15-30 ml/min) and none with a creatinine clearance of <15 mL/min. There was a statistically significant effect on belimumab clearance but this effect was small and not clinically relevant. This is not unexpected given that renal elimination is unlikely to play a significant role given the large size of the antibody molecule.

Effect of impaired hepatic function

There were no statistically significant differences in belimumab PK for differences in surrogate markers of hepatic function (alanine aminotransferase (ALT), aspartate aminotransferase (AST), international normalised ratio (INR) and bilirubin) although the degree of impairment of these surrogate markers was only moderate and there was only a small number of subjects with these derangements assessed as part of these POPPK studies. In general, hepatic clearance plays little role in antibody metabolism but given the limited data available with belimumab, no conclusive recommendation can be made.

Effect of disease state

The POPPK analysis assessed the impact of variables reflecting baseline disease state on belimumab PK, including anti-dsDNA, ANA, BLyS, complement levels, C-reactive protein, immunoglobulin levels, SELENA/SLEDAI scores, albumin and degree of proteinuria. There were modest increases in clearance from increasing baseline IgG levels (18% decrease at fifth percentile and 21% increase at the ninety-fifth percentile) and decreasing albumin concentrations (20% increase at fifth percentile and 13% decrease at ninety-fifth

percentile). Significant proteinuria (≥ 2g/24 hours) resulted in a modest increase in central clearance of belimumab (14%) which is likely to result from increased protein loss (including belimumab) by damaged glomeruli. Overall, these effects are modest only and not clinically relevant.

Effect of concomitant medications

Given that belimumab is unlikely to be metabolised by the cytochrome P450 system, drug interactions with other medications that are metabolised by this system are not expected. No specific studies have been conducted to examine for these effects. The Phase II and III clinical trials were conducted in subjects receiving standard care for SLE. Subjects were receiving a wide range of concomitant medications including immunosuppressants (such as methotrexate, azathioprine, and mycophenolate mofetil), anti-malarials (such as hydroxychloroquine), corticosteroids, HMG-CoA reductase inhibitors, angiotensin-converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs and aspirin. Only corticosteroids and ACE-inhibitors had statistically significant effects on any PK parameters. Both caused small increases in central clearance that were not clinically significant. Therefore, of the concomitant medications tested there were no clinically relevant effects on belimumab PK.

Effect from pregnancy or in children

No pharmacokinetic (or other) studies have been performed in pregnancy or in subjects younger than 18 years of age to make any conclusions about any changes in PK in these subpopulations.

Evaluator's overall conclusions on pharmacokinetics

The PK of belimumab is well described with a linear 2-compartment model with clearance from the central compartment. PK parameters appear to be dose proportional across the 1 to 20 mg/kg dose range that has been evaluated. The PK parameters (based upon the population estimates of the PK model) specific to the sponsor requested 10 mg/kg dosing in the Phase III population are as follows:

- Belimumab has a distribution half-life of 1.8 days and an elimination half-life of 19.4 days, and
- Belimumab clearance is 215 mL/day (3.2 mL/day/kg based on a median weight of 66.3 kg in the overall study population) and the steady-state volume of distribution is 5.3 L (80 mL/kg based on median weight of 66.3 kg) for the 10 mg/kg dose.

Population PK parameters are summarised in Table 4. Subject or disease characteristics such as sex, age, race, disease state, hepatic and renal function have no clinically meaningful impact on belimumab PK. However, body size appears to affect central clearance and volume of distribution. These body size effects are addressed by weight based dosing strategy. SLE co-medications evaluated in population PK analyses appear to have no meaningful impact on the PK of belimumab.

Pharmacodynamics

Introduction

Pharmacodynamic (PD) endpoints were assessed as part of the Phase I trials in both healthy individuals (**C1058**) and those with SLE (**LBSL-01**) as well as the Phase II **(LBSL-02**) and 3 trials in subjects with SLE (**C1056** and **C1057**). The design details of these

studies are outlined above. Additional PD data was obtained from an open label extension trial (**LBSL-99**) in which subjects that achieved a response to belimumab in the Phase II study after 52 weeks of the follow-up, were eligible to continue on treatment for a further 24 weeks. In this trial, 296 subjects received ongoing belimumab therapy and 223 subjects were in their fourth year of treatment. Subjects received 10 mg/kg belimumab IV every 28 days in the Phase II and III as well as open label extension studies.

The PD endpoints assessed in the clinical trial program included serum immunoglobulin levels, autoantibodies related to SLE (anti-dsDNA, anti-nuclear antibodies (ANA), anti-Smith antibodies (anti-Sm), anti-RNP, anti-SSA, anti-SSB, anti-ribosomal P), complement levels and B cell populations (including subsets of B cells).

Mechanism of action

Belimumab is a fully human $IgG_1\lambda$ monoclonal antibody that specifically binds to soluble B Lymphocyte Stimulator (BLyS) which is a B cell survival factor. Therefore, belimumab prevents BLyS from binding to its receptor on mature B cells and should therefore limit B cell survival. Hence, this type of drug may be expected to reduce B cell numbers and their products (such as serum immunoglobulins, including autoantibodies) and other markers of active autoimmune disease (such as increase or normalise serum complement levels). The choice of these endpoints seems appropriate as they reflect the proposed mechanism of action (upon B cell populations) and are clinically relevant serological markers of SLE disease activity (in particular, serum complement levels and autoantibodies such as anti-dsDNA levels).

Primary pharmacology

There were no statistically or clinically significant changes seen in the PD parameters assessed in the Phase I studies **(C1058** and **LBSL-01**) after 1 or 2 doses of belimumab. This is not unexpected as clinically apparent changes in the PD parameters measured will often require more than 2 doses of therapy. In the pivotal Phase III studies (**C1056** and **C1057**), belimumab demonstrated consistent and expected PD effects, albeit with no apparent dose response relationship.

In the Phase II Study **LBSL-02,** decreases in the levels of serum immunoglobulins, autoantibodies (anti-dsDNA antibody and ANA levels), some B cell subsets and increases in serum complement levels were observed with belimumab treatment. However, no significant dose response relationship was seen over 52 weeks of treatment (over the limited examined dose range of 1, 4 and 10 mg/kg) for any of these PD parameters. The results are summarised in the Table 7.

Table 7. Summary of Belimumab PD Parameters in Study LBSL-02

Parmeter[1]	Placebo	1 mg/kg	4 mg/kg	10 mg/kg	All Belimumab	P value[2]
Serum Immunoglobulins						
IgG	2.7%	-10.4%	-8.4%	-10.1%	-9.9%	< 0.0001
IgM	-4.9%	-28.2%	-30.0%	-30.5%	-29.4%	< 0.0001
IgA	-2.6%	-11.8%	-14.4%	-15.3%	-13.9%	< 0.0001
IgE	0.0%	-28.9%	-42.9%	-33.3%	-34.0%	< 0.0001
Anti-dsDNA in subjects with ≥ 30 IU/mL	-8.6%	-28.8%	-31.6%	-29.8%	-29.4%	0.0017
Complement						
C3	-6.5%	-3.1%	0.4%	-2.8%	-2.1%	0.0362
C4	7.7%%	25.5%	22.6%	20.0%	22.7%	< 0.0001
B cells						
CD19+	7.0%	-51.7%	-39.0%	-53.0%	-49.3%	< 0.0001
CD20+	3.9%	-57.0%	-45.5%	-56.0%	-54.1%	< 0.0001
Naïve (CD20+/CD27-)	5.9%	-71.9%	-66.9%	-74.5%	-70.8%	< 0.0001
Activated (CD20+/CD69+)	-16.7%	-72.1%	-68.3%	-67.9%	-70.4%	< 0.0001
Memory (CD20+/CD27+)	-14.4%	-14.4%	7.9%	1.9%	0.0%	NS
Plasmacytoid (CD20+/CD138+)	-33.3%	-66.7%	-50.0%	-66.7%	-62.5%	< 0.0001
SLE subset (CD19+/CD27^{BRIGHT}/ CD38^{BRIGHT})	28.6%	-11.3%	-25.9%	-18.2%	-18.2%	0.0027
Plasma (CD20-/CD138+)	25.6%	24.6%	4.5%	6.5%	12.5%	NS
CD20-/CD27^{BRIGHT} Plasma	96.1%	102.9%	89.7%	65.5%	90.8%	NS

NS – Not Significant.

[1] Baseline values by dose group are provided in the source tables.

[2] All active vs placebo.

The timing and nature of the PD assessments performed as part of two pivotal Phase III clinical trials are outlined in Table 8.

Table 8. PD Assessments Performed During Phase III SLE Studies

	Study Week When Assessment Made								
Assessment	**Pre-dose**	**8**	**16**	**24**	**32**	**40**	**52**	**64**	**76**
Immunoglobulins (IgG, IgA, IgM)									
C1056	X	X	X	X	X	X	X	X	X
C1057	X	X[1]		X[1]		X[1]	X		
Anti-dsDNA, C3, C4 C1056 and C0157	Predose, Week 4, and every 4 weeks thereafter (except for Weeks 56 and 64 in C1056) through Week 52/76 Exit visit.								
Anti-Smith anti-ribosomal P, aCL (IgG, IgA, IgM)[2]									
C1056	X	X		X			X		X
C1057	X	X[3]		X[3]			X		
B cells (C1056 only)[4]	X	X		X			X		X

1 IgG only.
2 After Day 0 (pre-dose), autoantibody titers were only run on subjects that tested positive at Day 0.
3 Anti-ribosomal P only.
4 B cell populations evaluated included: CD19+, CD20+, naïve (CD20+/CD27-), activated (CD20+/CD69+), plasmacytoid (CD20+/CD138+), plasma cells (CD20-/CD138+), short-lived plasma cells (CD20-/$CD27^{BRIGHT}$), the SLE B cell subset (CD19+/ $CD27^{BRIGHT}$/$CD38^{BRIGHT}$) and memory B cells (CD20+/CD27+).

A summary of the PD results obtained from the Phase III studies (individual and pooled) are shown in the Table 9. In general, the results were similar across the two Phase III trials and unless otherwise specified, the results from the pooled data of both trials will be discussed.

Table 9. Summary of PD Parameters Phase III SLE Studies

Parameter[1]	Dose Group Placebo	1 mg/kg	10 mg/kg	P-Value[2]
Serum Immunoglobulins				
IgG				
C1056	-0.8%	-13.5%	-14.4%	<0.0001
C1057	-3.6%	-14.1%	-15.6%	<0.0001
C1056 and C1057 Pooled	-2.5%	-13.8%	-15.3%	<0.0001
IgM				
C1056	-0.47%	-28.2%	-30.8%	<0.0001
C1057	-3.2%	-28.5%	-30.0%	<0.0001
IgA				
C1056	-0.65%	-16.1%	-17.7%	<0.0001
C1057	-2.7%	-16.8%	-16.0%	<0.0001
Anti-dsDNA in subjects with ≥ 30 IU/mL				
C1056	0.0%	-26.9%	-24.6%	<0.0001
C1057	0.0%	-13.9%	-17.7%	<0.005
C1056 and C1057 Pooled	0.0%	-18.1%	-19.3%	<0.0001
C3 in subjects with low C3 (< 900 mg/L) at baseline				
C1056	2.4%	22.0%	18.9%	<0.005
C1057	2.1%	10.1%	16.3%	<0.01
C1056 and C1057 Pooled	2.2%	14.7%	17.0%	<0.0001
C4 in subjects with low C4 (< 16 mg/dL) at baseline				
C1056	14.3%	33.3%	45.8%	<0.0001
C1057	12.5%	42.9%	50.0%	<0.0001
C1056 and C1057 Pooled	12.9%	37.5%	50.0%	<0.0001
B cells				
CD19+	-10.4%	-48.2%	-48.5%	<0.0001
CD20+	-9.2%	-46.1%	-46.1%	<0.0001
Naïve (CD20+/CD27-)	-8.9%	-66.7%	-69.6%	<0.0001
Activated (CD20+/CD69+)	-15.8%	-40.5%	-45.1%	NS/ 0.0171
Memory (CD20+/CD27+)	0	50.0%	35.0%	<0.0001
Plasmacytoid (CD20+/CD138+)	-14.4%	-50.6%	-65.8%	<0.0003
SLE subset ($CD19+/CD27^{BRIGHT}/CD38^{BRIGHT}$)	6.1%	-23.7%	-38.5%	NS/ <0.0001
Plasma (CD20-/CD138+)	-0.28%	-21.6%	-34.9%	NS/ 0.0020
Short-lived plasma cells ($CD20-/CD27^{BRIGHT}$)	1.2%	-11.3%	-35.4%	NS/ 0.0012

NA: not assessed.

NS: Not significant.

[1] Baseline values by dose group are provided in the source tables

[2] P-value applicable to either dose group vs. placebo unless 2 p-values given, in which case the 1st P-value is for the 1 mg/kg vs placebo and the 2nd p-value is for 10 mg/kg vs placebo.

Autoantibodies and other immunoglobulins

The main autoantibody of interest with regard to PD is anti-dsDNA levels as this is the serological marker that most closely reflects clinically relevant SLE disease activity. In Study **LBSL-02**, in which subjects were required to have elevated anti-dsDNA levels at baseline, there was a statistically and clinically relevant decrease in the median antibody level (-29.4% in all belimumab treated subjects compared with -8.6% for the placebo group). Furthermore, a larger proportion of subjects converted from anti-dsDNA positivity to negativity (15% [24/165] in all belimumab treated subjects compared with 3.5% [2/58] in the control group). In the open label extension trial (**LBSL-99**) that followed **LBSL-02**, this proportion of responding patients increased to 30%. However, given that the extension phase was an uncontrolled, single arm study, the result should be interpreted with caution.

Similar PD results were seen in the two Phase III trials:

- In subjects who were anti-dsDNA positive at baseline, a higher proportion of subjects treated with belimumab were more likely to convert to negative serology than placebo therapy plus standard of care treated individuals (13-17% for belimumab compared with 6-8% for control treatment)
- The median percentage reduction in anti-dsDNA levels was 25-27% in C1056 and 14-18% in C1057 compared with no change in the placebo groups. Reductions were generally apparent by 8 weeks and were sustained through to 52 weeks.

However, no apparent dose response relationship for the belimumab treatment groups (in either the Phase II or Phase III trials) was observed. Although clinically relevant changes were observed, the magnitude of these PD effects was modest.

Table 10 outlines the changes in the status of other SLE-related autoantibodies during the two Phase III trials. The sponsors claim that improvements were seen in the rate of conversion from seropositive to seronegative anti-Sm and anti-ribosomal P antibodies, as well as significant reductions in the titres of anti-Sm and anti-ribosomal P antibodies. However, no statistical analysis was performed and overall numbers were generally small. Therefore it is unclear whether these improvements are a true treatment effect and the clinical significance is unclear.

Table 10. Change SLE-related Autoantibodies During Phase III SLE Trials

	C1056			C1057			Both Studies		
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290	Placebo N = 562	1 mg/kg N = 559	10 mg/kg N = 563
Anti-dsDNA[1]									
Pos to Neg	10/121 (8.3%)	23/135 (17.0%)	19/131 (14.5%)	9/159 (5.7%)	24/179 (13.4%)	31/182 (17.0%)	19/280 (6.8%)	47/314 (15.0%)	50/313 (16.0%)
Neg to Pos	7/77 (9.1%)	3/75 (4.0%)	1/74 (1.4%)	7/66 (10.6%)	6/59 (10.2%)	3/60 (5.0%)	14/143 (9.8%)	9/134 (6.7%)	4/134 (3.0%)
ANA[2]									
Pos to Neg	7/179 (3.9%)	11/196 (5.6%)	8/179 (4.5%)	5/208 (2.4%)	10/225 (4.4%)	11/228 (4.8%)	12/387 (3.1%)	21/421 (5.0%)	19/407 (4.7%)
Neg to Pos	12/18 (66.7%)	6/12 (50.0%)	16/25 (64.5%)	8/15 (53.3%)	7/13 (53.8%)	5/14 (35.7%)	20/33 (60.6%)	13/25 (52.0%)	21/39 (53.8%)
Anti-Sm[3]									
Pos to Neg	9/50 (18.0%)	9/47 (19.1%)	13/47 (27.7%)	13/70 (18.6%)	23/78 (29.5%)	29/84 (34.5%)	22/120 (18.3%)	32/125 (25.6%)	42/131 (32.1%)
Neg to Pos	0/1	0/1	0/3	0/2 (0%)	0/1 (0%)	0/2 (0%)	0/3 (0%)	0/2 (0%)	0/5 (0%)
aCL[4,5,6]									
Pos to Neg	30/82 (36.6%)	23/69 (33.3%)	22/57 (38.6%)	26/65 (40.0%)	45/81 (55.6%)	44/91 (48.4%)	56/147 (38.1%)	68/150 (45.3%)	66/148 (44.6%)
Neg to Pos	-	-	0/3	0/1	0/2	0/3	0/1	0/2	0/6
aCL IgG[4]									
Pos to Neg	21/43 (48.8%)	21/38 (55.3%)	18/30 (60.0%)	13/42 (31.0%)	42/58 (72.4%)	30/56 (53.6%)	34/85 (40.0%)	63/96 (65.6%)	48/86 (55.8%)
Neg to Pos	1/3 (33.3%)	0/8	0/7	0/4	0/9	1/14 (7.1%)	1/7 (14.3%)	0/17 (0%)	1/21 (4.8%)
aCL IgM[5]									
Pos to Neg	2/6 (33.3%)	4/10 (40.0%)	5/9 (55.6%)	3/9 (33.3%)	7/19 (36.8%)	13/24 (54.2%)	5/15 (33.3%)	11/29 (37.9%)	18/33 (54.5%)
Neg to Pos	1/40 (2.5%)	0/36	0/28	0/37	1/48 (2.1%)	0/46	1/77 (1.3%)	1/84 (1.2%)	0/74
aCL IgA[6]									
Pos to Neg	14/50 (28.0%)	7/40 (17.5%)	15/42 (35.7%)	17/37 (45.9%)	22/43 (51.2%)	26/48 (54.2%)	31/87 (35.6%)	29/83 (34.9%)	41/90 (45.6%)

Total immunoglobulin (Ig) levels or levels of Ig subtypes are reasonable surrogate markers of B cell function and therefore useful as a PD parameter of interest. They are less relevant as surrogate markers of clinical efficacy (compared with SLE-specific autoantibodies or serum complement levels) but are more useful from a safety perspective as subjects with hypogammaglobulinaemia are more prone to infections. In general, the observed PD response of Ig isotypes to belimumab treatment were modest (median decreases of 120 mg/dL for IgG [9.9%], 26.0 mg/dL [29.4%] for IgM, 35.0 mg/dL [13.9%] for IgA and 5.0 KU/L [34.0%] for IgE compared with changes in the placebo of +2.7%, -4.9%, -2.6% and 0.0%, respectively) in the Phase II trial (**LBSL-02)**. The clinical significance of these changes is not clear.

Similar effects on Ig sub-type levels were seen in the two Phase III trials (**C1056** and **C1057**) with reductions of 15.3%, 30-30.8% and 16.0-17.7% for IgG, IgM and IgA, respectively. The reductions were seen within 8 weeks of commencing treatment and were maintained at a stable level through to 52 weeks. In subjects with hypergammaglobulinaemia (total gammaglobulin levels of > 16.18 g/L), a larger proportion of subjects experienced normalisation of these levels (50% compared with 20% in placebo group). Again, no apparent dose response relationship with belimumab was seen. Importantly, from a safety perspective, 94% of all subjects maintained IgG levels above the lower limit of normal range.

Complement activity

The changes in serum complement activity observed across the clinical study program have been inconsistent. The reason for these differences is not clear. In Study **LBSL-02** there was a modest increase in C4 levels (23% compared with 7.7% with placebo) but no change in C3 levels compared with baseline. A modest proportion of subject's normalised complement levels (21% for C3 and 40% for C4) at the end of the 52 week trial. No dose response relationship for belimumab was observed. In the open label extension period (Study **LBSL-99)** a higher proportion of subjects achieved normal serum complement levels (60-70%) but the open-label nature of the study without a parallel control group makes interpretation of these results as being of clinical relevance difficult.

Belimumab treatment improved serum complement levels in subjects with low baseline levels of complement in the pivotal phase trials (**C1056** and **C1057**) as early as 4 weeks of commencing treatment, with a sustained response also evident. The improvement in C3 levels was more pronounced in Study **C1056** and improvement in C4 levels was more pronounced in Study **C1057**. In the pooled dataset analysis, the median improvements in C3 were 2.2%, 15% and 17% for the placebo group and belimumab 1 mg/kg and 10 mg/kg groups respectively. With respect to the median improvements in C4 levels, these were 13%, 38% and 50% for the placebo, belimumab 1 mg/kg and belimumab 10 mg/kg groups respectively. Furthermore, subjects treated with belimumab were more likely to achieve normal complement levels compared with placebo (17%, 26% and 38% for C3; 18%, 35%, 44% for C4; for placebo, 1 mg/kg and 10 mg/kg groups, respectively). The sponsor claims that the improvements showed a dose response relationship; however, no statistical analyses were included in this submission comparing the belimumab treatment groups against one another (only each belimumab treatment group against placebo). Moreover, the differences in the median improvements seen between the 1 mg/kg and 10 mg/kg groups are small with a difference of only 2% (15% compared with 17%, which is not a clinically relevant difference) for C3; and 12% (38% compared with 50% and of limited clinical relevance) for C4. Therefore, it is difficult to justify the requested dosing regimen on these PD parameters alone.

B cell populations

PD data for B cell populations was generated in Study **LBSL-02** and one of the Phase III trials (**C1056**). The other Phase III study (**C1057**) did not collect this data. Belimumab treatment was associated with statistically significant and clinically relevant reductions in median B cell counts (CD19+, CD20+, activated and naïve) compared with placebo in both these trials. Median percentage reductions in these B cell populations were similar across the trials (48-49% for CD19+ cells, 46-54% for CD20+ cells, 67-70% for naïve B cells and 41-70% for activated B cells).

Interestingly, there was a significant increase in the number of memory B cells in both of these trials. In Study **C1056,** the increase occurred early in the treatment period (at Week 8 by 105% and 107% for the 1 mg/kg and 10 mg/kg groups, respectively) before trending

down towards baseline by 52 weeks (although remained 50% and 35% above baseline). No change was observed in the placebo treatment group over the 52 weeks of follow-up. The reason for these changes is unclear but they are not likely to be clinically relevant.

Belimumab therapy resulted in reductions in the numbers of CD19+/CD27 BRIGHT /CD38BRIGHT B cells (which is a type of B-cell population which may possibly reflect SLE disease activity), plasma cells (CD20-/CD138+) and short-lived plasma cells (CD20-/CD27 BRIGHT). Both plasma cells (predominately residing in bone marrow and the source of most anti-infectious IgG in the body) and memory B-cells (living in the follicular region of lymph nodes) are thought to be producers of autoantibodies. CD38 is a late cellular activation marker present on B and T-cells. The term "bright" signifies high levels of expression (versus "dim" or low expression) as seen on flow cytometry.

The sponsor claims that a clear dose response to belimumab was seen for these cellular markers of interest because only the belimumab 10 mg/kg treatment group (and not the 1 mg/kg treatment group) yielded statistically significant differences compared with placebo in the median percentage change at Weeks 8, 24, and 52. The median percent reductions in CD19+/CD27 BRIGHT /CD38BRIGHT B cells in subjects treated with belimumab 10 mg/kg were 24-39% at Week 52, while placebo treatment was associated with an increase of 6%. Reductions in plasma cells were similar to those for the CD19+/CD27 BRIGHT /CD38BRIGHT B cells, while reductions in plasmacytoid cells were more pronounced (51-66% versus 14%). However, the absolute differences seen between the belimumab 1 mg/kg and 10 mg/kg groups were generally small (ranging from 13-24%), not clinically relevant and no formal statistical analyses were presented comparing the 2 belimumab treatment groups. Therefore, the claims of a clear dose response relationship, although possible, are not clear and furthermore unlikely to be of clinical significance.

Secondary pharmacology

The results concerning tolerability on relevant dynamic endpoints such as vaccination responses will be considered in the safety section.

Evaluator's overall conclusions on pharmacodynamics

In conclusion, the effects of belimumab on the PD endpoints examined in the Phase II and III controlled studies in SLE are as follows:

- Compared with placebo, belimumab led to reductions in serum IgG and anti-dsDNA levels (in those individuals with high baseline levels of these markers) and increases in serum complement levels C3 and C4 (in those with low levels at baseline), though the result for a change in C3 levels was only observed in the Phase III studies,
- In subjects who were positive at baseline for anti-dsDNA antibodies, more belimumab-treated patients converted to a negative result at Week 52 compared with placebo,
- Significantly more belimumab-treated subjects with low serum complement at baseline had normalised complement levels at Week 52 compared with those receiving placebo,
- Belimumab therapy significantly reduced the numbers of B-cells (CD19+ and CD20+) and B-cell subsets and plasma cells at Week 52. However, memory B-cells increased initially and slowly declined thereafter to baseline levels; and
- There was no clear, consistent and clinically relevant dose response relationship for belimumab with any of the PD parameters assessed.

Efficacy

Introduction

The efficacy of belimumab in adult patients with active SLE was evaluated in 3 controlled studies involving a total of 2133 subjects. The 2 Phase III studies are considered pivotal in the assessment of this submission and supportive evidence of efficacy is provided by the Phase II trial. Preliminary evidence for possible long term efficacy is presented by the open label continuation phases of the 3 main SLE studies. A summary of the controlled trials is as follows:

Phase II

Study LBSL-02 (n = 476 randomised; 449 treated): This was a randomised, double blind, placebo controlled study involving adult patients with active SLE which was conducted in the USA and Canada. Belimumab was administered IV at doses of 1, 4 and 10 mg/kg and compared to placebo infusions. All patients continued their standard of care background treatment. Study medication was given for up to 48 weeks and the final efficacy assessment was conducted at 52 weeks. Following completion of the study, patients could elect to enter an open label extension (OLE) phase whereby they received belimumab for an additional 24 weeks. For the OLE, subjects who previously received placebo infusion in the controlled phase were switched to receive belimumab 10 mg/kg, while subjects who previously received belimumab 1 and 4 mg/kg could remain on that dose or switch to the higher 10 mg/kg dose. For those subjects who previously received belimumab 10 mg/kg, they could continue to receive the same treatment (belimumab 10 mg/kg) in a continuation trial.

Phase III

Study HGS1006-C1056 (n = 826 randomised; 819 treated): This was a randomised, double blind, placebo controlled trial conducted in adult subjects with active, autoantibody positive SLE recruited from within North America, Central America and Europe. Belimumab was given IV at doses of 1 and 10 mg/kg and compared with placebo infusions. Study medication was given in combination with the background standard of care treatment for up to 76 weeks. The primary efficacy endpoint was assessed at 52 weeks but efficacy continued to be evaluated through to 76 weeks as part of the secondary endpoint analysis. After completing the controlled period of the study, subjects could enter into 1 of 2 open label continuation trials depending on their geographical location (HGS1006-C1066 [or C1066] for USA subjects, or HGS1006-C1074 [or C1074] for ex-USA subjects). In the OLE phase, patients continued to receive belimumab treatment at a dose of 10 mg/kg.

Study HGS1006-C1057 (n = 867 randomised; 865 treated): This was a randomised, double blind, placebo controlled trial conducted in adult subjects with active, autoantibody positive SLE in the Asia-Pacific region, South America and Eastern Europe. Similarly, belimumab was given IV at doses of 1 and 10 mg/kg and compared with placebo infusions. Study medication was given in combination with the background standard of care treatment for up to 52 weeks. The primary efficacy endpoint was assessed at 52 weeks. After completing the controlled period of the study, subjects could enter into an open label continuation trial (**C1074**) and continue to receive belimumab 10 mg/kg.

Table 11 provides a tabular summary of all studies assessing belimumab efficacy in subjects with SLE.

Table 11. Tabular Summary of SLE Efficacy Studies. Table continued across two pages

Type of Study	Study Identifier	Title of Report	Location of Study Synopsis and Report	Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (per group)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety, Efficacy	LBSL02.CSR	A Phase 2, Multi-Center, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Evaluate the Safety, Tolerability, and Efficacy of LymphoStat-B® Antibody (Monoclonal Anti-BLyS Antibody) in Subjects with Systemic Lupus Erythematosus (SLE)	5.3.5.1 Synopsis Report	Safety, Efficacy	Dose ranging, double-blind, multi-center, parallel group, placebo-controlled, randomized	Belimumab (IV) Placebo (IV) Treatment period: 1 mg/kg 4 mg/kg 10 mg/kg (Days 0, 14, 28 and every 28 days thereafter) Extension period: 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)	449 (336 belimumab; 113 placebo) (114) (111) (111) (88) (19) (65) (24) (64) (85)	Active SLE disease defined as SS disease activity score ≥ 4 at screening, stable SLE treatment regimen and history of measurable autoantibodies	76 weeks (52 wk treatment phase and 24 wk extension phase)	Complete; Full

Type of Study	Study Identifier	Title of Report	Location of Study Synopsis and Report	Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (per group)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy, Safety	HGS1006-C1056.CSR (Interim)	A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 76-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006, LymphoStat-B™), a Fully Human Monoclonal Anti-BLyS Antibody, in Subjects with Systemic Lupus Erythematosus (SLE)	5.3.5.1 Synopsis Report	Efficacy, Safety	Double-blind, multicenter, parallel group, placebo-controlled, randomized	Placebo (IV) Belimumab (IV): 1 mg/kg 10 mg/kg Days 0, 14, 28 and every 28 days thereafter	819 (275 placebo; 544 belimumab) (271) (273)	Active SLE disease defined as SS disease activity score ≥ 6, stable SLE treatment regimen and positive ANA/anti-dsDNA test at 2 independent timepoints	76 wks	Complete; Full[1]

Type of Study	Study Identifier	Title of Report	Location of Study Synopsis and Report	Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (per group)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy, Safety	HGS1006-C1057.CSR	A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006, LymphoStat-B™), a Fully Human Monoclonal Anti-BLyS Antibody, in Subjects with Systemic Lupus Erythematosus (SLE)	5.3.5.1 Synopsis Report	Safety, Efficacy	Double-blind, multicenter, parallel group, placebo-controlled, randomized	Placebo (IV) Belimumab (IV): 1 mg/kg 10 mg/kg Days 0, 14, 28 and every 28 days thereafter	865 (287 placebo; 578 belimumab) 288 290	Active SLE disease defined as SS disease activity score ≥ 6, stable SLE treatment regimen and positive ANA/anti-dsDNA test at 2 independent timepoints	52 wks	Complete; Full
Safety	HGS1006-C1056.VAC	Effect of belimumab on functional antibodies to influenza, pneumococcal, and tetanus vaccines	5.3.5.1 Report	Safety	Data included in row for HGS1006-C1056.CSR above					Complete; Full

Type of Study	Study Identifier	Title of Report	Location of Study Synopsis and Report	Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects (per group)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety, Efficacy	LBSL99.CSR	A Multi-Center, Open-Label, Continuation Trial of LymphoStat-B® Antibody (Monoclonal Anti-BLyS Antibody) in Subjects with Systemic Lupus Erythematosus (SLE) who Completed the Phase 2 Protocol LBSL02	5.3.5.2 Synopsis Report	Provide continuing treatment to subjects with SLE, Long-term safety and efficacy	Continuation, multicenter, open-label, non-randomized, uncontrolled	Belimumab (IV) 10 mg/kg every 28 days	296	Subjects with SLE who completed the LBSL02 trial and achieved a satisfactory response	Continuation Study	Ongoing; Interim

Dose-response studies

The dose of belimumab investigated in the Phase III studies has not been adequately delineated and justified by the preceding trials and this is a major deficiency of the belimumab clinical development program in SLE. The sponsor claims that a 10 fold dose range for belimumab was examined in the 2 pivotal Phase III studies, however that dose range was limited to 2 actual explored doses (1 and 10 mg/kg). The evaluator recommended that the sponsor be asked to consider rigorously re-examining belimumab doses ranging between 1 and 10 mg/kg in further clinical trials. The finding of the optimal dose may assist with limiting side-effects while maintaining any potential efficacy outcomes. The dose scheduling (every 28 days after initial loading) seems to be justified by the PK data.

The Phase I study (**LBSL-01**) evaluated belimumab over a broad dose range of 1, 4, 10 and 20 mg/kg. Belimumab was given IV as either a single dose (n=57) or as 2 doses 21 days apart (n=26). No clear dose response was observed for biomarker effect or for safety data. Hence, the Phase II study (LBSL-02) explored a similar broad range of belimumab doses: 1, 4 and 10 mg/kg. Again, no clear consistent dose response effect was apparent in this Phase II trial. However, the sponsor claims there was a "suggestion" (not statistically conferred) of a faster onset of treatment effect and possibly greater corticosteroid dose reductions

(and fewer dose increases) with the belimumab 10 mg/kg dose in the subgroup of autoantibody adult subjects with active SLE (post hoc analysis). A similar dose-ranging, Phase II study (LBRA-01) in adult patients with active RA also explored the belimumab dose range of 1, 4 and 10 mg/kg. This trial failed to show a consistent dose response effect as well. The sponsor justifies the limited belimumab dose examined in the 2 Phase III studies based upon the post hoc findings (listed above) in Study **LBSL-02**, which are supported by a 6 month monkey toxicology study (not supplied with this part of the submission). In the animal study, belimumab was given at doses of 5, 15 and 50 mg/kg. All doses achieved a similar level of long term (6 month) decline in CD20+ and mature CD20+/CD21+ peripheral B-cells but at 3 months there was a trend for greater decreases in peripheral B-cells at the higher belimumab doses suggesting a possible faster onset of desired biological effect.

Main clinical efficacy studies

Methods

Objectives

The primary efficacy hypothesis of the pivotal Phase III program was to establish that belimumab in combination with the standard of care for SLE was superior to placebo infusions plus standard of care in achieving a composite response for adult patients with active autoantibody positive SLE over a controlled follow-up period of at least 52 weeks. The outcome measures assessed in the clinical trials reflected this hypothesis.

Study participants

The inclusion and exclusion for the 2 Phase III studies were identical. Prospective patients were required to have a clinical diagnosis of SLE according ACR criteria and active disease defined as a SELENA SLEDAI score at baseline of at least 6. They also had to have an unequivocally positive autoantibody result (ANA titre of at least 1:80 and/or anti-dsDNA of at least 30 IU/mL) at 2 independent time points, 1 result of which had to be during the screening phase. All subjects were required to be on stable SLE treatment for at least the 30 days immediately prior to study Day 0 (further details below). Key exclusion criterion were no prior B-cell targeted therapy, no other biological drug treatment (such as abatacept and anti-TNF medications), no active lupus nephritis in the preceding 90 days, no active central nervous system (CNS) lupus within 60 days, no IV cyclophosphamide within the last 180 days, no live vaccine within 30 days of study commencement or previous organ transplant (bone marrow or major solid organ).

For Study LBSL-02, the inclusion criteria were somewhat different but the exclusion criteria were equivalent. In particular, eligible subjects were also required to have a diagnosis of SLE according to the ACR criteria, as well as “active” SLE disease defined as a SELENA SLEDAI score of at least 4 at screening (a lower threshold of baseline disease activity). Strangely, eligible patients were also required to only have a history of measurable autoantibodies and a positive result at screening was not mandatorily required. This leads to the potential enrolment of patients without significantly active SLE at baseline, as the SELENA SLEDAI score only has high degree of accuracy for defining the inclusion population when combined with other disease related features (such as positive serology). At screening in Study **LBSL-02**, a positive ANA titre of at least 1:80 was only present in 70.7% (236/334) of all subjects and less than half (49.1%, 165/334) had a positive anti-dsDNA result (titre of at least 30 IU/mL). This is a significant deficiency of this study and may explain the subsequent null result for efficacy. Further data concerning baseline demographic characteristics and markers of disease activity for the patients involved in the studies are outlined in later sections of the efficacy report.

Treatments

Subjects participating in the Phase II and 3 SLE trials were randomised to IV treatment with either weight tiered belimumab therapy or placebo infusions plus a background of standard treatment for SLE. In all 3 efficacy trials, infusions of study medication were given IV on Days 0, 14 and 28; and every 28 days thereafter. To be eligible for inclusion in the studies, patients had to be on a stable treatment regimen for their SLE for at least 30 days prior to baseline consisting of any of the following therapies alone or in combination: oral prednisone or equivalent (from 0 to 40 mg/day when used in combination with other SLE treatment; or from 7.5 to 40 mg/day alone in the Phase III studies: or from 5 to 40 mg/day alone in LBSL-02), anti-malarials, NSAID, or any immunosuppressive therapy (methotrexate, azathioprine, leflunomide, mycophenolate). For the Phase III trials, the permitted immunosuppression therapies were expanded to also include calcineurin inhibitors, sirolimus, oral cyclophosphamide, 6-mercaptopurine or thalidomide.

In the Phase II trial (LSBL-02), the treating physician could change the patient's background medication as needed throughout the study. The only treatments prohibited were cyclosporine, IV cyclophosphamide, high dose prednisone > 100 mg/day (except for flare treatment), IV Immunoglobulin and any biologic DMARD.

In the Phase III studies, the control of background medication use for SLE was more rigorous. A summary of the rules for background medication use in these pivotal trials is as follows:

- No new immunosuppressant or immunomodulatory medication (such as MMF, azathioprine, oral cyclophosphamide, cyclosporine or tacrolimus) was permitted after Day 0 nor was an increase in dose of pre-existing treatment after the Week 16 (Day 112) visit;
- No new or increase in dose of antimalarials was permitted after the Week 16 (Day 112) visit;
- No increase in the dose of corticosteroids (> 25% relative increase or > 5 mg over Day 0, whichever is higher) for SLE activity was permitted after the Week 24 (Day 168) visit. Changes in the total dose of systemic steroids was permitted during the first 6 months of the trial (Week 24/Day 168 visit) but the total systemic dose must have returned to within 25% or 5 mg over the baseline (Day 0) dose, whichever was higher, by the Week 24 (Day 168) visit. In addition, within 8 weeks prior to the Week 52 visit, no new increase in steroids over the baseline (Day 0) or Week 44 visit dose, whichever is higher, was allowed. In Study C1056, within 8 weeks prior to the Week 76 visit no new increase in steroids over the baseline (Day 0) or Week 68 visit dose, whichever is higher, was allowed;
- No new HMG-CoA reductase inhibitor was permitted after the Week 24 (Day 168) visit;
- No new ACE inhibitors or angiotensin receptor antagonists were permitted after the Week 16 (Day 112) visit; and
- No new NSAID or aspirin > 1000 mg/day was permitted after the Week 44 (Day 308) visit (unless given for < 1 week); and
- Biologic disease modifying antirheumatic drugs (DMARDs), IV Immunoglobulin, IV cyclophosphamide and plasmapharesis were prohibited at any point in time.

Subjects requiring medication changes beyond those permitted by protocol were declared treatment failures for assessment of the primary efficacy endpoint and were to have their study medication discontinued. Dose reductions or discontinuation of any background

treatments were permitted at any time in the Phase II and III trials. These concomitant medication rules were agreed with FDA and EMA prior to initiation of the studies.

Primary efficacy endpoints

The primary efficacy endpoint in the 2 Phase III studies (**C1056** and **C1057**) was the SRI response rate at 52 weeks. The SRI is a composite endpoint of 3 well established and validated tools for evaluating SLE disease activity: the SELENA SLEDAI, BILAG and PGA.

A response was defined as:

- ≥ 4 point reduction from baseline in SELENA SLEDAI score, and
- No worsening (increase of < 0.30 points from baseline) in PGA, and
- No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline at the time of assessment (at Week 52 for the primary efficacy endpoint).

The primary efficacy endpoint is based on evidence for each of the individual outcomes and supported by the data from the Phase II SLE trial (**LBSL-02**). It includes an objective measure evaluating any possible reduction in global disease activity (reduction in SELENA SLEDAI score ≥ 4) for efficacy, as well as 2 measures to ensure that the improvement in disease activity (score) is not offset by a worsening of the patient's overall condition (no worsening in the PGA) or a worsening in any specific organ system (no new BILAG A or 2 new B flares).

The SELENA SLEDAI is a global composite index that includes 24 clinical and laboratory variables which are weighted (1, 2, 4 or 8 points) by the type of manifestation rather than severity. Certain disease manifestations such as vasculitis and pyschosis receive a score of 8, while other variables such as fever and leucopenia receive 1 point. The SELENA SLEDAI score captures the patients' condition over the 10 days prior to the assessment. To be determined a responder in the Phase III belimumab studies a subject must have at least a 4 point reduction in the SELENA SLEDAI score compared with their baseline value. Published evidence using the SELENA SLEDAI score classifies increased disease activity as an increase of at least 3 points or more (consistent with a mild flare by ACR criteria), whereby a reduction of more than 3 points in the SELENA SLEDAI score has also been defined as the minimal clinically significant improvement. The ACR additionally define a severe SLE flare as a change in SLEDAI score of at least 12 points. In the belimumab clinical trial program, a reduction ≥ 4 was pre-specified as evidence of improvement and this magnitude of response is modest at the lower level of change.

The choice of the BILAG score to assess clinical "worsening" is appropriate as it provides a reasonably sensitive measure of an increase in organ specific disease activity. The BILAG measures changes in disease activity over the prior 28 days and was specifically developed to identify the need to alter a subject's treatment based on organ specific disease involvement. A total of 8 organ systems can be evaluated. In the belimumab studies, an A or 2 B flare represents either an increase in disease activity thought to be sufficient to require alteration of therapy with corticosteroids or immunosuppressants (=A), or mild problems in 2 organ systems (= 2 B).

The PGA is included in the combined response endpoint to ensure that improvement in disease activity measured by SELENA SLEDAI is not achieved at the expense of a worsening of the patient's overall condition. The PGA is a sensitive, semi-quantitative test of a patient's condition. It uses a graduated 10 cm visual analogue scale (0 to 3) on which the treating physician marks their assessment. A score of 1 corresponds to "mild" lupus disease activity, a score of 2 to 2.5 with "moderate" disease activity, and a score of 3 with

"severe" disease activity. A change of 1 unit on the PGA is considered to be associated with worsening of disease activity. An increase of ≥ 1 unit from the last assessment resulting in a PGA score of ≤ 2.5 is considered a mild-moderate flare. If the increase in PGA is to > 2.5 then it is considered a severe flare. The minimum clinically significant improvement was 6.2% or 0.62 cm on a patient global assessment 10 cm VAS scale in RA and the minimum significant worsening was 16.3% or 1.63 cm. Therefore, the sponsor assumed an increase of at least 0.3 points (> 10% on the 3-point 10 cm VAS) from baseline was considered to be a conservative estimate for the minimum clinically significant worsening.

The primary efficacy endpoint was agreed with USA and European regulatory authorities prior to initiation of the Phase III clinical trial program (and was included in the SPA agreement with the FDA). It is also consistent with the recommendations outlined in the draft guidance for industry[7]. In addition, the primary efficacy endpoint and the Phase III clinical trial design are consistent with the recommendations of the Task Force on SLE of the EULAR Standing Committee for International Clinical Studies Including Therapeutics and the recently issued EMA Committee for Medicinal Products for Human Use (CHMP) concept paper on the need for a guideline on the clinical investigation of medicinal products intended for the treatment of SLE[8].

The primary efficacy endpoints in Study **LBSL-02** were the percentage reduction in SELENA SLEDAI score at Week 24 and the time to first SLE flare (SFI) over 52 weeks of follow-up.

Major secondary endpoints

In the two Phase III studies (**C1056** and **C1057**), the major secondary endpoints were:

- Proportion of subjects achieving at least a 4 point reduction in SELENA SLEDAI at 52 weeks
- Mean change in PGA at 24 weeks
- Proportion of subjects achieving at least a 25% reduction in their baseline prednisone dose to equal to or less than 7.5 mg/day during Weeks 40-52 (only assessed in those subjects with a baseline prednisone dose > 7.5 mg/day)
- Mean change in the SF-36 PCS at 24 weeks

Because Study **C1056** had a longer duration of blinded follow-up, the response rate at Week 76 for the SRI was additionally assessed as a major secondary efficacy outcome.

In the Phase II trial (**LBSL-02**), the above 4 secondary outcome measures were also evaluated. However, for the variable that examined a significant reduction in baseline prednisone dose the threshold of response was higher in the Phase II trial compared to the Phase III studies. Patients were required to have at least a 50% reduction from baseline in their daily prednisone dose. Furthermore, the percentage of subjects achieving at least a 4 point reduction in SELENA SLEDAI at Week 52 was only examined as a post hoc analysis with study drop-out equating to treatment failure, but without the concomitant medication failure rules of the Phase III studies.

[7] Draft Guidance for Industry: Systemic Lupus Erythematosus-Developing Drugs for Treatment (March 2005).
[8] EMEA/CHMP/EWP/604040/2009.
Concept Paper On The Need For A Guideline On The Clinical Investigation Of Medicinal Products Intended For Treatment Of Systemic And Cutaneous Lupus Erythematosus.
http://www.tga.gov.au/pdf/euguide/ewp60404009en.pdf

Sample size

For each of the Phase III trials, it was estimated that 810 subjects were required to be treated (at least 270 subjects per treatment group). This sample size was to provide at least 90% power at a 5% level of significance to detect a minimum of a 14% absolute improvement in the response rate for the belimumab 10 mg/kg group (or both 10 mg/kg and 1 mg/kg belimumab groups) relative to the control group at 52 weeks. The selection of the 14% absolute improvement is based on the observed response rate in the Phase II study (LBSL-02) in which autoantibody positive subjects assuming "dropout = failure" (13%; 41% active versus 28% placebo) and the observed response rate using Last Observation Carried Forward (LOCF) imputation method (17%; 46% active versus 29% placebo). The sample size calculation uses the most conservative estimate for the standard deviation (SD) in the population (population SD = 50%) yielding an assumption of a 43% placebo response rate versus 57% belimumab response rate, with an average population response rate of 50% under the null hypothesis (active = placebo). The sample size for the Phase III trials was agreed with FDA and EMA prior to the commencement of the trials.

Randomisation

In the Phase II SLE trial **LBSL-02** subjects were randomised to 1 of 4 treatment groups in blocks of 8 with an equal allocation (2:2:2:2) ratio. Randomisation was stratified by the SELENA SLEDAI score (4-7, or ≥8) at baseline so as to balance the distribution of disease activity among the treatment groups. The 4 treatment group were belimumab at a dose of 1 mg/kg, 4 mg/kg or 10 mg/kg; or placebo infusions (all given IV).

Subjects enrolled in the Phase III trials were randomised in blocks of 6 in a 2:2:2 ratio to 1 of 3 treatment groups (1 mg/kg or 10 mg/kg belimumab; or placebo infusions). The randomisation method used for both Studies **C1066** and **C1074** employed additional stratification criteria according to the screening SELENA SLEDAI score (6-9, or ≥ 10), proteinuria level at baseline (< 2 g/24 hour, or ≥ 2 g/24 hour) and race (African descent or indigenous American descent versus all other ethnic backgrounds). The stratification selection of a higher baseline SELENA SLEDAI score in the Phase III studies was based upon the distribution finding of subjects involved in the Phase II SLE study (**LBSL-02**) whereby the mean baseline SELENA SLEDAI score was 9.9 in the autoantibody positive subgroup as well as the desire to increase the likelihood for a balanced distribution of subjects with moderate to severe disease activity, particularly those subjects with a SELENA SLEDAI score ≥ 10. This approach is prudent in the overall clinical development program. With regard to the screening stratification by level of proteinuria, this again is valid given that > 2 g/24 hour of proteinuria is clinically significant, most likely persistent and frequently associated with active nephritis. The racial stratification in the Phase III trials was selected because there is published data showing that race as an important independent factor in determining disease severity and outcomes in patients with SLE.

Blinding

For the Phase II and III trials, the blinding procedures were similar for the double blind assessment phases. Once a subject had undergone all screening procedures and had been determined to be eligible for the study, the site study personnel contacted a central service (IVRS) to randomise the subject. Belimumab for injection was supplied to the study sites as open label vials and third party unblinding was employed. The study agent was reconstituted and diluted by an unblinded site pharmacist or designee, who was independent of the study person responsible for receiving and dispensing study medication. The studies were conducted with a mechanism for drug accountability at the sites and to confirm that subjects received the correct study medication at the correct dose level. The subjects themselves and all other study site personnel remained blinded to the

study medication received and to the results of certain biomarkers (such as antibody levels, serum immunoglobulins, B cell subsets for Study **C1056**) and PK results.

Statistical methods

Primary efficacy analysis in Phase III trials

In the Phase III studies, the proportion of subjects achieving a response at 52 weeks was compared between each of the belimumab treatment groups and the control arm using a logistic regression model. The independent variables in the model included treatment groups (10 mg/kg versus placebo and then 1 mg/kg versus placebo), baseline SELENA SLEDAI score (< 9 versus ≥ 10), baseline proteinuria level (< 2 g/24 hour versus ≥ 2 g/24 hour equivalent) and race (African descent or indigenous American descent versus other). The analysis was performed on a modified intention-to-treatment (mITT) population, defined as all subjects who were randomised and treated with at least 1 dose of study medication. Any subject who withdrew from the Phase III study before the Day 364 (Week 52) visit, missed the Day 364 (Week 52) visit (± 28 day window allowed) and/or started a prohibited medication or dose prior to the Day 364 (Week 52) visit was considered a treatment failure for the Week 52 primary efficacy analysis.

For the primary efficacy endpoint analysis, a step-down sequential testing procedure was used to control for Type 1 error. Firstly, the belimumab 10 mg/kg treatment group was compared with the control group (2-sided alpha = 0.05). If that result was found to be statistically significant, then superiority of belimumab10 mg/kg versus placebo plus standard of care was established, and then the belimumab 1 mg/kg treated group was tested against control treatment (2-sided alpha = 0.05). The statistical analysis plan for the Phase III trials was agreed with FDA and EMA prior to the start of the trials.

Sensitivity analyses of the primary efficacy endpoint in Phase III trials

As a sensitivity analysis of the primary efficacy endpoint, a logistic regression model without adjustment for any covariates was used to analyse the rates of treatment responses between each of the belimumab treatment groups and the control arm at Week 52. In order to examine the robustness of the study results, an LOCF analysis (as opposed to dropout = failure), a 'completer' analysis and a per-protocol analysis were performed on the primary efficacy endpoint adjusting for the same covariates as in the primary analysis. When performed on the Phase III trial data, the sensitivity analyses supported the outcome of the primary analysis.

Subgroup analyses of primary efficacy endpoint in Phase III trials

The comparison between each belimumab treatment group and the control arm was performed for various subgroups of interest. These subgroups were pre-specified in each of the Phase III study analytical plans and included baseline SELENA SLEDAI score (≤ 9 versus ≥ 10), baseline anti-dsDNA level (≥ 30 IU/mL versus < 30 IU/mL), baseline prednisone dose level (≤ 7.5 mg/day versus > 7.5 mg/day), baseline C3 and C4 levels (normal/high versus low), race and region (North America, Western Europe (including Australia and Israel), Eastern Europe, other Americas and Asia).

The subgroup analyses of the primary efficacy endpoint in the integrated dataset were not subjected to any multiple comparison procedure but were adjusted for covariates. The independent variables in the model include the same covariates as in the primary analysis as well as a study variable (**C1056** versus **C1057**). Because subgroup analyses are based on a subset of the total population and therefore have decreased power relative to the total sample, the sponsor decided pool the data from the 2 Phase III trials for the subgroup analyses in order to provide adequate statistical power.

Analysis of the secondary efficacy endpoints in Phase III trials

The proportion of subjects who achieved at least a 4 point reduction from baseline in SELENA SLEDAI score at Week 52 and the percentage of patients who were able to reduce their average prednisone dose by at least 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through to 52 were compared between each belimumab treatment group and the control arm using a logistic regression model, adjusted for the same covariates as in the primary efficacy endpoint analysis. The prednisone reduction analysis was performed only on a subgroup of subjects who were receiving > 7.5 mg/day prednisone (or equivalent) at baseline and as such the sponsor decided to pool that data across the trials because the individual studies lacked sufficient power. In the pooled data analysis, a variable for study (**C1056** versus **C1057**) was added as an additional covariate in the model to control for potential variability between the 2 Phase III studies. An analysis of covariance (ANCOVA) model was used to compare the effect of each belimumab treatment group versus placebo plus standard of care group on the absolute and percentage change from baseline.

Participant flow

In Study **C1056**, 1353 subjects were screened to yield 826 randomised subjects, of whom 819 received at least 1 dose of study medication. In Study **C1057**, 1266 subjects were screened to yield 867 randomised subjects, of whom 865 received at least 1 dose of study medication. Table 12 outlines the patient disposition from these 2 trials, including the number of subjects completing follow-up to 52 weeks and the number and reason for withdrawal.

Table 12. Patient Disposition Phase III SLE Studies

	C1056			C1057			Both Studies		
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290	Placebo N = 562	1 mg/kg N = 559	10 mg/kg N = 563
Completed Week 52 visit and/or ongoing[1]	205 (74.5%)	216 (79.7%)	209 (76.6%)	226 (78.7%)	240 (83.3%)	241 (83.1%)	431 (76.7%)	456 (81.6%)	450 (79.9%)
Withdrawn prior to Week 52	70 (25.5%)	55 (20.3%)	64 (23.4%)	61 (21.3%)	48 (16.7%)	49 (16.9%)	131 (23.3%)	103 (18.4%)	113 (20.1%)
Subject Request	24 (8.7%)	14 (5.2%)	13 (4.8%)	7 (2.4%)	6 (2.1%)	3 (1.0%)	31 (5.5%)	20 (3.6%)	16 (2.8%)
Adverse Event	16 (5.8%)	13 (4.8%)	19 (7.0%)	19 (6.6%)	16 (5.6%)	15 (5.2%)	35 (6.2%)	29 (5.2%)	34 (6.0%)
Lack of Efficacy	15 (5.5%)	12 (4.4%)	14 (5.1%)	16 (5.6%)	12 (4.2%)	12 (4.1%)	31 (5.5%)	24 (4.3%)	26 (4.6%)
Lack of Compliance	2 (0.7%)	1 (0.4%)	2 (0.7%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	3 (0.5%)	2 (0.4%)	3 (0.5%)
Lost to Follow-up	3 (1.1%)	4 (1.5%)	6 (2.2%)	4 (1.4%)	6 (2.1%)	3 (1.0%)	7 (1.2%)	10 (1.8%)	9 (1.6%)
Protocol Violation	5 (1.8%)	2 (0.7%)	5 (1.8%)	7 (2.4%)	2 (0.7%)	3 (1.0%)	12 (2.1%)	4 (0.7%)	8 (1.4%)
Investigator Decision	2 (0.7%)	3 (1.1%)	3 (1.1%)	3 (1.0%)	2 (0.7%)	3 (1.0%)	5 (0.9%)	5 (0.9%)	6 (1.1%)
Other	3 (1.1%)	6 (2.2%)	2 (0.7%)	4 (1.4%)	3 (1.0%)	9 (3.1%)	7 (1.2%)	9 (1.6%)	11 (2.0%)
Pregnancy[2]	-	2 (0.7%)	1 (0.4%)	4 (1.4%)	3 (1.0%)	8 (2.8%)	4 (0.75)	5 (0.9%)	9 (1.6%)

[1] Including completers in C1057 and subjects who did not withdraw before the Week 52 visit in C1056.

[2] In addition, in Study C1056 1 additional subject in the 10 mg/kg group was pregnant and lost to followup and another in the 1 mg/kg group discontinued treatment due to pregnancy after Week 52, while in Study C1057 1 additional subject in the placebo group discontinued treatment due to an AE of spontaneous abortion and another in the 10 mg/kg group discontinued treatment due to investigator decision (pregnancy).

Recruitment

Subjects were recruited into the efficacy trials on the following time intervals:

- LSBL-02 (Phase 2): 6h October 2003 through to 26 June 2006

- C1056 (Phase III): 8 February 2007 through to 22 September 2009
- C1057 (Phase III): 25 May 2007 through to 19 May 2009

Conduct of the study

Both of the Phase III studies did not have any protocol amendments that would have significantly altered the conduct, results and analysis of the outcomes.

Baseline data

The baseline data outline in this section relates to the two Phase III SLE studies (**C1056**, **C1057**). Demographic and baseline activity data for the Phase II study (**LBSL-02**) is described later. Tables 13 and 14 outline the subject demographics and region of enrolment in these two Phase III studies.

Table 13. Baseline Demographics Phase III SLE Studies

	C1056				C1057				Both Studies			
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	All N = 819	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290	All N = 865	Placebo N = 562	1 mg/kg N = 559	10 mg/kg N = 563	All N = 1684
Sex												
Female	252 (91.6%)	253 (93.4%)	259 (94.9%)	764 (93.3%)	270 (94.1%)	271 (94.1%)	280 (96.6%)	821 (94.9%)	522 (92.9%)	524 (93.7%)	539 (95.7%)	1585 (94.1%)
Race[1]												
White/Caucasian	188 (68.4%)	192 (70.8%)	189 (69.2%)	569 (69.5%)	82 (28.6%)	76 (26.4%)	71 (24.5%)	229 (26.5%)	270 (48.0%)	268 (47.9%)	260 (46.2%)	798 (47.4%)
Asian	11 (4.0%)	6 (2.2%)	11 (4.0%)	28 (3.4%)	105 (36.6%)	106 (36.8%)	116 (40.0%)	327 (37.8%)	116 (20.6%)	112 (20.0%)	127 (22.6%)	355 (21.1%)
Black – African American	39 (14.2%)	40 (14.8%)	39 (14.3%)	118 (14.4%)	11 (3.8%)	8 (2.8%)	11 (3.8%)	30 (3.5%)	50 (8.9%)	48 (8.6%)	50 (8.9%)	148 (8.8%)
Alaska Native or American Indian from North/Central/South America	36 (13.1%)	33 (12.2%)	34 (12.5%)	103 (12.6%)	89 (31.0%)	98 (34.0%)	92 (31.7%)	279 (32.3%)	125 (22.2%)	131 (23.4%)	126 (22.4%)	382 (22.7%)
Native Hawaiian or Other Pacific Islander	1 (0.4%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.1%)
Multiracial	2 (0.7%)	3 (1.1%)	3 (1.1%)	8 (1.0%)	1 (0.3%)	3 (1.0%)	1 (0.3%)	5 (0.6%)	3 (0.5%)	6 (1.1%)	4 (0.7%)	13 (0.8%)
Hispanic or Latino origin	55 (20.0%)	62 (22.9%)	56 (20.5%)	173 (21.1%)	143 (49.8%)	141 (49.0%)	136 (46.9%)	420 (48.6%)	198 (35.2%)	203 (36.3%)	192 (34.1%)	593 (35.2%)
Age (years) Mean ± SD	40.0 ± 11.9	40.0 ± 11.4	40.5 ± 11.1	40.2 ± 11.5	36.2 ± 11.8	35.0 ± 10.6	35.4 ± 10.8	35.5 ± 11.1	38.1 ± 12.0	37.4 ± 11.3	37.9 ± 11.3	37.8 ± 11.5
Age (years)												
≤ 45	189 (68.7%)	184 (67.9%)	178 (65.2%)	551 (67.3%)	225 (78.4%)	236 (81.9%)	236 (81.4%)	697 (80.6%)	414 (73.7%)	420 (75.1%)	414 (73.5%)	1248 (74.1%)
> 45 - < 65	77 (28.0%)	83 (30.6%)	92 (33.7%)	252 (30.8%)	57 (19.9%)	48 (16.7%)	52 (17.9%)	157 (18.2%)	134 (23.8%)	131 (23.4%)	144 (25.6%)	409 (24.3%)
≥ 65	9 (3.3%)	4 (1.5%)	3 (1.1%)	16 (2.0%)	5 (1.7%)	4 (1.4%)	2 (0.7%)	11 (1.3%)	14 (2.5%)	8 (1.4%)	5 (0.9%)	27 (1.6%)

[1] Subjects who checked more than 1 race category are counted under individual race category according to the minority rule as well as the multiracial category.

Table 14. Enrolment by Region Phase III Studies

	C1056 All N = 819	C1057 All N = 865	Phase 3 Pooled All N = 1684
USA/Canada	436 (53.2%)	-	436 (25.9%)
America excluding US/Canada	88 (10.7%)	428 (49.5%)	516 (30.6%)
Western Europe/Australia/Israel	202 (24.7%)	15 (1.7%)	217 (12.9%)
Eastern Europe	93 (11.4%)	98 (11.3%)	191 (11.3%)
Asia		324 (37.5%)	324 (19.2%)

Over 94% of the subjects in the Phase III trials were female. The majority of subjects were 45 years of age or less. Although there were more young subjects (≤ 45 years of age) in

C1057 (81%) compared with **C1056** (67%), within the trials the ages were generally balanced across treatment groups. There were differences in racial balances in the populations between the 2 studies reflective of the racial distributions in the geographic regions in which the trials were conducted; with Study **C1056** enrolling predominantly White subjects (70%) and Study **C1057** enrolling predominantly Asian (38%) and Indigenous American Indian (32%) subjects. In **C1056**, which included over 50% representation from the USA, approximately 14% of the population was Black which can be compared with 3.5% in Study C1057. Subjects of Hispanic descent comprised 21% and 49% of the populations in Studies C1056 and C1057, respectively. Subjects in C1056 had higher baseline mean weights (73 kg versus 61 kg) and body mass index (BMI) scores (27 versus 24) compared with subjects in C1057, reflecting higher rates of obesity in the USA and in Western Europe. The populations chosen reflect the type of patients for which the sponsor requests licensing approval.

Baseline disease activity are summarised in Table 15. Subjects in the Phase III trials had SLE for a mean duration of 6.4 years. For the 11 disease characteristics comprising the ACR classification of SLE, at least 50% experienced the following conditions since the time of their original diagnosis: positive ANA (98%), arthritis (89%), immunologic disorder (77%), malar rash (73%), photosensitivity (70%), haematological disorder (55%) and oral ulcers (50%).

In the Phase III program, approximately 60.8% (1024/1684) of subjects had BILAG activity with at least 1A or 2B organ domain scores and 15.8% (263/1684) had at least a BILAG 1A organ domain score. The baseline SELENA SLEDAI score was ≥ 10 for 52.1% (878/1684) (of subjects, ≤ 9 for 47.9% (806/1684) of subjects, with a mean score of 9.71 (CI 5.95 - 13.47). At baseline, 22% (370/1684) of subjects presented with a flare (SFI) and 1.1% (19/1684) had a severe SLE flare. The mean baseline PGA score was 1.43 (CI 0.95-1.96). The mean SLICC/ACR damage index was 0.77 at baseline, the baseline proteinuria was < 2 gm/24 hour equivalent for 94.1% (1585/1684) of subjects and the mean proteinuria was 0.49 g/24 hour equivalent for the overall population.

Table 15. Selected Baseline Disease Activity Data

	C1056				C1057				Both Studies			
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	All N = 819	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290	All N = 865	Placebo N = 562	1 mg/kg N = 559	10 mg/kg N = 563	All N = 1684
SLE Disease duration (yr)[1]												
Mean ± SD	7.42 ± 6.72	7.93 ± 7.13	7.20 ± 7.45	7.52 ± 7.10	5.93 ± 6.17	4.96 ± 4.58	5.03 ± 5.07	5.31 ± 5.32	6.66 ± 6.48	6.40 ± 6.13	6.08 ± 6.42	6.38 ± 6.35
BILAG organ domain involvement												
at least 1A or 2B	187 (68.0%)	173 (63.8%)	160 (58.6%)	520 (63.5%)	166 (57.8%)	166 (57.6%)	172 (59.3%)	504 (58.3%)	353 (62.8%)	339 (60.6%)	332 (59.0%)	1024 (60.8%)
at least 1A	37 (13.5%)	38 (14.0%)	24 (8.8%)	99 (12.1%)	52 (18.1%)	58 (20.1%)	54 (18.6%)	164 (19.0%)	89 (15.8%)	96 (17.2%)	78 (13.9%)	263 (15.6%)
SELENA SLEDAI category												
0 - 3	3 (1.1%)	5 (1.8%)	8 (2.9%)	16 (2.0%)	1 (0.3%)	4 (1.4%)	3 (1.0%)	8 (0.9%)	4 (0.7%)	9 (1.6%)	11 (2.0%)	24 (1.4%)
4 - 9	131 (47.6%)	122 (45.0%)	129 (47.3%)	382 (46.6%)	128 (44.6%)	145 (50.3%)	127 (43.8%)	400 (46.2%)	259 (46.1%)	267 (47.8%)	256 (45.5%)	782 (46.4%)
10 - 11	62 (22.5%)	72 (26.6%)	65 (23.8%)	199 (24.3%)	75 (26.1%)	53 (18.4%)	72 (24.8%)	200 (23.1%)	137 (24.4%)	125 (22.4%)	137 (24.3%)	399 (23.7%)
≥ 12	79 (28.7%)	72 (26.6%)	71 (26.0%)	222 (27.1%)	83 (28.9%)	86 (29.9%)	88 (30.3%)	257 (29.7%)	162 (28.8%)	158 (28.3%)	159 (28.2%)	479 (28.4%)
SELENA SLEDAI score												
Mean ± SD	9.80 ± 3.97	9.70 ± 3.65	9.52 ± 3.64	9.67 ± 3.75	9.70 ± 3.62	9.56 ± 3.78	9.97 ± 3.88	9.75 ± 3.76	9.75 ± 3.79	9.63 ± 3.71	9.75 ± 3.77	9.71 ± 3.76
SLE flare index												
At least 1 flare	82 (29.8%)	63 (23.2%)	59 (21.6%)	204 (24.9%)	57 (19.9%)	53 (18.4%)	56 (19.3%)	166 (19.2%)	139 (24.7%)	116 (20.8%)	115 (20.4%)	370 (22.0%)
PGA category												
0 - 1	33 (12.0%)	39 (14.4%)	51 (18.7%)	123 (15.0%)	43 (15.0%)	38 (13.2%)	32 (11.0%)	113 (13.1%)	76 (13.5%)	77 (13.8%)	83 (14.7%)	236 (14.0%)
> 1 - 2.5	239 (86.9%)	230 (84.9%)	219 (80.2%)	688 (84.0%)	243 (84.7%)	247 (85.8%)	256 (88.3%)	746 (86.2%)	482 (85.8%)	477 (85.3%)	475 (84.4%)	1434 (85.2%)
> 2.5 - 3	3 (1.1%)	2 (0.7%)	3 (1.1%)	8 (1.0%)	1 (0.3%)	3 (1.0%)	2 (0.7%)	6 (0.7%)	4 (0.7%)	5 (0.9%)	5 (0.9%)	14 (0.8%)
Physician Global Assessment												
Mean ± SD	1.48 ± 0.47	1.44 ± 0.50	1.40 ± 0.54	1.44 ± 0.50	1.42 ± 0.48	1.42 ± 0.47	1.41 ± 0.45	1.42 ± 0.47	1.45 ± 0.48	1.43 ± 0.48	1.41 ± 0.49	1.43 ± 0.48
SLICC Damage Index score												
Mean ± SD	0.99 ± 1.45	1.04 ± 1.39	0.94 ± 1.38	0.99 ± 1.41	0.55 ± 0.93	0.60 ± 1.06	0.55 ± 1.00	0.57 ± 1.00	0.77 ± 1.23	0.81 ± 1.25	0.74 ± 1.21	0.77 ± 1.23
Proteinuria category (g/24 hour)												
≥ 2	11 (4.0%)	7 (2.6%)	15 (5.5%)	33 (4.0%)	21 (7.3%)	26 (9.0%)	19 (6.6%)	66 (7.6%)	32 (5.7%)	33 (5.9%)	34 (6.0%)	99 (5.9%)
Proteinuria level (g/24 hour)												
Mean ± SD	0.39 ± 0.81	0.33 ± 0.65	0.40 ± 0.73	0.37 ± 0.74	0.62 ± 1.15	0.63 ± 1.13	0.54 ± 0.91	0.60 ± 1.07	0.50 ± 1.00	0.48 ± 0.94	0.48 ± 0.83	0.49 ± 0.93

[1] Time elapsed between date of SLE diagnosis and the date of informed consent.

	C1056				C1057				Both Studies			
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	All N = 819	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290	All N = 865	Placebo N = 562	1 mg/kg N = 559	10 mg/kg N = 563	All N = 1684
Anti-dsDNA/ANA positive[1]	265 (96.4%)	262 (96.7%)	261 (95.6%)	788 (96.2%)	280 (97.6%)	281 (97.6%)	284 (97.9%)	845 (97.7%)	545 (97.0%)	543 (97.1%)	545 (96.8%)	1633 (97.0%)
Anti-dsDNA (> 30 IU/mL)	174 (63.3%)	171 (63.1%)	179 (65.6%)	524 (64.0%)	205 (71.4%)	221 (76.7%)	218 (75.2%)	644 (74.5%)	379 (67.4%)	392 (70.1%)	397 (70.5%)	1168 (69.4%)
30-200	83 (30.2%)	102 (37.6%)	97 (35.5%)	282 (34.4%)	109 (38.0%)	119 (41.3%)	116 (40.0%)	344 (39.8%)	192 (34.2%)	221 (39.5%)	213 (37.8%)	626 (37.2%)
>200	91 (33.1%)	69 (25.5%)	82 (30.0%)	242 (29.5%)	96 (33.4%)	102 (35.4%)	102 (35.2%)	300 (34.7%)	187 (33.3%)	171 (30.6%)	184 (32.7%)	542 (32.2%)
Anti-Smith (n)												
Positive (≥ 15 U/mL)	72/269 (26.8%)	69/269 (25.7%)	75/265 (28.3%)	216/803 (26.9%)	101/287 (35.2%)	102/288 (35.4%)	105/287 (36.6%)	308/862 (35.7%)	173/556 (31.1%)	171/557 (30.7%)	180/552 (32.6%)	524/1665 (31.5%)

Disease characteristics for subjects involved in studies **C1056** and **C1057** were similar across the 2 studies and generally balanced between treatments within the studies with a few exceptions. By some measures, subjects in Study **C1057** had higher disease activity at baseline as reflected by more subjects with SELENA SLEDAI scores of at least 10 (52.8% [421/819] versus 51.4% [457/865] in **C1056**), mean proteinuria level (0.60 versus 0.37 g/24 hours equivalent in **C1056**) and at least 1A BILAG organ domain score (19%

[164/865] versus 12.1% [99/819] in **C1056**). However, subjects in Study **C1056** had longer disease duration (mean/median 7.5/5.6 years versus 5.3/3.7 years in Study **C1057**) and more organ damage as reflected by higher SLICC damage scores (mean 0.99 versus 0.57 in Study **C1057**). PGA scores at baseline were similar across trials with 84-86% of subjects with scores between >1 and ≤ 2.5, and mean scores of 1.42-1.44.

Within trials, these baseline characteristics were generally balanced across treatment groups but there were some exceptions. In Study **C1056**, the belimumab groups and in particular the 10 mg/kg group, had fewer subjects with the following characteristics: at least 1A/2B BILAG organ domain, at least 1 SLE flare, and PGA score > 1. In addition, the number of subjects with SELENA SLEDAI scores of 0-3 at baseline (thereby making the subject unable to achieve a response of ≥ 4 points) was slightly imbalanced at 3, 5 and 8 in the placebo, 1 mg/kg and 10 mg/kg belimumab groups, respectively. In Study **C1057**, these and other factors were generally well-balanced across treatment groups.

Overall, these differences between studies and between treatment groups within the studies are minor and should not materially affect the results.

Results

Study C1056

The proportion of patients who achieved an SLE response at 52 weeks was 33.8% (93/275) for the control group compared with 40.6% (110/271) for the belimumab 1 mg/kg arm and 43.2% (118/273) for the belimumab 10 mg/kg groups. The observed difference in the response rates between the 1 mg/kg belimumab group and placebo arm did not reach statistical significance (p=0.1041). The difference in SLE response rates between the belimumab 10 mg/kg group and placebo plus standard of care was statistically significant (p=0.0207). However, the overall magnitude of difference in response rates between the placebo and 10 mg/kg belimumab groups was modest at 9.41% with an OR of 1.52 (95% CI 1.07, 2.15). No pair-wise statistical analysis was performed comparing the 2 belimumab dose groups (1 mg/kg and the 10 mg/kg) but given the small magnitude of the difference, it is unlikely that a treatment difference would be statistically significant. Hence, no clear dose-response relationship for the primary efficacy endpoint of SLE response can be assumed from Study **C1056**. Table 16 summarises the results of the primary efficacy analysis in Study **C1056**.

Table 16. Primary Efficacy Endpoint C1056

	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273
Response	93 (33.8%)	110 (40.6%)	118 (43.2%)
Observed difference vs Placebo	-	6.77%	9.41%
OR (95% CI)[1] vs placebo	-	1.34 (0.94, 1.91)	1.52 (1.07, 2.15)
P-value[1]	-	0.1041	0.0207

[1] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other).

Each individual component comprising the primary efficacy endpoint of SLE response was analysed separately for data obtained at 52 weeks. Table 17 provides a summary of those efficacy outcomes. The only statistically significant difference evident between the placebo and the belimumab 10 mg/kg group was seen in the *≥4-point reduction in SELENA SLEDAI* (35.6% [98/275] for control group compared with 46.9% [128/273] for belimumab 10 mg/kg). The magnitude of this difference (11.3%) and hence the clinical significance, is modest. Interestingly, there was a statistically significant difference in the number of

subjects with *No New 1A/2B BILAG domain scores* between the placebo and belimumab 1 mg/kg groups but this observation was not seen in the pair-wise comparison of the placebo belimumab and 10 mg/kg groups. This result is consistent with the lack of a dose-response relationship for belimumab in treating active SLE.

Table 17. Components of SRI C1056

	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273
4-point reduction in SELENA SLEDAI	98 (35.6%)	116 (42.8%)	128 (46.9%)
OR (95% CI)[1] vs placebo	-	1.36 (0.96, 1.93)	1.63 (1.15, 2.32)
P-value[1]	-	0.0869	0.0062
No worsening in PGA	173 (62.9%)	197 (72.7%)	189 (69.2%)
OR (95% CI)[2] vs placebo	-	1.60 (1.11, 2.30)	1.32 (0.92, 1.90)
P-value[2]	-	0.0120	0.1258
No New 1A/2B BILAG domain scores	179 (65.1%)	203 (74.9%)	189 (69.2%)
OR (95% CI)[3] vs placebo	-	1.63 (1.12, 2.37)	1.20 (0.84, 1.73)
P-value[3]	-	0.0108	0.3193

[1] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other).

[2] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline PGA.

[3] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline BILAG domain involvement (at least 1A/2B vs at most 1B).

Table 18 outlines the major secondary efficacy endpoints analysed in Study **C1056**. No statistically significant treatment difference was observed in patients who received placebo infusions plus standard of care compared with either belimumab treatment group for:

- Mean change from baseline in PGA at Week 24
- The percentage of patients able to successfully achieve a prednisone reduction by ≥ 25% from baseline to ≤ 7.5mg/day during Weeks 40 to 52
- Mean change from baseline in the SF-36 PCS score at Week 24

Table 18. Major Secondary Efficacy Endpoints C1056

	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273
SELENA SLEDAI ≥ 4 point reduction from baseline at Week 52			
Response	98 (35.6%)	116 (42.8%)	128 (46.9%)
Observed difference vs placebo	-	7.17%	11.25%
OR (95% CI)[1] vs placebo	-	1.36 (0.96, 1.93)	1.63 (1.15, 2.32)
P-value[1]	-	0.0869	0.0062
PGA change from baseline at Week 24			
Mean ± SE	-0.49 ± 0.04	-0.47 ± 0.04	-0.44 ± 0.03
Median (Min, Max)	-0.51 (-2.10, 1.53)	-0.42 (-2.40, 1.68)	-0.42 (-2.13, 1.38)
LS Mean ± SE2	-0.49 ± 0.05	-0.49 ± 0.06	-0.48 ± 0.05
Treatment differences (95% CI)2 vs placebo	-	-0.00 (-0.09, 0.09)	0.01 (-0.08, 0.10)
P-value2	-	0.9545	0.7987
Prednisone reduction by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52[3]			
N	126	130	120
Response	16 (12.7%)	25 (19.2%)	20 (16.7%)
Observed difference vs placebo	-	6.53%	3.97%
OR (95% CI)1 vs placebo	-	1.57 (0.78, 3.14)	1.26 (0.61, 2.60)
P-value1	-	0.2034	0.5323
SF-36 PCS score change from baseline at Week 24			
n	274	270	269
Mean ± SE	3.36 ± 0.51	3.78 ± 0.46	3.22 ± 0.43
Median (Min, Max)	3.03 (-27.48, 26.62)	3.21 (-20.75, 29.05)	2.66 (-23.57, 25.49)
LS Mean ± SE2	5.63 ± 0.74	6.16 ± 0.75	5.36 ± 0.72
Treatment differences (95% CI)2 vs placebo	-	0.53 (-0.67, 1.74)	-0.27 (-1.48, 0.94)
P-value2	-	0.3848	0.6601

1 Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other).

2 All statistics, including the difference in LSM (least square means), were from ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for the covariates in footnote 1 and baseline PGA score.

3 Includes only subjects with baseline prednisone > 7.5 mg/day.

By 76 weeks of treatment and follow-up (that is, end of trial), the statistical difference in treatment effect for the SLE Responder Index was no longer apparent (38.5% [105/273] for belimumab 10 mg/kg versus 32.4% [88/275] for placebo; p = 0.1323). A similar observation of lack of treatment effect was seen for the comparison treatment between the belimumab 1 mg/kg group (39.1%, 106/271) compared with placebo (32.4%, 88/275; p = 0.1050). The same pattern of results is also seen for the individual components of the SRI, with no statistically significant treatment difference in any of the three individual components at 76 weeks. Hence, any difference in SLE response seen with belimumab therapy over the placebo (and standard of care) is not sustained beyond 52 weeks of treatment. [9]

[9] Sponsor comment:"Patients were able to adjust their background therapies at 52 weeks which may have contributed to a reduced difference in the treatment effect observed at 76 weeks."

Study C1057

In the primary efficacy endpoint analysis of Study **C1057** (SRI at 52 weeks), both doses of the 1 and 10 mg/kg belimumab demonstrated superiority over placebo infusions plus standard of care. Table 19 shows that the proportion of patients achieving SRI was 51.4% (148/288) for belimumab 1 mg/kg and 57.6% (167/290) for belimumab 10 mg/kg compared with 43.6% (125/287) for placebo plus standard of care (see Table 19). The corresponding pair-wise statistical comparisons between placebo and both doses of belimumab were in favour of belimumab therapy (p = 0.0129 for 1 mg/kg versus control, and p = 0.0006 for control versus 10 mg/kg). Although statistically significant, the treatment difference is moderate in magnitude and represents a modest clinical benefit. The sponsor also claims that this result represents a dose-response relationship for belimumab but no formal statistical analysis was supplied to support that claim.

Table 19. Primary Efficacy Endpoint C1057

	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290
Response	125 (43.6%)	148 (51.4%)	167 (57.6%)
Observed difference vs placebo	-	7.83	14.03
OR (95% CI)[1] vs placebo	-	1.55 (1.10, 2.19)	1.83 (1.30, 2.59)
P-value[1]	-	0.0129	0.0006

[1] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other).

Each individual component comprising the SRI was analysed separately after 52 weeks of treatment (see Table 20). In summary, there was statistically significant difference for each of the three components when comparing the placebo and belimumab 10 mg/kg groups and two of the three variables were statistically in favour of belimumab treatment when placebo plus standard of care was compared to the belimumab 1 mg/kg group (plus standard of care). No difference was seen for the *No New 1A/2B BILAG domain scores* variable when the belimumab 1 mg/kg arm was compared to standard of care only.

Table 20. Components of SRI C1057

	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290
4-point reduction in SELENA SLEDAI	132 (46.0%)	153 (53.1%)	169 (58.3%)
OR (95% CI)[1] vs placebo		1.51 (1.07, 2.14)	1.71 (1.21, 2.41)
P-value[1]		0.0189	0.0024
No worsening in PGA	199 (69.3%)	227 (78.8%)	231 (79.7%)
OR (95% CI)[2] vs placebo		1.68 (1.15, 2.47)	1.74 (1.18, 2.55)
P-value[2]		0.0078	0.0048
No New 1A/2B BILAG domain scores	210 (73.2%)	226 (78.5%)	236 (81.4%)
OR (95% CI)[3] vs placebo		1.38 (0.93, 2.04)	1.62 (1.09, 2.42)
P-value[3]		0.1064	0.0181

1 Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other).

2 Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline PGA.

3 Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline BILAG domain involvement (at least 1A/2B vs at most 1B).

The major secondary endpoint analyses for Study C1057 are outlined in Table 21. The belimumab 10 mg/kg dose group was able to achieve a statistically significant better mean change from baseline at week 24 in the PGA (mean score improvement of 0.54) compared with placebo plus standard of care (mean score improvement of 0.39; p = 0.0003). However, there was no statistically significant treatment difference in the percentage of subjects achieving prednisone reduction by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40-52 when the placebo plus standard of care group (12.0%, 23/192) was compared to the belimumab 10 mg/kg group (18.6%, 38/204; p = 0.526) but this outcome was favourable for belimumab therapy when the 1 mg/kg dose group (20.6%, 42/204) was compared with placebo plus standard of care (p = 0.0252). Furthermore, no treatment difference was seen for the mean change from baseline in the SF-36 PCS score at Week 24 between either of the belimumab doses and the control arm.

Table 21. Major Secondary Endpoints C1057

	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290
SELENA SLEDAI ≥ 4 point reduction from baseline at Week 52			
Response	132 (46.0%)	153 (53.1%)	169 (58.3%)
Observed difference vs placebo	-	7.13	12.28
OR (95% CI)[1] vs placebo	-	1.51 (1.07, 2.14)	1.71 (1.21, 2.41)
P-value[1]	-	0.0189	0.0024
PGA change from baseline at Week 24			
Mean ± SE	-0.39 ± 0.03	-0.44 ± 0.03	-0.54 ± 0.03
Median (Min, Max)	-0.33 (-2.07, 0.99)	-0.42 (-2.04, 1.11)	-0.48 (-2.13, 1.62)
LS Mean ± SE[2]	-0.35 ± 0.04	-0.39 ± 0.04	-0.50 ± 0.04
Treatment differences (95% CI)[2] vs placebo	-	-0.05 (-0.13, 0.04)	-0.15 (-0.23, -0.07)
P-value[2]	-	0.2712	0.0003
Prednisone reduction by ≥ 25% from baseline to ≤ 7.5 mg/day during Weeks 40 through 52[3]			
N	192	204	204
Response	23 (12.0%)	42 (20.6%)	38 (18.6%)
Observed difference vs placebo	-	8.61	6.65
OR (95% CI)[1] vs placebo	-	1.89 (1.08, 3.31)	1.75 (0.99, 3.08)
P-value[1]	-	0.0252	0.0526
SF-36 PCS score change from baseline at Week 24			
N	286	283	284
Mean ± SE	3.64 ± 0.42	3.65 ± 0.43	3.58 ± 0.46
Median (Min, Max)	3.11 (-22.20, 32.93)	2.68 (-22.72, 33.80)	3.06 (-24.41, 30.24)
LS Mean ± SE[2]	3.26 ± 0.54	3.39 ± 0.53	3.34 ± 0.55
Treatment differences (95% CI)[2] vs placebo	-	0.13 (-0.95, 1.21)	0.08 (-1.00, 1.15)
P-value[2]	-	0.8127	0.8870

[1] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other).

[2] All statistics, including the difference in LSM (least square means), were from ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for the covariates in footnote 1 and baseline PGA score.

[3] Includes only subjects with baseline prednisone > 7.5 mg/day.

Subgroup analyses of primary efficacy endpoint

The subgroup analyses were only conducted on the pooled Phase III trial dataset and examined the primary efficacy endpoint (rate of SRI response at 52 weeks). The subgroup analysis showed 2 important treatment-by-subgroup interactions for belimumab. Firstly, Black patients had significantly higher SRI rates when receiving SOC treatment only (44.0% [22/50] compared to 38.8% [218/562] overall) as well as significantly lower SRI response rates to belimumab (for example, for the 10 mg/kg dose the rate of SRI at 52 weeks was 36.0% [18/50] versus 50.6% [285/563] overall). Although the overall number of participating black subjects is small, this raises concern about the effect of belimumab in patients with SLE of this ethnic background. Secondly, patients recruited from North America had significantly lower rates of response in all 3 treatment groups which was more marked in the belimumab treatment groups. The rate of SRI in North Americans receiving belimumab 10 mg/kg was only 34.6% (47/136) compared to 50.6% (285/563) overall. The control arm SRI rate was 31.7% (46/145) for patients recruited from

USA/Canada. Hence, no statistically significant treatment effect could be demonstrated in patients enrolled from this geographic region.

Biomarkers

The results of the secondary efficacy endpoints involving biomarkers are discussed in detail in the section on *Primary Pharmacology*.

Ancillary analyses

There were a large number of secondary analyses performed individually on the two Phase III trials (**C1056** and **C1057**), as well as on the data obtained from pooling the results of both studies. The clinical relevance of each of these analyses will be discussed in turn.

i. Response and Components of Response over Time

The onset of clinical improvement as measured by the SRI with belimumab 10 mg/kg reached statistical significance at 16 weeks in Study **C1057** and the pooled dataset and was sustained until Week 52. However, a statistically significant difference in clinical response with belimumab 10 mg/kg compared with placebo plus standard of care was not seen in Study **C1056** until 52 weeks of follow-up.

Figures 2 and 3 display the results of differences seen in the response for each individual component of the SRI. In general, whenever a sustained response was achieved (that is, evident at 52 weeks), a statistical difference was observed to onset after 16-24 weeks of therapy (as observed in Study **C1057** and for the pooled dataset). However, as expected, differences observed in Study **C1056** appeared to be become evident much later in the treatment course (typically at 48-52 weeks). The reason for the inconsistency between the 2 Phase III trials is not clear but it does not appear to be related to differences in the baseline characteristics of the subjects. Although it is not unusual for a disease-modifying anti-rheumatic therapy to take 3 or more months to become efficacious, it is disadvantageous for it to take 6 or more months to onset in response when subjects have active disease manifestations.

Post hoc analyses indicate that subjects (from any trial) who had more extensive disease manifestations at baseline (as evidenced by higher SELENA SLEDAI scores), presence of anti-dsDNA antibodies and use of prior corticosteroids appear to respond better and earlier to belimumab in addition to standard of care compared with subjects who continued to receive standard of care only.

Figure 2. Change in SELENA SLEDIA Score Phase III Studies

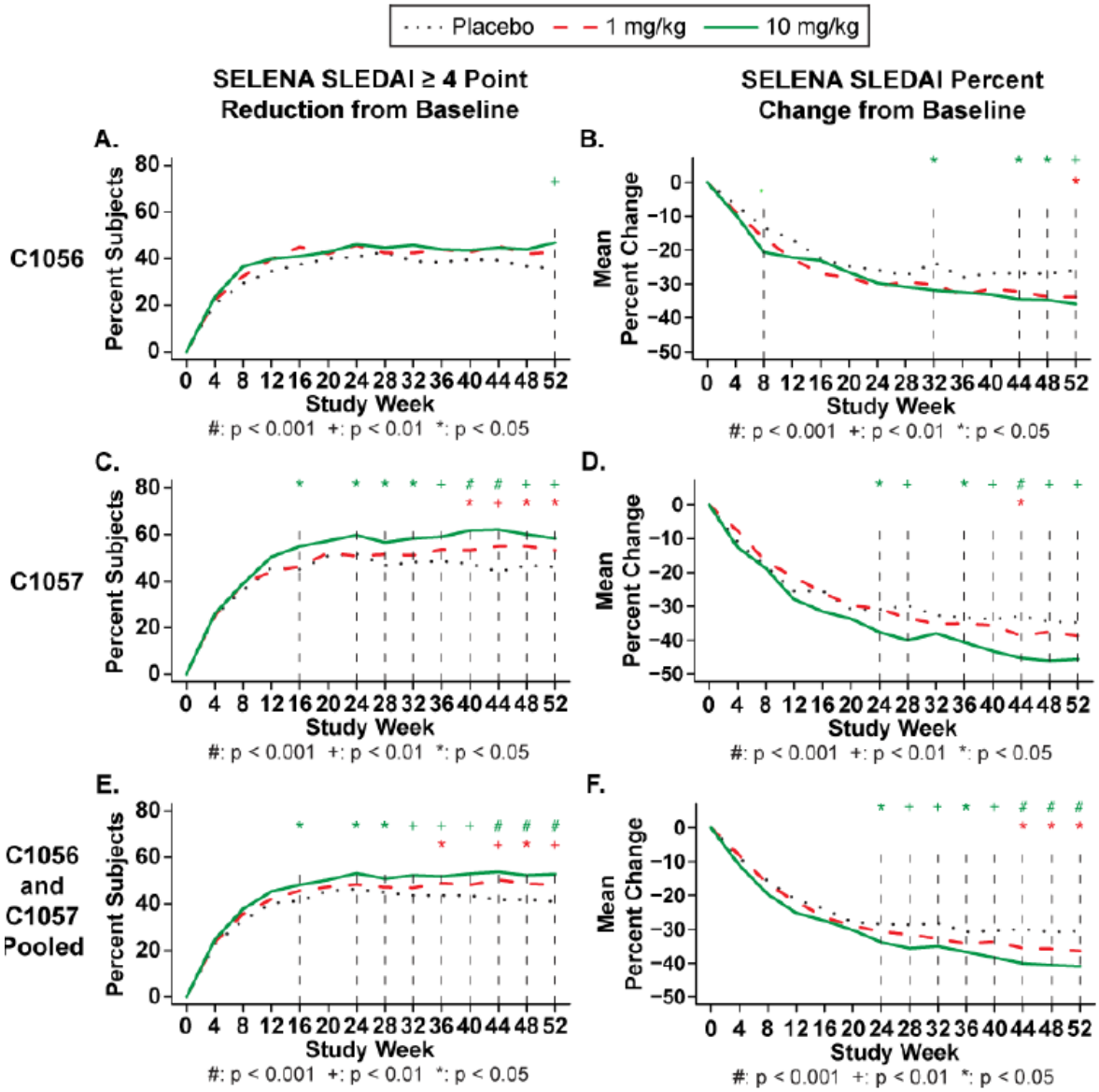
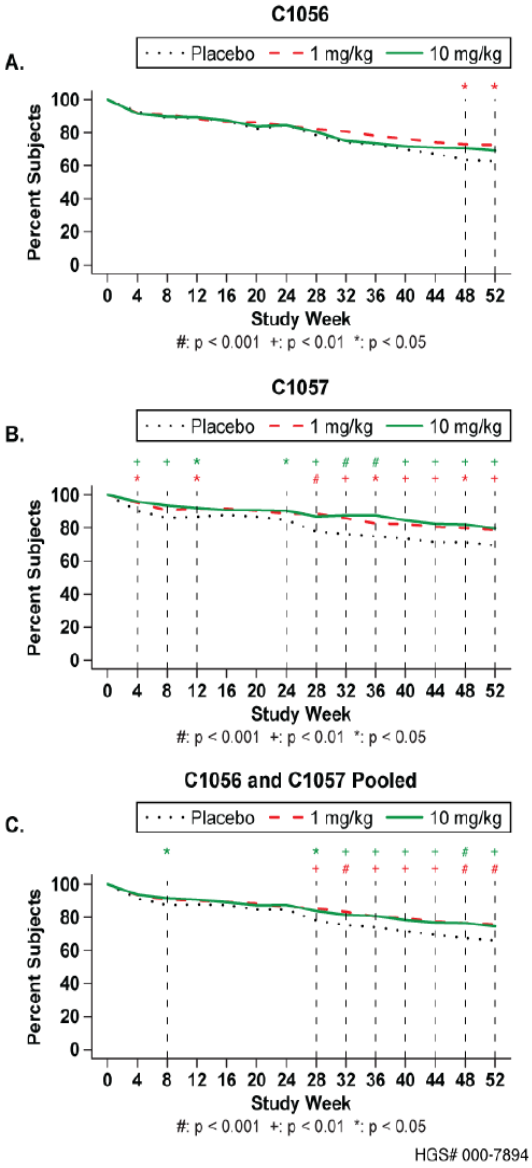
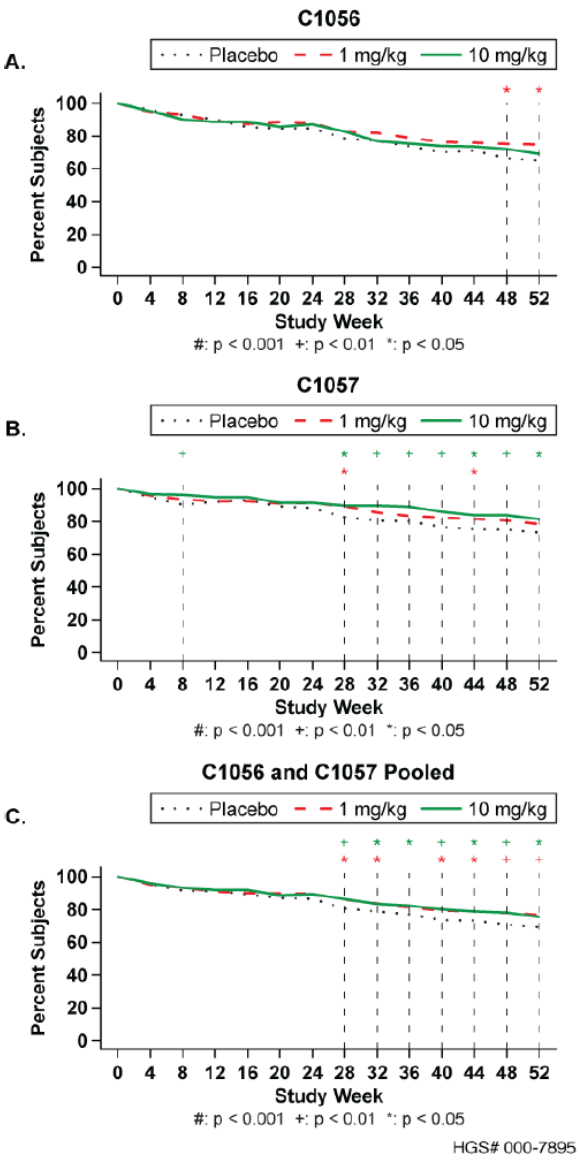


Figure 3. No Change in PGA and No New BILAG 1A/2B Over Time Phase III



No worsening in PGA score by visit in Phase 3 trials (drop-out = failure)



No new BILAB 1A/2B organ domain scores by visit in Phase 3 trials

ii. Mean Change from Baseline in the SELENA SLEDAI Score

Table 22 outlines the difference in mean change of the SELENA SLEDAI score for each of the Phase III trials and pooled dataset of both trials results.

Table 22. Mean Change in SELENA SLEDIA Score in Phase III Studies

	C1056			C1057			Both Studies[2]		
Change from Baseline at Week 52	Placebo N= 275	1 mg/kg N= 271	10 mg/kg N= 273	Placebo N= 287	1 mg/kg N= 288	10 mg/kg N= 290	Placebo N= 562	1 mg/kg N= 559	10 mg/kg N= 563
Mean change from baseline (± SE)	-2.77 ± 0.25	-3.58 ± 0.26	-3.70 ± 0.27	-3.57 ± 0.24	-4.04 ± 0.25	-4.97 ± 0.27	-3.18 ± 0.18	-3.82 ± 0.18	-4.36 ± 0.19
P-value[1]		0.0224	0.0063		0.0297	<0.0001		0.0027	<0.0001
Mean % change (± SE)	-25.97 ± 2.72	-33.87 ± 2.44	-35.94 ± 2.80	-34.76 ± 2.50	-38.73 ± 2.44	-45.60 ± 2.45	-30.47 ± 1.85	-36.38 ± 1.73	-40.93 ± 1.86
P-value[1]		0.0379	0.0073		0.1281	0.0018		0.0140	<0.0001

[1] ANCOVA model for the comparison between each belimumab dose and placebo, adjusted for baseline SELENA SLEDAI score (≤ 9 vs. ≥ 10), baseline proteinuria level (< 2 g/24 hour vs. ≥ 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs. other). For pooled data analysis, study was also included as an additional covariate.

[2] No treatment-by-study interactions observed (all p-values > 0.367).

Statistically significant mean differences in the SELENA SLEDAI score were seen at 52 weeks of follow-up in the pooled belimumab treatment dataset compared with control treatment. The mean reduction for placebo plus standard of care was -3.18 compared with -3.82 in the belimumab 1 mg/kg group and -4.36 for the belimumab 10 mg/kg group. However, the magnitude of difference with active versus control treatment appears to be modest and is of unclear clinical relevance.

The sponsor also performed a post hoc analysis to assess which components of the SELENA SLEDAI score showed most improvement. In the pooled dataset, there was statistically significant improvement from baseline to Week 52 in the CNS, vascular, musculoskeletal, immunology, and mucocutaneous organ system domains for belimumab-treated subjects (at least 1 dose) compared with placebo plus standard of care. However, given the post hoc nature of the analysis and the small overall improvement in SELENA SLEDAI score, the clinical relevance of these differences is uncertain but nonetheless hypothesis generating for any future studies that may be considered.

iii. Reduction in Prednisone Dose

As mentioned above, the proportion of subjects who were able to achieve a prednisone reduction by ≥ 25% to ≤ 7.5mg/day during Weeks 40-52 (in subjects taking more than 7.5 mg/day prednisone at baseline) was a pre defined secondary outcome measure. In the individual data analysis of the 2 Phase III trials (**C1056** and **C1057**), only subjects in the belimumab 1 mg/kg treatment group were able achieve a statistically significant reduction in corticosteroid use. In the pooled dataset, a statistically significant reduction in the number of subjects that were able to reduce their prednisone dose by ≥ 25% to ≤7.5 mg/day during Weeks 40-52 was demonstrated for both belimumab dose groups (compared with placebo plus standard of care), although the overall numbers were small (20.1% [67/334] for belimumab 1 mg/kg, 17.9% [58/324] for belimumab 10 mg/kg, and 12.3% [39/318] for placebo plus standard of care). It is acceptable to pool the datasets for this analysis given that each individual trial was not powered to assess this outcome.

Conversely, there was no statistically or clinically significant reduction in the mean prednisone dose in the pooled dataset at 52 weeks. The mean reduction of prednisone dose for the 1 mg/kg group was 0.36 mg (95% CI -1.16, 0.45; p = 0.3871) and 0.35 mg for the 10 mg/kg belimumab group (95% CI 1.16, 0.46; p = 0.3946). Therefore, the overall

reduction in prednisone use in the treatment groups compared with placebo are small and of modest clinical benefit.

iv. SLE Flares

The probability of developing a flare of SLE (Overall; as well as mild, moderate or severe in intensity) was evaluated over 52 weeks of follow-up. It was also a pre-specified analysis between Weeks 24 and 52 to allow for determination of onset of drug action and to evaluate the treatment effect when background standard of care therapy was more restricted. Table 23 outlines the number of flares (total and severe) per subject year for Day 0 to Week 52 and also for Weeks 24-52. There was a statistically significant decrease in the total number of flares for both belimumab treatment groups compared with placebo plus standard of care for Weeks 24 to 52. The magnitude of this treatment effect equates to approximately one less overall flare per subject-year (with no clear dose-response relationship). However, with respect to severe flares only the belimumab 10 mg/kg dose was able to achieve a statistically significant difference in the number of severe flares per subject-year (both in the pooled dataset and individual trial data). This result would be of clinical interest and the magnitude of the treatment difference approximates 0.22-0.33 severe SLE flare per subject-year (that is, unclear clinical relevance). No data was presented about the incidence of SLE flare to 76 weeks of follow-up and therefore it is not clear if these potential benefits are maintained beyond 52 weeks of therapy.

Table 23. SLE Flares to 52 Weeks in Phase III Studies

	C1056			C1057			Both Studies		
Flares per Subject-Year Weeks 0 to 52[1]	**Placebo N = 272**	**1 mg/kg N = 267**	**10 mg/kg N = 270**	**Placebo N = 284**	**1 mg/kg N = 286**	**10 mg/kg N = 287**	**Placebo N = 556**	**1 mg/kg N = 553**	**10 mg/kg N = 557**
Mean ± SE	3.81 ± 0.18	3.33 ± 0.18	3.42 ± 0.19	3.22 ± 0.17	2.50 ± 0.17	2.37 ± 0.16	3.51 ± 0.13	2.90 ± 0.12	2.88 ± 0.13
P-value[2]	-	0.0632	0.1276	-	**0.0012**	**0.0002**	-	**0.0005**	**0.0002**
Severe Flares per Subject-Year Weeks 0 to 52[1]									
Mean ± SE	1.11 ± 0.14	0.93 ± 0.15	1.00 ± 0.15	0.92 ± 0.12	0.80 ± 0.12	0.59 ± 0.10	1.01 ± 0.09	0.86 ± 0.10	0.79 ± 0.09
P-value[2]	-	0.3680	0.5775	-	0.3544	**0.0381**	-	0.2380	0.0754
Flares per Subject-Year Weeks 24 to 52[1]	**Placebo N = 227**	**1 mg/kg N = 236**	**10 mg/kg N = 229**	**Placebo N = 246**	**1 mg/kg N = 257**	**10 mg/kg N = 264**	**Placebo N = 473**	**1 mg/kg N = 493**	**10 mg/kg N = 493**
Mean ± SE	3.89 ± 0.26	3.06 ± 0.21	2.95 ± 0.22	3.00 ± 0.24	1.92 ± 0.18	1.90 ± 0.15	3.43 ± 0.18	2.47 ± 0.14	2.39 ± 0.13
P-value[2]	-	**0.0091**	**0.0045**	-	**<0.0001**	**<0.0001**	-	**<0.0001**	**<0.0001**
Severe Flares per Subject-Year Weeks 24 to 52[1]									
Mean ± SE	1.09 ± 0.20	0.79 ± 0.17	0.82 ± 0.16	0.82 ± 0.18	0.58 ± 0.14	0.45 ± 0.10	0.95 ± 0.13	0.68 ± 0.11	0.62 ± 0.09
P-value[2]	-	0.1898	0.3106	-	0.1851	0.0714	-	0.0830	**0.0429**

[1] Includes subjects who did not dropout or med failed before Day 28 post 24-week; 0 flares assigned for missing visits before exit/treatment failure date
[2] All statistics, including the difference in LSM (least square means), were from ANCOVA model for the comparison between each belimumab dose and placebo with covariates. For individual studies, covariates include baseline SELENA SLEDAI score (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other). For pooled data analysis, study was also included as an additional covariate.

v. Analysis Using Higher SELENA SLEDAI Score Cut-off

The sponsor performed a post hoc analysis of the SRI using higher thresholds for SELENA-SLEDAI reduction in order for a subject to be declared a responder (SELENA-SLEDAI ≥ 5 point reduction [SRI5], ≥ 6 [SRI6], and ≥ 7 [SRI7]). At several time points throughout the Phase III trials the 1 mg/kg group, the 10 mg/kg belimumab treatment group or both groups had a statistically significant better response rate than standard of care only at 1 or more of the higher SELENA- SLEDAI cut-off scores. This analysis included statistically significant improvements at all cut-off levels in both belimumab dose groups at 76 weeks. However, due to the post hoc nature of the analyses and the large number of individual analyses performed caution should be applied when interpreting these results, particular given that the overall response rates seen at 76 weeks were no different when comparing placebo plus standard of care and either belimumab treatment group.

Clinical studies in special populations

There were no special studies performed in specific populations of special interest as defined by the TGA. Patients with significantly impaired renal and hepatic function were

excluded from the clinical trials. The overall number of subjects involved in the 2 Phase III trials that were elderly in age (> 65 years) was small and therefore meaningful interpretation of the results is limited.

Analysis performed across trials (pooled analyses)

Results of the pooled analysis of patients who received belimumab in the 2 Phase III studies have been discussed in detail above.

Supportive studies

Phase I dose escalation Study LBSL-01

This trial did not specifically examine efficacy outcomes but did report a lack of correlation between changes in disease activity variables (SELENA-SLEDAI score and PGA) and changes in biomarkers (anti-dsDNA, CD20+ cells, CD138+ cells, and IgG levels). This is not unexpected given the limited patient exposure to belimumab (n=57).

Phase II Study LBSL-02

A total of 336 subjects received belimumab and 113 patients were given placebo infusions in this trial. The majority of subjects were enrolled from the USA (446 in total). Three subjects were recruited from Canada. A total of 364 subjects completed the 52 week treatment period of the study, 345 of whom received treatment in the optional 24 week extension period. Of the 321 subjects completing the extension period, 296 were enrolled and treated in Study **LBSL-99** which is an ongoing study. The overall dropout rate in the initial 52 week treatment period was 19% (85/449) with no apparent difference among treatment groups. The most frequent reasons for withdrawal from the study were subject request and lack of compliance (5.3% each) in the placebo arm; and subject request (7.4%) followed by adverse event (AE) (6.0%) in all active groups combined. During the 52 week treatment period, the mean number of doses received was 13 (of a planned 14) in all groups with a range of 1 to 15. Table 24 outlines the baseline characteristics of subjects in this study and Table 25 the baseline disease activity.

Table 24. Baseline Characteristics LBSL-02

	Placebo N = 113	1 mg/kg N = 114	4 mg/kg N = 111	10 mg/kg N = 111	All Active N = 336	All Groups N = 449
Sex						
Female	102 (90.3%)	107 (93.9%)	105 (94.6%)	105 (94.6%)	317 (94.3%)	419 (93.3%)
Race						
White	80 (70.8%)	82 (71.9%)	75 (67.6%)	78 (70.3%)	235 (69.9%)	315 (70.2%)
Asian	4 (3.5%)	3 (2.6%)	1 (0.9%)	4 (3.6%)	8 (2.4%)	12 (2.7%)
Black or African American	23 (20.4%)	24 (21.1%)	31 (27.9%)	28 (25.2%)	83 (24.7%)	106 (23.6%)
American Indian or Alaska Native	2 (1.8%)	2 (1.8%)	3 (2.7%)	-	5 (1.5%)	7 (1.6%)
Native Hawaiian or Other Pacific Islander	2 (1.8%)	1 (0.9%)	-	1 (0.9%)	2 (0.6%)	4 (0.9%)
Multiracial[1]	2 (1.8%)	2 (1.8%)	1 (0.9%)	-	3 (0.9%)	5 (1.1%)
Hispanic or Latino origin	21 (18.6%)	17 (14.9%)	24 (21.6%)	21 (18.9%)	62 (18.5%)	83 (18.5%)
Age (years)						
Mean ± SD	42.2 ± 10.9	42.0 ± 11.7	42.6 ± 10.7	41.8 ± 11.7	42.1 ± 11.3	42.2 ± 11.2

[1] Subject checked more than 1 race category.

Table 25. Baseline Disease Activity LBSL-02

	Placebo N = 113	1 mg/kg N = 114	4 mg/kg N = 111	10 mg/kg N = 111	All Active N = 336	All Groups N = 449
Disease duration (yr)[1]						
Mean ± SD	8.1 ± 7.4	8.5 ± 7.2	10.1 ± 9.2	8.5 ± 8.0	9.0 ± 8.2	8.8 ± 8.0
SELENA SLEDAI Score Group						
2[2]	1 (0.9%)	1 (0.9%)	2 (1.8%)	1 (0.9%)	4 (1.2%)	5 (1.1%)
4-7	42 (37.2%)	32 (28.1%)	37 (33.3%)	33 (29.7%)	102 (30.4%)	144 (32.1%)
8-16	62 (54.9%)	71 (62.3%)	62 (55.9%)	69 (62.2%)	202 (60.1%)	264 (58.8%)
> 16	8 (7.1%)	10 (8.8%)	10 (9.0%)	8 (7.2%)	28 (8.3%)	36 (8.0%)
SELENA SLEDAI Score						
Mean ± SE	9.5 ± 0.50	9.9 ± 0.44	9.4 ± 0.45	9.5 ± 0.39	9.6 ± 0.25	9.6 ± 0.22
BILAG organ domain involvement						
A	21 (18.6%)	20 (17.5%)	21 (18.9%)	18 (16.2%)	59 (17.6%)	80 (17.8%)
B	99 (87.6%)	104 (91.2%)	105 (94.6%)	106 (95.5%)	315 (93.8%)	414 (92.2%)
A or B	102 (90.3%)	109 (95.6%)	107 (96.4%)	106 (95.5%)	322 (95.8%)	424 (94.4%)
BILAG Score						
Mean ± SE	9.5 ± 0.45	9.8 ± 0.41	10.1 ± 0.50	10.0 ± 0.40	10.0 ± 0.25	9.8 ± 0.22
PGA						
Mean ± SE	1.4 ± 0.05	1.6 ± 0.05	1.5 ± 0.05	1.5 ± 0.05	1.5 ± 0.03	1.5 ± 0.02
Daily prednisone use at baseline						
Yes	82 (72.6%)	78 (68.4%)	73 (65.8%)	74 (66.7%)	225 (67.0%)	307 (68.4%)
Daily prednisone use > 7.5 mg at baseline						
Yes	48 (42.5%)	40 (35.1%)	35 (31.5%)	38 (34.2%)	113 (33.6%)	161(35.9%)

[1] Time elapsed between date of SLE diagnosis and the date of informed consent.
[2] Subject(s) had SELENA SLEDAI of ≥ 4 at Screening.

The co-primary efficacy endpoint of this study (the percentage change in SELENA SLEDAI score at Week 24) was not achieved. No statistically significant improvements were seen in any belimumab treatment group or in the pooled analyses. There was no consistent dose response relationship seen. In fact, the belimumab 4 mg/kg group was numerically worse than the 2 other belimumab treatment groups and placebo + SOC. For the 1 and 10 mg/kg dose groups the mean decrease in SELENA SLEDIA was 23.3% and 23.7% respectively, compared with 17.2% in the placebo group, while the 4 mg/kg group had a mean percent decrease of 11.3% (see Table 26). Belimumab did not show benefit as measured by the pre specified major secondary endpoints involving the SELENA SLEDAI score, including area under the curve (AUC) and percent change of SELENA SLEDAI at Week 52. No pre specified subgroup showed an effect with belimumab for SELENA SLEDAI changes at Week 24.

Table 26. Percentage Change in SELENA SLEDAI from baseline to 24 weeks LBSL-02

	Placebo N = 113	1.0 mg/kg N = 114	4.0 mg/kg N = 111	10.0 mg/kg N = 111	All Active N = 336
Mean ± SE	-17.2 ± 5.10	-23.3 ± 4.43	-11.3 ± 5.40	-23.7 ± 4.22	-19.5 ± 2.73
Mean difference from placebo		-6.10	5.94	-6.48	-2.25
P value from t-test[2]		0.3677	0.4244	0.3296	0.6863

[1] Last Observation Carried Forward.
[2] P value for pairwise comparison between each active treatment and placebo group.

The other major secondary endpoints showed a consistent negative result for belimumab treatment compared with placebo, which included the Week 52 BILAG disease activity score, the Week 52 AUC of BILAG, the time to the first SLE flare (as defined using the BILAG) over 52 weeks and the percent of subjects with average prednisone dose ≤ 7.5 mg/day and/or reduced by a minimum of 50% from baseline during Weeks 40-52 (in subjects whose prednisone was > 7.5 mg/day at baseline). In the analysis of prednisone reduction from Weeks 40-52 there was a trend towards benefit for the belimumab 10 mg/kg dose (45%) compared with placebo (27%; p = 0.0882) but this did not reach statistical significance.

Open-label, long-term continuation trials in subjects with SLE

The long-term continuation trials conducted with belimumab in SLE include Studies **LBSL-99**, **C1066** and **C1074**. However, given that these open label extension phase trials no longer had a parallel control group and were primarily designed to assess long term safety, any information garnered with regard to long term efficacy needs to be considered with caution.

Study **LBSL-99** is the continuation trial of the Phase II Study **LBSL-02**. The sponsor claims the following efficacy observations are evident in Study **LSBL-99**:

- There was sustained improvement in SLE disease activity over 5 years of follow-up (mean reduction from baseline of between 4.12 and 4.91 points on the SELENA SLEDAI score), which was more apparent in autoantibody positive subjects;
- The frequency of overall and severe flares as measured by relative change in the SELENA SLEDAI index decreased over the 5 year follow-up period (70.3% [296/421] in first 6 months, compared with 21.4% [22/103] after 4.5 years) with new BILAG 1A or 2B flares stabilising (26.0% [109/420] in first 6 months compared with 10.0% [1/10] at 5 years);
- Mean PGA scores improved over the 5 year study period (mean decrease of 0.65 points in all subjects on active treatment); and
- The frequency of C3 and C4 normalisation increased to 60-70% subjects on belimumab therapy over 5 years (from 21% for C3 and 40% for C4 at the end of Week 52).

Study C1066 collected safety data (including laboratory results), efficacy evaluations (SELENA SLEDAI, BILAG, SFI, and PGA), biomarkers (B cell subsets, anti-dsDNA levels and complement), SLICC/ACR damage index, and quality of life assessments (SF-36, FACIT-Fatigue). Study C1074 collected safety data and SLICC/ACR damage index only.

Evaluator's overall conclusions on clinical efficacy

The sponsor provided the efficacy data from 3 randomised multicentre, double blind, active controlled clinical trials in support of the efficacy of belimumab for treating adult patients with active SLE. The 2 Phase III studies (**C1056** and **C1057**) can be considered pivotal in the assessment of efficacy. Supportive data is supplied by the controlled Phase II study (**LBSL-02**) and the open label extension phases of each of these forerunner trials. In general, the studies were of adequate design with a clear and appropriate plan of analysis. All 3 of the controlled studies assessed subjects for up to 52-76 weeks, which is of adequate duration to evaluate short term outcomes in a chronic condition like SLE that is heterogeneous in disease manifestations.

The primary efficacy endpoint in the 2 Phase III studies was the novel, sponsor developed outcome called the SLE Responder Index (SRI) which is a composite outcome measure of 3 previously validated measures of SLE disease activity; the SELENA SLEDAI index, BILAG score and PGA score. Each of the components of the SRI was assessed individually as

major secondary endpoints. Various other secondary endpoints including the proportion of patients achieving a reduction in their background corticosteroid use, mean changes in the SF-36 PCS score (as a measure of HR-QOL) and the likelihood of SLE flare were also assessed. All of the efficacy endpoints examined has some degree of clinical utility but the precise magnitude of clinical relevance for the SRI is not established. Nonetheless, the efficacy endpoints (primary and major secondary) utilised in the Phase III studies were agreed with USA and European regulatory authorities prior to the initiation of the trials and address the indications being sought for by the sponsor in this application.

Furthermore, the endpoints are broadly consistent with the recommendations outlined in the FDA developed Draft Guidance for Industry: Systemic Lupus Erythematosus-Developing Drugs for Treatment (March 2005)[10] as well as the recommendations of the Task Force on SLE of the EULAR Standing Committee for International Clinical Studies Including Therapeutics and the recently issued EMA Committee for Medicinal Products for Human Use (CHMP) concept paper on the need for a guideline on the clinical investigation of medicinal products intended for the treatment of SLE which has been adopted by the TGA. [11]

Patients involved in the 2 Phase III studies had a clinical diagnosis of SLE according to ACR criteria, at least moderate disease activity at baseline (SELENA-SLEDAI of at least 6), were autoantibody positive (ANA or anti-dsDNA) and did not have severe active lupus nephritis or CNS lupus. The sponsor's requested indication is not of adequate description to meet the criterion for entry into the Phase III studies. There is no specific comment about the level of baseline disease activity (at least moderate) nor that patients with recent lupus nephritis were excluded which appear to be significant omissions of detail. Patients involved in Phase II study (**LBSL-02**) had a lower level of disease activity at baseline (the entry criteria required the SELENA-SLEDAI to be only 4 or more) and a "history" of measurable autoantibodies. However, only 72% of subjects in the Phase II trial had a positive autoantibody at screening.

In the 3 controlled studies patients were appropriately maintained on their background SLE medication, which is also elucidated in the sponsor's requested indication. The protocol rules about concurrent medication changes during the 2 Phase III studies were rigorously defined and less so in the Phase II trial. This provision was appropriate as it allowed patients an opportunity to have their disease optimally managed over time with medication adjustments. In addition to receiving the SOC background treatment, subjects received intravenous belimumab or matching placebo infusions on Days 0, 14, 28 and every 28 days thereafter in the controlled studies which appropriately maintained blinding.

The dose of belimumab investigated in the Phase III studies and being requested by the sponsor for commercial licensing (10 mg/kg) has not been adequately justified by the trials. This is a major deficiency of the belimumab clinical development program in SLE. The Phase III studies examined only 2 potential doses (1 and 10 mg/kg) and have not clearly explored the belimumab dose range between 1 and 10 mg/kg. No consistent and clear dose response effect has been established for clinically relevant endpoints in any of the belimumab studies. The dose scheduling (every 28 days after initial loading) seems to be justified by the PK data.

The key efficacy conclusions provided by the 2 Phase III studies (**C1056** and **C1057)** are:

[10]http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072063.pdf
[11] EMEA/CHMP/EWP/604040/2009 http://www.tga.gov.au/pdf/euguide/ewp60404009en.pdf

- Both doses of belimumab (1 and 10 mg/kg) achieved the primary efficacy endpoint of increased rates of SRI compared to placebo + SOC treatment at 52 weeks of follow-up.[12]
- No statistically significant difference in treatment effect was observed between the 2 studied doses of belimumab (1 and 10 mg/kg) for the rates of SRI at 52 weeks,
- By 76 weeks of follow-up in Study C1056, no statistically significant result was observed for the overall rates of SRI (and each of its individual components) for either dose of belimumab (1 or 10 mg/kg) compared with placebo infusions + SOC,
- Either dose of belimumab demonstrated significantly significant improvements compared with SOC only in the relative proportion of patients showing at least a 4 point reduction in their SELENA-SLEDAI score at 52 weeks compared to baseline,
- Belimumab + SOC treatment inconsistently demonstrated benefit at 52 weeks over placebo + SOC for each of the other individual components comprising the SRI (no worsening of PGA or BILAG score),
- Belimumab treatment (either dose) inconsistently demonstrated benefit over placebo + SOC for the proportion of subjects able to achieve a prednisone reduction between Weeks 40-52 (a statistically significant result for belimumab 1 mg/kg versus control in Study C1057 only),
- Belimumab treatment (either dose) was able to produce a modest reduction in overall flares (~1 flare per subject-year) between Weeks 24-52 compared to control treatment and belimumab 10 mg/kg only was able to reduce the frequency of severe flare (~0.3 flare per subject-year) over the same time frame compared to placebo infusions + SOC,
- Neither dose of belimumab was able to demonstrate a statistically improvement in the mean change from baseline in the SF-36 PCS score at 24 weeks compared to SOC, and
- The primary response rate (rate of SRI at 52 weeks) to belimumab in those of Black race and those recruited from within North America was significantly lower than their comparator group. These are the only subgroup analyses of note and are a minority population represented in Australia.

In summary, the efficacy results of the Phase III clinical trial program indicate a mixed response to belimumab treatment (which is not clearly and consistently dose related) and that the magnitude of any potential benefit be of modest clinical effect. Furthermore, there is no controlled data to indicate that there is maintenance of clinical effect beyond 52 weeks of therapy.

The key efficacy conclusions demonstrated by the supporting studies (the Phase II trial and open label extension studies) are as follows:

- The co-primary efficacy endpoints of Study LBSL-02 (the mean percent decrease from baseline in the SELENA-SLEDAI score at 24 weeks and the time to first SLE flare) were not achieved with belimumab treatment compared to the SOC,
- Several pre specified secondary outcomes (such as AUC and percent change in SELENA-SLEDAI score to 52 weeks) showed belimumab was not superior to SOC,
- Post hoc analyses of Study LBSL-02 suggested that belimumab increase the time to first SLE flare and reduce background corticosteroid use in those individuals taking at least 7.5 mg/day (these results are hypothesis generating for the Phase III studies and should not be considered proof of efficacy), and

[12] Sponsor comment: "The 10 mg/kg dose achieved the primary efficacy endpoint for both Phase III studies (C1056 and C1057)."

- Patients continuing in the open label extension studies showed moderate improvements in some disease measures but this efficacy have limited interpretation with respect to a sustained effect as there was no parallel control group.

In conclusion, the Phase II study showed a null result for pre-specified outcomes examining the efficacy of belimumab in treating adult patients with SLE. However, post hoc analyses allowed for the generation of hypotheses that were assessed in the Phase III studies. The open label continuation studies provide limited evidence of efficacy (uncontrolled) in selected patients who had been considered responders to belimumab in the controlled trials.

Safety

Introduction

The safety assessment for belimumab use in adult patients considered data obtained from the following sources:

- Two pivotal Phase III studies (**C1056** and **C1057**) with additional data from their open label extension periods (**C1066** and **C1074**)
- A single supporting Phase II study (**LBSL-02**) and its open label continuation phase (**LBSL-99**)
- Two Phase I trials; 1 of which involved healthy subjects (**C1058**) and another recruited adults with SLE (**LBSL-01**). Belimumab was administered both IV and by SC injection
- Two studies involving adult subjects with active RA (**LBRA-01** and **LBRA99**) whereby belimumab was given IV, and
- Two trials of SC administered belimumab (Study **C1058** involved healthy volunteers and Study **C1070** included adult subjects with SLE

No formal statistical analysis was conducted of the safety analysis data.

Patient exposure

In total, 2578 subjects have participated in the belimumab clinical development program and 2272 of these subjects have received treatment with belimumab. The majority of the subjects were enrolled in the IV SLE studies (2203 subjects) with smaller overall numbers involved in the IV RA studies (283 subjects) and SC studies (92 subjects). Table 27 outlines the subject enrolment and active treatment recipient numbers in the sponsor supported studies as of December 31 2009. Subjects who participated in the double blind studies and then enrolled in the optional extension phases are only counted once in these totals. Patient demographics are outlined in efficacy section of this report. Using all studies, the cumulative subject exposure to belimumab is approximately 4212 subject-years and there are 769.66 subject-years of exposure for placebo treatment.

Table 27. Total Number of Patients Exposed to Belimumab

Belimumab Clinical Studies	Total Enrolled	Total Belimumab Treatment
All Studies	2578	2272
IV SLE Studies	2203	1910
Primary Safety Population	2133	1546
Phase II (LBSL02, LBSL99)	449	424
Phase III (C1056, C1057)	1684	1122
C1056	819	544
C1057	865	578
Other Completed Studies		
Phase I (LBSL01)	70	57
Other Ongoing Studies		
C1066/C1074		307[1]
IV RA Studies (Secondary Safety Population)	283	270
Phase II (LBRA01, LBRA99)	283	270
SC Studies	92	92
Phase I - Healthy volunteer (C1058)	36	36
Phase II - SLE (C1070)	56	56

[1] Denotes number of subjects from parent studies (C1056 and C1057) who, upon enrollment in these continuation studies, switched from placebo to belimumab treatment. In total, 945 subjects from C1056 and C1057 enrolled in C1066 and C1074, as of 31 December 2009.

The primary safety population for this submission consists of all subjects recruited to the SLE trials who received either IV belimumab (at any dose) or placebo infusions. This constitutes the majority of subjects (2133/2578, 83%) participating in the belimumab clinical development program. A total of 1546 of these subjects received treatment with belimumab. This group encompasses patients from the supporting Phase II (**LBSL-02**) and the 2 pivotal 3 studies (**C1056** and **C1057**) as well as their respective open label extension periods.

Study **LBSL-99** is the open label extension phase of **LBSL-02** in which 296 subjects continued to receive belimumab 10 mg/kg every 28 days. Study **C1066** is a continuation trial for subjects in the USA who completed the forerunner Phase III Study **C1056**. Study **C1074** enrolled subjects outside of the USA who completed either of the 2 Phase III studies. In both extension trials, subjects continue to receive IV belimumab in the dose received during the initial trials, while subjects receiving placebo were be switched to belimumab 10 mg/kg.

Table 28 outlines the duration of exposure to belimumab therapy across 5 SLE specific studies (**LBSL-01**, **LBSL-02**, **LBSL-99**, **C1057** and **C1056**). At the time of data cut-off for the ongoing studies (**LBSL-99** and **C1056**), 1386 subjects (87% of the enrolled continuation period participants) had been treated with belimumab for at least 6 months; and 1107 (69%), 274 (17%), 248 (16%), 175 (11%) and 38 (2.4%) subjects had been treated for ≥ 1, ≥2, ≥ 3, ≥4, and ≥ 5 years, respectively.

Table 28. Overall Patient Exposure to Belimumab

	Placebo N=688	1 mg/kg N=688	4 mg/kg N=125	10 mg/kg[2] N=946	20 mg/kg N=14	All Active N=1603[3]
Duration of exposure[1] (days)						
Mean ± SD	346.72 ± 123.34	358.78 ± 130.80	358.27 ± 164.84	619.83 ± 495.46	38.36 ± 10.76	548.05 ± 486.55
Median	368.0	370.0	393.0	392.0	38.0	371.0
(Min, Max)	(28.0, 553.0)	(28.0, 625.0)	(28.0, 589.0)	(28.0, 1933.0)	(28.0, 50.0)	(28.0, 1937.0)
Duration of exposure[1] (months)						
3	636 (92.4%)	637 (92.6%)	106 (84.8%)	876 (92.6%)	--	1463 (91.3%)
6	598 (86.9%)	604 (87.8%)	102 (81.6%)	828 (87.5%)	--	1386 (86.5%)
9	544 (79.1%)	566 (82.3%)	99 (79.2%)	779 (82.3%)	--	1302 (81.2%)
12	458 (66.6%)	473 (68.8%)	93 (74.4%)	677 (71.6%)	--	1107 (69.1%)
18	1 (0.1%)	20 (2.9%)	23 (18.4%)	271 (28.6%)	--	297 (18.5%)
24[3]	--	--	--	257 (27.2%)	--	274 (17.1%)
30[3]	--	--	--	242 (25.6%)	--	257 (16.0%)
36[3]	--	--	--	226 (23.9%)	--	248 (15.5%)
42[3]	--	--	--	181 (19.1%)	--	229 (14.3%)
48[3]	--	--	--	73 (7.7%)	--	175 (10.9%)
54[3]	--	--	--	53 (5.6%)	--	151 (9.4%)
60[3]	--	--	--	16 (1.7%)	--	38 (2.4%)

Studies LBSL01, LBSL02, LBSL99, C1057 and C1056.

1 Duration is calculated as last infusion date - first infusion date + 28 days. A 3 month interval is defined as 13 weeks.

2 Includes subjects who were randomized to the 10 mg/kg group and subjects who switched to the 10 mg/kg group. For subjects who switched to the 10 mg/kg group, exposure was calculated after their 1st dose of 10 mg/kg belimumab treatment.

3 In the "10 mg/kg" column: Only the exposure to belimumab 10 mg/kg treatment was counted. In the "All Active" column": For patients who switched to belimumab 10 mg/kg group from belimumab 1 mg/kg or 4 mg/kg groups, the initial exposure to belimumab 1 mg/kg or 4 mg/kg treatment was counted in addition to the exposure to belimumab 10 mg/kg treatment.

The primary safety population dataset is robust in its size and extent of drug exposure for an assessment of short to medium term safety concerns, including AEs of interest (such as infusion reactions, infections, and haematological and biochemical parameters). However, it is not sufficient in size or duration of exposure to properly assess the risks of potential longer term AEs such as malignancy and mortality. This may be achieved with substantial post marketing surveillance or continued follow-up of the extension phases. Furthermore, in special populations (particularly pregnancy, the elderly or children) there is limited data available. Similarly, the long term safety data in male subjects is limited by small overall numbers in the clinical study program as SLE is a condition that predominately affects young to middle-aged women and the study populations reflected the affected demographic.

Adverse events

The overall incidence of subjects with at least 1 AE in the integrated IV SLE controlled repeat dose studies was similar for each of the belimumab dose groups (93.0% [626/673] for the 1 mg/kg and 92.7% [625/674] for the 10 mg/kg groups) and similar to the overall incidence in the placebo infusion group (92.4%, 624/675). There were no remarkable differences between the belimumab 1 and 10 mg/kg groups and the control arm when AEs were categorised by relationship to study agent, severity, seriousness or whether the AE

resulted in interruption or discontinuation of the study agent (refer to Table 29). Hence, no apparent dose response safety relationship for belimumab 1 and 10 mg/kg was observed. The rate of AEs was generally higher in Study **LBSL-02** compared with the controlled Phase III trials. The continuation Study **LBSL-99** was the only extension trial that included an option for on-going belimumab therapy at a dose of 4 mg/k, and the rate of overall AEs for this dose group was generally higher than for the other belimumab doses in the other extension trials (by indirect data comparison of differing studies). The reason for this discrepancy is not clear but the sponsor reasonably suggests that this may be the result of differences between the studies' populations (such as geographic region and entry criteria). Within Study **LBSL-02,** the rates of AEs were similar between all treatment groups (placebo infusion; and belimumab 1, 4 and 10 mg/kg). Therefore it is reasonable, Because of the limited patient numbers with dosing of belimumab at 4 mg/kg, the sponsor has appropriately focussed attention on the AEs involving subjects treated with belimumab 1 and 10 mg/kg and placebo plus standard of care.

Table 29. Number of Adverse Events in Phase II and III SLE Studies

	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
At least 1 AE	624 (92.4%)	626 (93.0%)	107 (96.4%)	625 (92.7%)
At least 1 related[1] AE	285 (42.2%)	270 (40.1%)	53 (47.7%)	269 (39.9%)
At least 1 serious AE	107 (15.9%)	125 (18.6%)	15 (13.5%)	117 (17.4%)
At least 1 severe[2] AE	104 (15.4%)	104 (15.5%)	26 (23.4%)	103 (15.3%)
At least 1 serious and/or severe[2] AE	145 (21.5%)	155 (23.0%)	32 (28.8%)	152 (22.6%)
At least 1 related serious AE	34 (5.0%)	35 (5.2%)	1 (0.9%)	31 (4.6%)
At least 1 related severe[2] AE	28 (4.1%)	28 (4.2%)	5 (4.5%)	25 (3.7%)
At least 1 related serious and/or severe[2] AE	43 (6.4%)	44 (6.5%)	5 (4.5%)	39 (5.8%)
At least 1 ongoing[3] AE	427 (63.3%)	397 (59.0%)	81 (73.0%)	411 (61.0%)
Ongoing AE at 8-Week FU[4]	153/241 (63.5%)	116/223 (52.0%)	16/23 (69.6%)	132/222 (59.5%)
At least 1 ongoing[3] serious AE	26 (3.9%)	27 (4.0%)	3 (2.7%)	33 (4.9%)
Ongoing serious AE at 8-Week FU[4]	12/241 (5.0%)	18/223 (8.1%)	2/23 (8.7%)	17/222 (7.7%)
At least 1 ongoing[3] severe AE	33 (4.9%)	33 (4.9%)	6 (5.4%)	36 (5.3%)
Ongoing severe AE at 8-Week FU[4]	20/241 (8.3%)	18/223 (8.1%)	2/23 (8.7%)	24/222 (10.8%)
At least 1 AE resulting in dosing interruption	85 (12.6%)	86 (12.8%)	25 (22.5%)	91 (13.5%)
At least 1 AE resulting in study agent discontinuation	48 (7.1%)	42 (6.2%)	4 (3.6%)	45 (6.7%)
Deaths	3 (0.4%)	5 (0.7%)	--	6 (0.9%)

Studies LBSL02, C1056, and C1057

1 Related is define as possibly, probably or definitely related to study agent.

2 Severe refers to Grade 3 and Grade 4.

3 Ongoing as of date of the last visit or withdrawal excluding 8 week Follow-up.

4 Ongoing as of the last contact among subjects who exited the study but did not enter the continuation studies (C1066 or C1074) or LBSL02 extension period.

Table 30 outlines the number and percentage of AEs by System Organ Class (SOC). Overall, there were similar incidences of AEs in each SOC in the belimumab 1 and 10 mg/kg groups compared with placebo care. The most frequent SOC group was "Infections and infestations" with 66.7% (450/675) of patients in placebo recording this type of AE compared with a marginally higher rate of the in each of the belimumab treatment groups (71.0% [478/673] for the 1 mg/kg and 69.9% [471/674] for the 10 mg/kg belimumab groups). Other commonly reported AEs in terms of SOC classification were Gastrointestinal disorders (39.7% for placebo versus 38.8-42.7% for belimumab), Nervous system (35.7% for placebo versus 34.3-36.9% for belimumab), Musculoskeletal and connective tissue (45.9% for placebo versus 42.5-44.1% for belimumab) and General

disorders and administration site conditions (30.5% for placebo versus 28.7-31.9% for belimumab).

Table 30. Number of Adverse Events by Organ Class in Phase II and III SLE Studies

System Organ Class	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
Blood and lymphatic system disorders	90 (13.3%)	85 (12.6%)	21 (18.9%)	87 (12.9%)
Cardiac disorders	45 (6.7%)	44 (6.5%)	14 (12.6%)	55 (8.2%)
Congenital, familial and genetic disorders	1 (0.1%)	1 (0.1%)	1 (0.9%)	2 (0.3%)
Ear and labyrinth disorders	33 (4.9%)	45 (6.7%)	9 (8.1%)	28 (4.2%)
Endocrine disorders	8 (1.2%)	13 (1.9%)	5 (4.5%)	11 (1.6%)
Eye disorders	59 (8.7%)	70 (10.4%)	15 (13.5%)	73 (10.8%)
Gastrointestinal disorders	268 (39.7%)	261 (38.8%)	61 (55.0%)	288 (42.7%)
General disorders and administration site conditions	206 (30.5%)	193 (28.7%)	63 (56.8%)	215 (31.9%)
Hepatobiliary disorders	18 (2.7%)	16 (2.4%)	6 (5.4%)	15 (2.2%)
Immune system disorders	21 (3.1%)	30 (4.5%)	5 (4.5%)	19 (2.8%)
Infections and infestations	450 (66.7%)	478 (71.0%)	88 (79.3%)	471 (69.9%)
Injury, poisoning and procedural complications	114 (16.9%)	112 (16.6%)	37 (33.3%)	123 (18.2%)
Investigations	103 (15.3%)	93 (13.8%)	41 (36.9%)	95 (14.1%)
Metabolism and nutrition disorders	67 (9.9%)	62 (9.2%)	18 (16.2%)	78 (11.6%)
Musculoskeletal and connective tissue disorders	310 (45.9%)	286 (42.5%)	72 (64.9%)	297 (44.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	25 (3.7%)	24 (3.6%)	3 (2.7%)	18 (2.7%)
Nervous system disorders	241 (35.7%)	231 (34.3%)	58 (52.3%)	249 (36.9%)
Pregnancy, puerperium and perinatal conditions	4 (0.6%)	3 (0.4%)	--	5 (0.7%)
Psychiatric disorders	82 (12.1%)	103 (15.3%)	25 (22.5%)	100 (14.8%)
Renal and urinary disorders	82 (12.1%)	63 (9.4%)	15 (13.5%)	73 (10.8%)
Reproductive system and breast disorders	68 (10.1%)	73 (10.8%)	12 (10.8%)	69 (10.2%)
Respiratory, thoracic and mediastinal disorders	179 (26.5%)	176 (26.2%)	39 (35.1%)	159 (23.6%)
Skin and subcutaneous tissue disorders	235 (34.8%)	251 (37.3%)	65 (58.6%)	233 (34.6%)
Social circumstances	--	2 (0.3%)	--	--
Surgical and medical procedures	13 (1.9%)	9 (1.3%)	10 (9.0%)	14 (2.1%)
Vascular disorders	103 (15.3%)	94 (14.0%)	23 (20.7%)	95 (14.1%)

Studies LBSL02, C1056, C1057

The most frequent AEs by the preferred term nomenclature (affecting at least 5% of individuals in any treatment group) are shown in Table 31. Overall, the incidence of the most frequent AEs was similar between the 3 treatment groups of interest (belimumab 1 and 10 mg/kg group and the placebo group). More than 10% of all subjects in the belimumab 1 mg/kg and 10 mg/kg groups and in the placebo group experienced headache (21%), upper respiratory tract infections (URTI) (18%-19%), arthralgia (15%-16%), nausea (12%-15%), urinary tract infection (UTI) (12%-14%) and fatigue (10%-11%). The remaining events occurred at an incidence of less than 10%.

Table 31. Most Frequent Adverse Events in Phase II and III SLE Studies. Table continued across two pages

Preferred Term [1]	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
Headache	140 (20.7%)	138 (20.5%)	30 (27.0%)	142 (21.1%)
Upper respiratory tract infection	130 (19.3%)	128 (19.0%)	36 (32.4%)	118 (17.5%)
Arthralgia	112 (16.6%)	100 (14.9%)	32 (28.8%)	109 (16.2%)
Nausea	82 (12.1%)	88 (13.1%)	22 (19.8%)	99 (14.7%)
Urinary tract infection	82 (12.1%)	92 (13.7%)	19 (17.1%)	87 (12.9%)
Diarrhoea	62 (9.2%)	81 (12.0%)	23 (20.7%)	80 (11.9%)
Fatigue	70 (10.4%)	71 (10.5%)	33 (29.7%)	66 (9.8%)
Back pain	62 (9.2%)	64 (9.5%)	15 (13.5%)	60 (8.9%)
Oedema peripheral	54 (8.0%)	62 (9.2%)	19 (17.1%)	56 (8.3%)
Pyrexia	52 (7.7%)	52 (7.7%)	17 (15.3%)	65 (9.6%)
Nasopharyngitis	48 (7.1%)	57 (8.5%)	2 (1.8%)	61 (9.1%)
Cough	49 (7.3%)	54 (8.0%)	8 (7.2%)	52 (7.7%)
Vomiting	44 (6.5%)	49 (7.3%)	15 (13.5%)	46 (6.8%)
Sinusitis	54 (8.0%)	34 (5.1%)	15 (13.5%)	49 (7.3%)
Bronchitis	35 (5.2%)	43 (6.4%)	12 (10.8%)	60 (8.9%)
Myalgia	47 (7.0%)	46 (6.8%)	10 (9.0%)	46 (6.8%)
Influenza	42 (6.2%)	47 (7.0%)	11 (9.9%)	47 (7.0%)
Hypertension	55 (8.1%)	42 (6.2%)	5 (4.5%)	43 (6.4%)
Arthritis	41 (6.1%)	35 (5.2%)	21 (18.9%)	40 (5.9%)
Rash	35 (5.2%)	46 (6.8%)	17 (15.3%)	35 (5.2%)
Dizziness	42 (6.2%)	38 (5.6%)	12 (10.8%)	37 (5.5%)
Insomnia	36 (5.3%)	37 (5.5%)	5 (4.5%)	44 (6.5%)
Pain in extremity	27 (4.0%)	35 (5.2%)	13 (11.7%)	40 (5.9%)
Depression	25 (3.7%)	41 (6.1%)	12 (10.8%)	35 (5.2%)
Mouth ulceration	35 (5.2%)	23 (3.4%)	12 (10.8%)	36 (5.3%)
Abdominal pain	35 (5.2%)	33 (4.9%)	5 (4.5%)	32 (4.7%)
Gastroenteritis	32 (4.7%)	36 (5.3%)	3 (2.7%)	25 (3.7%)
Anaemia	31 (4.6%)	27 (4.0%)	7 (6.3%)	30 (4.5%)
Alopecia	33 (4.9%)	24 (3.6%)	9 (8.1%)	26 (3.9%)
Non-cardiac chest pain	34 (5.0%)	23 (3.4%)	6 (5.4%)	28 (4.2%)
Migraine	27 (4.0%)	23 (3.4%)	6 (5.4%)	34 (5.0%)
Weight increased	24 (3.6%)	24 (3.6%)	8 (7.2%)	27 (4.0%)
Dyspnoea	31 (4.6%)	20 (3.0%)	8 (7.2%)	15 (2.2%)
Viral upper respiratory tract infection	21 (3.1%)	22 (3.3%)	8 (7.2%)	21 (3.1%)
Musculoskeletal pain	22 (3.3%)	18 (2.7%)	11 (9.9%)	20 (3.0%)
Anxiety	17 (2.5%)	30 (4.5%)	7 (6.3%)	15 (2.2%)

Table 31. continued

Vulvovaginal mycotic infection	22 (3.3%)	20 (3.0%)	8 (7.2%)	18 (2.7%)
Leukopenia	15 (2.2%)	20 (3.0%)	6 (5.4%)	25 (3.7%)
Joint swelling	18 (2.7%)	17 (2.5%)	11 (9.9%)	18 (2.7%)
Contusion	17 (2.5%)	18 (2.7%)	7 (6.3%)	19 (2.8%)
Rash maculo-papular	25 (3.7%)	15 (2.2%)	6 (5.4%)	14 (2.1%)
Musculoskeletal chest pain	15 (2.2%)	19 (2.8%)	6 (5.4%)	15 (2.2%)
Proteinuria	21 (3.1%)	11 (1.6%)	7 (6.3%)	15 (2.2%)
Urticaria	15 (2.2%)	14 (2.1%)	7 (6.3%)	15 (2.2%)
Erythema	12 (1.8%)	19 (2.8%)	10 (9.0%)	8 (1.2%)
Pain	6 (0.9%)	5 (0.7%)	6 (5.4%)	13 (1.9%)
Infusion site extravasation	9 (1.3%)	6 (0.9%)	12 (10.8%)	2 (0.3%)
Synovitis	5 (0.7%)	5 (0.7%)	6 (5.4%)	10 (1.5%)
Creatinine renal clearance decreased	4 (0.6%)	5 (0.7%)	8 (7.2%)	5 (0.7%)
Viral infection	4 (0.6%)	5 (0.7%)	7 (6.3%)	1 (0.1%)

Studies LBSL02, C1056, C1057

[1] Sorted by descending frequency across all treatment groups combined. T21 (Appendix 15)

The most frequent AE that occurred more commonly in the belimumab treatment groups compared to the placebo arm was diarrhoea (12.0% [81/673] in the 1 mg/kg and 11.9% [80/674] in the 10 mg/kg groups compared with 9.2% [62/675] in the placebo group). In addition, bronchitis occurred at a higher frequency in the belimumab 10 mg/kg group (8.9%, 60/674) than in the belimumab 1 mg/kg (6.4%, 43/673) and placebo groups (5.2%, 35/675). Nausea also occurred at a slightly higher frequency in the belimumab 10 mg/kg group (14.7%, 99/674) than in the belimumab 1 mg/kg (13.1%, 88/673) and placebo groups (12.1%, 82/675). Other AEs that occurred at a slightly higher incidence in the belimumab treatment groups compared with placebo were pyrexia (7.7%, 7.7%, and 9.6% for the placebo, 1 mg/kg and 10 mg/kg groups, respectively) and nasopharyngitis (7.1%, 8.5%, and 9.1% for the placebo, 1 mg/kg and 10 mg/kg groups, respectively). Also noteworthy is that some AEs occurred at higher incidence in the placebo group than in the belimumab groups (such as hypertension, dyspnoea and maculo-papular rash). The differences in the AE incidence rates between the belimumab 1 and 10 mg/kg groups and the control arm were generally small and there was no indication of an increasing incidence of AE at the higher belimumab dose.

In addition, there does not seem to be any clinically relevant differences in the quantity or type of AE that occurs in the first 6 months of therapy or the second 6 months of treatment. The numbers of subjects treated with belimumab for more than 12 months are such that there is insufficient data to assess whether the rate or type of adverse events changes with treatment beyond 12 months. Therefore, based on current dataset there does not appear to be increased incidence of AEs with cumulative belimumab exposure but there are limitations to the quality of that current dataset for an appropriate assessment of that claim.

The overall incidence of AEs considered by the investigator to be at least possibly related to study medication was 42% for the placebo group and 40% for the belimumab 1 mg/kg and 10 mg/kg groups. Severe and serious AEs considered related to study medication occurred at similar rates across placebo and active treatment groups. The incidence rates of individual AE types considered at least possibly related to study agent by the investigators were generally equal to or lower in the belimumab groups than that observed in the placebo group. Certain infections considered possibly related to study medication such as bronchitis, pharyngitis, viral upper respiratory infections and cellulitis (each of which occurred at a rate less than 3% across all groups) occurred more frequently in belimumab treatment groups. This will be discussed further under *Adverse Events of*

Special Interest, Infections below. It is difficult to assess whether the investigators assessment of what constituted a drug-related AE is accurate, especially given that there were similar incidences across all treatment groups for most types of AEs. Given the mechanism of action of belimumab, the increased incidence of certain infections that were thought to be drug-related is biologically plausible.

Data on common adverse events in the RA, healthy volunteer and SC belimumab studies are consistent with the findings reported for the IV SLE studies but given the smaller numbers of subjects, detection of a true difference would be difficult.

Adverse events of special interest

Infusion reactions, including hypersensitivity reactions, have been reported with the administration of therapeutic proteins including monoclonal antibodies. Monoclonal antibodies directed against components of the immune system can also exert immunomodulatory effects and as such may increase both the risk of infections and the risk of developing malignancies. Given these potential risks, a group of AEs of special interest that was pre specified:

- Infusion-related reactions and hypersensitivity reactions (that is, those occurring on the day of infusion),
- Infections, and
- Malignant neoplasms.

Infusion and hypersensitivity reactions

In the IV administered, randomised, controlled trials involving patients with SLE (Studies **LBSL-02**, **C1056** and **C1057**), infusion and hypersensitivity reactions occurred in all treatment groups but at an incidence that was generally higher in the belimumab treatment groups compared with the placebo arm. The overall incidence of infusion or hypersensitivity reactions was 14.7% (99/675) in the placebo group and 16.6 (112/673) and 16.8% (113/674) each in the belimumab 1 and 10 mg/kg groups. At least half of the subjects in each treatment group who experienced infusion or hypersensitivity reactions had events that were considered related to study medication by the study investigator (9.0%, 8.5%, and 12% for the placebo, 1 and 10 mg/kg groups, respectively). Few subjects (≤1% in each group) had infusion and hypersensitivity AEs that were serious or severe, led to withdrawal, or resulted in dosing interruption, although observed at a slightly higher incidence in the 2 belimumab dose groups compared with placebo. Refer to Table 32.

Table 32. Number of Hypersensitivity and Infusion Reactions in Phase II and III SLE Studies

	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
At least 1 AE	99 (14.7%)	112 (16.6%)	26 (23.4%)	113 (16.8%)
At least 1 related[1] AE	61 (9.0%)	57 (8.5%)	15 (13.5%)	80 (11.9%)
At least 1 serious AE	3 (0.4%)	6 (0.9%)	--	6 (0.9%)
At least 1 severe[2] AE	2 (0.3%)	5 (0.7%)	--	7 (1.0%)
At least 1 serious and/or severe[2] AE	4 (0.6%)	8 (1.2%)	--	8 (1.2%)
At least 1 related serious AE	2 (0.3%)	6 (0.9%)	--	6 (0.9%)
At least 1 related severe[2] AE	2 (0.3%)	4 (0.6%)	--	6 (0.9%)
At least 1 related serious and/or severe[2] AE	3 (0.4%)	7 (1.0%)	--	7 (1.0%)
At least 1 ongoing[3] AE	--	--	--	1 (0.1%)
Ongoing AE at 8-Week FU[4]	--	--	--	--
At least 1 ongoing[3] serious AE	--	--	--	--
Ongoing serious AE at 8-Week FU[4]	--	--	--	--
At least 1 ongoing[3] severe AE	--	--	--	--
Ongoing severe AE at 8-Week FU[4]	--	--	--	--
At least 1 AE resulting in dosing interruption	3 (0.4%)	1 (0.1%)	1 (0.9%)	5 (0.7%)
At least 1 AE resulting in study agent discontinuation	2 (0.3%)	4 (0.6%)	1 (0.9%)	7 (1.0%)
Deaths	--	--	--	--

Studies LBSL02, C1056, and C1057

1 Related is defined as possibly, probably or definitely related to study agent.

2 Severe refers to Grade 3 and Grade 4.

3 Ongoing as of date of the last visit or withdrawal excluding 8 week Follow-up.

4 Ongoing as of the last contact among subjects who exited the study but did not enter the BLISS continuation studies or LBSL02 extension period.

The highest incidence of infusion-related AE involved the Nervous system disorders SOC (6.8%, 5.1%, and 5.3% in the placebo, 1 mg/kg and 10 mg/kg groups, respectively) and headache was the most common type of AE (4.0%, 3.7% and 3.6%, respectively). The second highest incidence of infusion-related AE involved Gastrointestinal disorders SOC (3.6%, 3.1% and 3.9%, respectively) with nausea being reported most often (2.8%, 2.5% and 3.3%, respectively). Other frequently reported infusion and hypersensitivity AEs included dizziness, hypotension, hypertension, infusion-related reaction (not otherwise specified), pyrexia and arthralgia. Of all the infusion and hypersensitivity events reported in ≥5 subjects, only infusion-related reaction, pyrexia, and arthralgia occurred more frequently in the belimumab treatment groups than in the placebo group.

The sponsor states that the immunogenicity status of subjects was most reliably measured in the Phase III studies. In these two studies (**C1056** and **C1057**), a total of 76, 88 and 84 subjects in the placebo, belimumab 1 mg/kg and 10 mg/kg groups (respectively) experienced an infusion or hypersensitivity reaction. Of these, 4 subjects (1 in the placebo group, 2 in the 1 mg/kg group, and 1 in the 10 mg/kg group) also had persistent positive immune responses to belimumab. Eight subjects in the 1 mg/kg group who experienced an infusion or hypersensitivity reaction had transient immune responses to belimumab and the remaining subjects who experienced an infusion or hypersensitivity reaction did not have detectable anti-belimumab antibodies. Given there are only a small number of subjects who developed anti-belimumab antibodies who experienced infusion-related reactions, there is little evidence to confirm causality at present.

The majority of infusion and hypersensitivity reactions occurred during the first 6 months of treatment and the overall rates (AEs per 100 subject-years) were 24.9, 25.2, and 29.1

for the placebo, 1 and 10 mg/kg groups respectively, with the highest incidence occurring with the first infusion (4.1%, 5.8%, and 7.3% in the placebo, 1 and 10 mg/kg belimumab groups, respectively) and continued to decline with each subsequent infusion. There appeared to be a treatment and dose-related relationship in the incidence of these reactions for the first 2 infusions, however, no formal statistical analyses were performed and the absolute and relative differences between treatment groups were small.

The incidence of serious or severe infusion and hypersensitivity reactions was low but tended to occur in more subjects treated with belimumab than with placebo. Fifteen subjects had serious infusion or hypersensitivity reactions: 3 (0.4%) in the placebo group and 6 (0.9%) each in the 1 mg/kg and 10 mg/kg belimumab groups. Specific symptoms reported with serious infusion-related reactions were variable. Dyspnoea was the only symptom reported by more than 1 subject (1 in the 1 mg/kg group and 2 in the 10 mg/kg group). Other infusion and hypersensitivity reaction SAEs occurring in more than 1 subject included anaphylactic reaction (2 subjects in the 1 mg/kg group and 1 subject in the 10 mg/kg group) and angioedema (1 subject in each belimumab group).

Ten subjects had infusion or hypersensitivity reactions which led to dosing interruption: 3 (0.4%), 1 (0.1%), 1 (0.9%), and 5 (0.7%) subjects in the placebo, 1, 4, and 10 mg/kg groups, respectively. Fourteen subjects had their study medication discontinued due to either an infusion or hypersensitivity reaction. More subjects in the belimumab groups had study drug discontinued (4 subjects [0.6%] in the 1 mg/kg group, 1 subject [0.9%] in the 4 mg/kg group, and 7 subjects [1.0%] in 10 mg/kg group) compared with the placebo group (2 subjects, 0.3%). Events which led to study drug discontinuation included infusion-related reaction (not otherwise specified), anaphylactic reaction, angioedema, bradycardia, drug hypersensitivity (not otherwise specified), dyspnoea and generalised pruritus. Table 33 outlines the details of the 4 subjects (of a total of 1458) that suffered serious and/or severe hypersensitivity reactions that occurred on the day of infusion. A fifth subject is also likely to have had a hypersensitivity reaction (receiving belimumab 1 mg/kg) but it had been incorrectly labelled by a study investigator as not being a hypersensitivity reaction.

Table 33. Severe and/or Serious Hypersensitivity Reactions

Treatment Group	Protocol/ Subject ID	Preferred Term	AE Duration	Study day / # infusions	Serious?/ Severity[1]/ Relationship[2]/ Action[3]
1 mg/kg	C1057 IN005-027	Anaphylactic reaction	1 day	0 / 1	Yes/ Mild/ DR/ Disc
	C1057 TW004-008	Anaphylactic reaction	1 day	0 / 1	Yes/ LT/ DR/ None
		Angioedema	1 day	0 / 1	Yes/ LT/ DR/ Disc
10 mg/kg	C1057 IN005-017	Anaphylactic reaction	1 day	0 / 1	Yes/ LT/ DR/ Disc
		Angioedema	12 days	0 / 1	Yes/ Sev/ DR/ Intrr
	C1057 PH002-001	Drug hypersensitivity	2 days	0 / 1	Yes/ Sev/ DR/ Disc

1 AE Severity: Mild (Mild), Mod (Moderate), Sev (Severe), LT (Life Threatening.)
2 AE Relationship: NR (Not Related), PNR (Probably Not Related), PR (Possibly Related), PrR (Probably Related), DR (Definitely Related.)
3 AE Action: None (None), Intrr (Interrupted), Decr (Decreased), Disc (Discontinued).

Overall, the incidence of infusion-related reactions tended to be higher in belimumab treated subjects, which is an expected outcome. Serious or severe reactions were uncommon (<2% in total) and occurred in both placebo infusion and belimumab treated patients. Additionally, serious/severe hypersensitivity reactions were also infrequent (0.3%, 5/1458 subjects receiving belimumab). All but 1 of these AEs occurred with the

first infusion. All serious or severe events resolved either spontaneously, with supportive care or following discontinuation of study agent. No fatal infusion or hypersensitivity events were identified.

Infusion-related and hypersensitivity reaction adverse event data from the remainder of the safety population (Studies **LBLS-99**, **C1066**, **C1074**, **LBRA-01**, **LBRA-99**, **LBSL-01** and **C1058**) were not demonstrably different from that obtained from the pivotal Phase II and 3 trials (**LBSL-02**, **C1056** and **C1057**), however the overall number of affected subjects is much smaller.

Infections

Given the mechanism of action of belimumab (inhibition of BLyS) with its subsequent effects on B cells and immunoglobulins, an increased susceptibility to infection was paid special attention in the clinical development program.

Table 34 outlines the infection adverse reactions seen in the IV SLE randomised controlled trials (**LBSL-02**, **C1056**, **and C1057**). In these studies, generally the incidence of infections was slightly higher in the belimumab treatment groups compared with the placebo group. The overall incidence of infections was 66.7% in the placebo group, 71.0% in the belimumab 1 mg/kg group, and 69.9% in the belimumab 10 mg/kg treatment group. Infectious AEs that resulted in discontinuation of study medication occurred at similar incidences in the placebo group (1%) and the belimumab groups (<1%), while infection-related AEs that resulted in dosing interruptions occurred at a slightly higher incidence in the belimumab groups (9-11%) compared to the placebo group (6%). Slightly more infectious AEs occurred during the first 6 months of treatment compared with the second 6 months of therapy. There were 106, 113, and 112 AEs per 100 subject-years for the placebo, 1 mg/kg, and 10 mg/kg groups (respectively) in the first 6 months compared with incidence rates of 94, 104, and 101 AEs per 100 subject-years in the second 6 months of treatment.

Table 34. Infection Adverse Events in Phase II and III SLE Studies

System Organ Class Preferred Term [1]	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
Infections and infestations	450 (66.7%)	478 (71.0%)	88 (79.3%)	471 (69.9%)
Upper respiratory tract infection	130 (19.3%)	128 (19.0%)	36 (32.4%)	118 (17.5%)
Urinary tract infection	82 (12.1%)	92 (13.7%)	19 (17.1%)	87 (12.9%)
Nasopharyngitis	48 (7.1%)	57 (8.5%)	2 (1.8%)	61 (9.1%)
Sinusitis	54 (8.0%)	34 (5.1%)	15 (13.5%)	49 (7.3%)
Bronchitis	35 (5.2%)	43 (6.4%)	12 (10.8%)	60 (8.9%)
Influenza	42 (6.2%)	47 (7.0%)	11 (9.9%)	47 (7.0%)
Gastroenteritis	32 (4.7%)	36 (5.3%)	3 (2.7%)	25 (3.7%)
Viral upper respiratory tract infection	21 (3.1%)	22 (3.3%)	8 (7.2%)	21 (3.1%)
Vulvovaginal mycotic infection	22 (3.3%)	20 (3.0%)	8 (7.2%)	18 (2.7%)

Studies LBSL02, C1056, C1057

[1] Preferred terms are sorted by descending frequency across all treatment groups combined within a SOC

URTI and UTI were the most frequently reported infections and occurred at similar incidences across the placebo, 1 mg/kg and 10 mg/kg belimumab groups. There was a slightly higher incidence of nasopharyngitis and bronchitis in the belimumab groups compared with placebo, while the rates of sinusitis were slightly lower in the belimumab 1 and 10 mg/kg groups compared with placebo. Gastroenteritis, viral URTI and vulvovaginal fungal infections were reported at similar incidences in the belimumab and placebo treatment groups. The remaining types of common infectious AEs were reported at either low rates (<5%) for the belimumab arms or at similar incidence across the placebo and belimumab (both 1 and 10 mg/kg) groups.

Serious infections

In the SLE randomised controlled trials (**LBSL-02**, **C1056** and **C1057**), the incidence rate of serious infections per 100 subject-years was statistically comparable between the belimumab (5.97, 95% CI: 4.79, 7.36) and placebo (5.21, 95%CI: 3.63, 7.24; RR 1.15, 95% CI: 0.77, 1.75) groups. As the 95% confidence intervals cross zero, there is no evidence of a statistically significant difference by treatment effect. However, this does not necessarily exclude a true difference and may reflect that the study was not powered to detect such a difference. Whether a difference of 0.76 serious infections per 100 patient-years is a clinically relevant is open to debate. The sponsor states that these rates are similar to incidence rates of serious infections reported in the published literature for SLE patients: incidence rate 2.64 (95% CI: 1.95, 3.51) to 5.75 (95% CI: 3.64, 8.63) per 100 subject-years[13,14]. However, when reviewing the articles by *Gladman et al* and *Zonana-Nacach et al*, these incidence rates are not apparent in the published data. Nonetheless, the populations in the 2 quoted studies are different in multiple respects from the belimumab study populations with respect to ethnicity, baseline medications (prednisone and immunosuppressant drugs) and disease activity. It is therefore difficult to compare rates of serious infections across these studies. The most frequent serious infections in these belimumab studies are outlined in Table 35.

Table 35. Most Frequent Infections in Phase II and III SLE Studies

System Organ Class Preferred Term [1]	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
Serious Infections and infestations	35 (5.2%)	46 (6.8%)	7 (6.3%)	35 (5.2%)
Pneumonia	10 (1.5%)	7 (1.0%)	1 (0.9%)	6 (0.9%)
Urinary tract infection	4 (0.6%)	7 (1.0%)	1 (0.9%)	5 (0.7%)
Cellulitis	2 (0.3%)	7 (1.0%)	1 (0.9%)	1 (0.1%)
Bronchitis	1 (0.1%)	2 (0.3%)	1 (0.9%)	3 (0.4%)
Pyelonephritis	3 (0.4%)	3 (0.4%)	--	--

Studies LBSL02, C1056, C1057

[1] Preferred terms are sorted by descending frequency across all treatment groups.

The sponsor has pre-defined infectious AEs of special interest to include:

- Cellulitis (including similar events such as erysipelas, impetigo, and abscess),
- Fungal and Herpes infections,
- Sepsis,
- Respiratory tract infections, and
- Opportunistic infections.

The reported infections of special interest are summarised in Table 36. Among these, rates of fungal and herpes viral infections in the belimumab 1 and 10 mg/kg treatment groups were similar to, or less than that reported in the control group. Cellulitis was reported in a slightly higher proportion of belimumab treated subjects who received either 1 or 4 mg/kg than placebo but there was no difference when comparing control treatment with the belimumab 10 mg/kg group. Hence, there was no apparent belimumab dose-response relationship for this type of AE. For sepsis, the numbers overall were small with a slightly greater incidence in the belimumab groups compared with placebo. There was a slightly higher rate of lower respiratory tract infections (LRTI) in belimumab treated subjects but

[13] Gladman DD, Hussain F, Iban D, Urowitz MB. The nature and outcome of infection in systemic lupus erythematosus. Lupus 2002; 11:234-239.

[14] Zonana-Nacach A, Camargo-Corone A, Yanez P, Sanchez L et al. Infections in outpatients with systemic lupus erythematosus: a prospective study. Lupus 2001; 10:505-10.

the difference does not appear to be driven by pneumonias, which were reported in similar proportions of subjects across all treatment groups. The only 2 possible opportunistic infections occurred in subjects treated with belimumab 10 mg/kg; disseminated CMV infection and *Acinetobacter bacteraemia*. Overall, there appears to be no clinically relevant differences in the rate of infectious AEs of special interest with the exception of respiratory tract infections (though overall numbers were small). However, the current studies are not likely to be powered to detect any differences for this outcome.

Table 36. Infections of Special Interest in the Phase II and III3 SLE Studies

	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
Cellulitis	43 (6.4%)	55 (8.2%)	9 (8.1%)	43 (6.4%)
Fungal infections	22 (3.3%)	20 (3.0%)	4 (3.6%)	17 (2.5%)
Herpes viral infections	54 (8.0%)	51 (7.6%)	5 (4.5%)	44 (6.5%)
Sepsis	3 (0.4%)	4 (0.6%)	1 (0.9%)	5 (0.7%)
All respiratory infections	327 (48.4%)	342 (50.8%)	66 (59.5%)	350 (51.9%)
Upper respiratory infections	292 (43.3%)	294 (43.7%)	61 (55.0%)	302 (44.8%)
Lower respiratory infections	58 (8.6%)	76 (11.3%)	13 (11.7%)	81 (12.0%)
Pneumonia	17 (2.5%)	21 (3.1%)	2 (1.8%)	16 (2.4%)
Possible opportunistic infections	--	--	--	2 (0.3%)

Studies LBSL02, C1056, C1057
Respiratory tract infections coded to MedDRA high-level term (HLT) Respiratory Tract Infections NEC are unspecified in terms of location (ie, lower or upper) and therefore are counted under "All respiratory infections" only.

Serious infections of special interest occurred infrequently overall (3-4%) and there appeared to be little differences between the belimumab treatment and placebo + SOC groups. The details of these are outlined in Table 37. Severe infections occurred in from 2 to 5% of subjects across treatment groups with no apparent belimumab treatment effect or dose relationship (see Table 38). However, given the very small numbers of infections in all groups, the sponsor's studies are not powered to detect a difference in either serious or severe infections.

Table 37. Serious Infections of Special Interest

	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
At least 1 serious AE	20 (3.0%)	27 (4.0%)	4 (3.6%)	22 (3.3%)
Cellulitis	5 (0.7%)	9 (1.3%)	1 (0.9%)	3 (0.4%)
Fungal infections	1 (0.1%)	--	--	--
Herpes viral infections	3 (0.4%)	4 (0.6%)		5 (0.7%)
Sepsis	1 (0.1%)	4 (0.6%)	1 (0.9%)	5 (0.7%)
All respiratory infections	12 (1.8%)	12 (1.8%)	3 (2.7%)	10 (1.5%)
Upper respiratory infections	1 (0.1%)	--	--	2 (0.3%)
Lower respiratory infections	11 (1.6%)	12 (1.8%)	3 (2.7%)	9 (1.3%)
Pneumonia	10 (1.5%)	9 (1.3%)	2 (1.8%)	7 (1.0%)
Possible opportunistic infections	--	--	--	2 (0.3%)

Studies LBSL02, C1056, C1057
Respiratory tract infections coded to HLT Respiratory Tract Infections NEC are unspecified in terms of location (ie, lower or upper) and therefore are counted under "All respiratory infections" only.

Table 38. Severe Infections of Special Interest

	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
At least 1 severe AE	14 (2.1%)	14 (2.1%)	5 (4.5%)	15 (2.2%)
Cellulitis	2 (0.3%)	3 (0.4%)	1 (0.9%)	1 (0.1%)
Fungal infections	--	--	--	1 (0.1%)
Herpes viral infections	4 (0.6%)	2 (0.3%)	--	3 (0.4%)
Sepsis	2 (0.3%)	2 (0.3%)	--	5 (0.7%)
All respiratory infections	6 (0.9%)	9 (1.3%)	4 (3.6%)	7 (1.0%)
Upper respiratory infections	3 (0.4%)	--	2 (1.8%)	2 (0.3%)
Lower respiratory infections	5 (0.7%)	9 (1.3%)	2 (1.8%)	5 (0.7%)
Pneumonia	3 (0.4%)	8 (1.2%)	1 (0.9%)	3 (0.4%)
Possible opportunistic infections	--	--	--	2 (0.3%)

Studies LBSL02, C1056, C1057
Severe refers to Grade 3 and Grade 4
Respiratory tract infections coded to HLT Respiratory Tract Infections NEC are unspecified in terms of location (ie, lower or upper) and therefore are counted under "All respiratory infections" only.

The sponsor's submission also tried to examine whether or not a correlation between severe (Grade 3 or 4) lymphopenia, neutropenia and hypogammaglobulinemia and increased risk of infection existed. The sponsor states that the results of these analyses are difficult to interpret because of the multifactorial impact of disease activity, baseline laboratory parameters and potentially of belimumab on these measures. In addition, the sponsor could not establish a temporal relationship between the onset of an infection and laboratory measures due to lack of data obtained at the corresponding time point. Considering those limitations, there were no significant changes in the rate of Grade 3 or Grade 4 lymphopenia, neutropenia or hypogammaglobulinemia between the placebo, 1 mg/kg and 10 mg/kg belimumab groups. In addition, the proportion of subjects with Grade 3 and 4 recorded white blood cell count toxicities was small. Therefore, it is difficult to attribute any changes in infection rate to changes in lymphocyte or neutrophil count or hypogammaglobulinaemia.

There did not appear to be a clinically significant difference in infection rates in subgroups of patients involved with the SLE controlled repeat dose studies (**LBSL-02**, **C1056** and **C1057**). Any differences appeared to be minor and confounded by the small number of subjects in some subgroups (such as males n = 129; age > 65 years, n = 35). There appeared to be an increase in infection rates in subjects taking mycophenolate mofetil compared to patients taking other immunosuppressant medications (10 per 100 subject-years for mycophenolate versus 3.5 per 100 subject-years for other immunosuppression treatment). However, this difference occurred irrespective of whether subjects were in the placebo or belimumab treatment groups, inferring that mycophenolate mofetil (and not belimumab) was more likely to be the cause of increased infection rates.

In the long term SLE studies (such as **LBSL-99**) the incidence of infections, including serious and severe infections, remained stable or declined over time. Adverse event profiles in these studies are reflective of those seen in the controlled studies.

Malignant neoplasms

In the controlled SLE trials (**LBSL-02**, **C1056** and **C1057**), the rate of malignant neoplasms per 100 subject-years for all malignancies (including non-melanoma skin cancers) was comparable between the belimumab (0.41; 95% CI: 0.15, 0.89) and placebo (0.45; 95% CI: 0.09, 1.30) groups; the rate ratio was 0.91 (95% CI: 0.19, 5.64) (Table 39). This infers that there was no clinically or statistically significant difference by treatment effect. This rate is comparable to a large, international SLE cohort study when non-melanoma skin cancers

are excluded. The sponsor did this on the assumption that these cancers are less likely to be reported in non-trial setting which is an appropriate assumption. No pattern of malignancies or an increase in any particular type of malignancy was identified with belimumab treatment in the controlled studies. The 8 cases of solid tumour involved various organs (breast, lung and ovary) and there were 4 cases of thyroid neoplasm and 5 cases of skin cancer (including 1 subject with malignant melanoma).

Table 39. Comparative Death Rates

Total Across All SLE Trials (LBSL01, LBSL02, C1056, C1057, C1066, C1074, C1070, and LBSL99)	Background Rate[1] n = 9547 76,948 subj-yrs	Belimumab[2] n = 1955 3507.0 subj-yrs	Rate Ratio
Subjects with events	410 (4.3%)	17 (0.9%)	
Rate/100 subj-yrs (95% CI)	0.53 (0.48, 0.59)	0.48 (0.28, 0.78)	0.91 (0.52, 1.47)

[1] Bernatsky, 2005 (data from a large, international SLE cohort study. Observed cancers were determined by linkage to regional cancer registries which were not designed to capture non-melanoma skin cancers).

[2] Includes the following subjects with events unspecified as benign or malignant: (a) LBSL99-US040-010 with hepatic and lung neoplasm (b) LBSL99-US046-029 with lung neoplasm (c) LBSL99-US007-002 with thyroid and lung neoplasm. Does not include the following subjects with events unspecified as benign or malignant: LBSL02-US052-009, LBSL99-US028-001, LBSL99-US031-007 and LBSL99-US045-003 with thyroid neoplasms and LBSL99-US029-001 with soft tissue tumor.

However, the overall length of follow-up is insufficient to properly assess from any change in malignancy rates as most malignancies develop over of longer period of time than 12 months and often are not recognised and diagnosed for several years.

Psychiatric disorders

Neuropsychiatric events are well recognised as occurring in the SLE population with a wide range of incidence. In a recent international inception cohort study[15], neuropsychiatric events occurred in 28% of subjects near the time of SLE diagnosis and the incidence of mood disorders attributed to SLE ranged from 4% to 13% depending on the attribution model used. Another study[16] found the prevalence rates of many psychiatric disorders (such as major depression, bipolar and panic disorder) were significantly higher in patients with SLE than the general population.

Psychiatric disorders were reported at a slightly higher incidence in the belimumab groups (15% each in the belimumab 1 and 10 mg/kg groups) compared with placebo (12%) and were driven primarily by mild/moderate events of insomnia (5.3%, 5.5%, 6.5% in the placebo, 1 mg/kg and 10 mg/kg groups, respectively), depression (3.7%, 6.1%, 5.2% in the placebo, 1 mg/kg and 10 mg/kg groups, respectively) and anxiety (2.5%, 4.5%, 2.2% in the placebo, 1 mg/kg and 10 mg/kg groups, respectively). There were no differences between the treatment groups in rates of related (0.7%, 0.9%, 0.4%) or severe events (0.3%, 0.6%, 0.6%). There was a slightly higher rate of serious psychiatric disorders in the belimumab 1 mg/kg (0.6%) and 10 mg/kg groups (1.2%) compared with placebo (0.4%). This was primarily accounted for by 6 events of depression (3 each in the belimumab 1 and 10 mg/kg groups) compared with 1 event in the placebo group. Four of the subjects suffering from serious depression attempted suicide (another 2 subjects died because of suicide). Given the low numbers of these events, it is difficult to be sure of whether this difference in psychiatric disorders is a true difference or not. Equally, it is

[15] Hanly JG, Urowitz MB, Sanchez-Guerrero J. Neuropsychiatric events at the time of diagnosis of systemic lupus erythematosus. Arthritis Rheum 2007; 56(1):265-73.

[16] Bachen EA, Chesney MA, Criswell LA. Prevalence of mood and anxiety disorders in women with systemic lupus erythematosus. Arthritis & Rheum (Arthritis Care and Research) 2009; 61(6):822-829.

unclear whether any differences can be attributed to the belimumab treatment or whether some other confounder could be contributing. It is not clear, given what is known about the pharmacodynamic effects of belimumab, how a difference in psychiatric disorders would be caused belimumab therapy (that is, there is no clear biologically plausible link apparent at this time).

Serious adverse events and deaths

The overall incidence of SAEs (fatal and non fatal) in the SLE repeat dose controlled studies was 16% in the placebo group, 19% in the belimumab 1 mg/kg group, and 17% in the belimumab 10 mg/kg group. For most categories of SAEs, the incidence was similar between the placebo infusion and belimumab therapy groups (Table 40). The SOC with the highest incidence of SAE (> 5% in any treatment group) was Infections and infestations: 5.2% in the placebo group, 6.8% in the 1 mg/kg group, and 5.2% in the 10 mg/kg group. The SOCs with the next highest incidence of SAEs (> 2% in any group) were Musculoskeletal and connective tissue disorders, Gastrointestinal disorders, General disorders and administration site conditions, Nervous system disorders and Renal and urinary disorders. With the exception of Nervous system disorders (at rates of 1.2%, 1.5%, and 2.4% in the placebo, 1 mg/kg and 10 mg/kg groups, respectively), no dose related trends were apparent for the incidence of subjects with SAEs in these SOCs. The incidence of subjects with SAEs in the Psychiatric disorders SOC was slightly higher in the belimumab groups (0.6% and 1.2% in the 1 and 10 mg/kg groups, respectively) compared with the placebo group (0.4%).

By preferred term, pneumonia, pyrexia and UTI were the most common individual types of SAEs. Generally the incidence of other SAE types was similar across the treatment groups, however pyrexia and anaemia occurred more frequently in the belimumab 10 mg/kg group (1.3% and 0.9%, respectively) compared with the placebo group (0.4% and 0.1%, respectively). Serious depression also occurred with a higher incidence in the belimumab groups (0.4% each) compared with the placebo group (0.1%).

Table 40. Serious Adverse Events by System Organ Class

System Organ Class	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
Blood and lymphatic system disorders	7 (1.0%)	4 (0.6%)	--	11 (1.6%)
Cardiac disorders	13 (1.9%)	6 (0.9%)	2 (1.8%)	11 (1.6%)
Ear and labyrinth disorders	--	1 (0.1%)	--	--
Endocrine disorders	--	2 (0.3%)	--	1 (0.1%)
Eye disorders	--	2 (0.3%)	--	1 (0.1%)
Gastrointestinal disorders	17 (2.5%)	13 (1.9%)	3 (2.7%)	10 (1.5%)
General disorders and administration site conditions	13 (1.9%)	10 (1.5%)	--	17 (2.5%)
Hepatobiliary disorders	6 (0.9%)	8 (1.2%)	2 (1.8%)	5 (0.7%)
Immune system disorders	1 (0.1%)	2 (0.3%)	--	2 (0.3%)
Infections and infestations	35 (5.2%)	46 (6.8%)	7 (6.3%)	35 (5.2%)
Injury, poisoning and procedural complications	7 (1.0%)	6 (0.9%)	3 (2.7%)	7 (1.0%)
Investigations	1 (0.1%)	--	--	3 (0.4%)
Metabolism and nutrition disorders	3 (0.4%)	3 (0.4%)	--	1 (0.1%)
Musculoskeletal and connective tissue disorders	14 (2.1%)	16 (2.4%)	1 (0.9%)	13 (1.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.4%)	5 (0.7%)	--	1 (0.1%)
Nervous system disorders	8 (1.2%)	10 (1.5%)	1 (0.9%)	16 (2.4%)
Pregnancy, puerperium and perinatal conditions	1 (0.1%)	2 (0.3%)	--	5 (0.7%)
Psychiatric disorders	3 (0.4%)	4 (0.6%)	--	8 (1.2%)
Renal and urinary disorders	12 (1.8%)	9 (1.3%)	--	14 (2.1%)
Reproductive system and breast disorders	5 (0.7%)	3 (0.4%)	--	7 (1.0%)
Respiratory, thoracic and mediastinal disorders	11 (1.6%)	7 (1.0%)	1 (0.9%)	8 (1.2%)
Skin and subcutaneous tissue disorders	6 (0.9%)	5 (0.7%)	--	5 (0.7%)
Surgical and medical procedures	1 (0.1%)	--	--	--
Vascular disorders	7 (1.0%)	6 (0.9%)	2 (1.8%)	11 (1.6%)

Studies LBSL02, C1056, C1057

SAEs reported from the other belimumab treatment studies were numerically small and occurred in a pattern similar to the controlled SLE studies. No new or concerning trends were identified.

On the current evidence, there is no definitive evidence that the incidence of SAEs increases with cumulative exposure to belimumab. The majority of SAEs occurred within the first 6 months of treatment, however the incidences rates overall were low (0.3 to 2.2 per 100 subject- years in first 6 months, and 0.3 to 1.3 for the second 6 months of therapy). However, given the small absolute numbers of subjects treated beyond 12 months with belimumab and the low overall incidence of SAEs, no definitive conclusion definitively about cumulative SAE incidence exposure to belimumab can be made.

Deaths

As of December 31 2009 there had been 28 deaths (4 in the placebo group and 24 in the belimumab groups) across the belimumab clinical development program (including completed and ongoing SLE and RA studies). The median age of death was 46 years with an age range of 18 to 71 years. The death incidence rate per 100 subject-years is similar for placebo-treated (0.52 per 100 subject-years; 95% CI: 0.14, 1.33) and belimumab-treated subjects (0.57 per 100 subject-years; 95% CI: 0.37, 0.85). These incidences are very close with widely overlapping confidence intervals and therefore are considered statistically equivalent.

The death narratives reveal that 5 of the 24 deaths in belimumab treated patients were a consequence of infection; in particular, sepsis with or without septic shock in 3 cases; 1

case of CMV pneumonia; and 1 case of infectious diarrhoea. No infection related deaths were identified in the placebo + SOC population. Of note, 3 subjects all of who were young women (23-43 years old) and taking belimumab committed suicide. Given the mechanism of action of belimumab an increase in fatal infections is biologically plausible but there is no obvious mechanism to explain suicides. Even though the overall death rate incidences between belimumab and control treatment are similar because of the greater total belimumab exposure in the complete dataset (compared with placebo) it is difficult to know whether these death events represent a true trend or whether the differences are related to chance alone. However, given the possible increase in depressive illnesses as well as these suicides, some concerns are raised.

No other apparent patterns are identifiable from the death narratives.

Laboratory findings and vital signs

Expectedly, lymphopenia was the most frequent severe laboratory abnormality seen in the SLE studies and occurred in similar proportions of subjects across all treatment groups. Likely contributors to this observation are SLE disease activity, as well as concurrent background immunosuppressant and corticosteroid use. Prolonged prothrombin time (PT), haemoglobin and neutrophil counts were also noted as Grade 3 or 4 haematology abnormalities but also occurred in similar proportions of subjects across treatment groups (Table 41).

Table 41. Grade 3 and 4 Haematology Toxicities

Worst Grade Observed	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
Hemoglobin	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	30 (4.5%)	21 (3.1%)	4 (3.6%)	9 (1.3%)
Grade 4	2 (0.3%)	3 (0.4%)	1 (0.9%)	1 (0.1%)
Lymphocyte Count	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	155 (23.0%)	175 (26.2%)	22 (20.0%)	160 (23.8%)
Grade 4	19 (2.8%)	12 (1.8%)	2 (1.8%)	20 (3.0%)
Neutrophil Count	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	25 (3.7%)	29 (4.3%)	9 (8.2%)	28 (4.2%)
Grade 4	7 (1.0%)	4 (0.6%)	1 (0.9%)	7 (1.0%)
Platelet	(n=673)	(n=668)	(n=110)	(n=671)
Grade 3	6 (0.9%)	6 (0.9%)	--	5 (0.7%)
Grade 4	4 (0.6%)	5 (0.7%)	--	--
Prothrombin Time (PT)	(n=664)	(n=663)	(n=110)	(n=664)
Grade 3	32 (4.8%)	39 (5.9%)	13 (11.8%)	36 (5.4%)
Grade 4	23 (3.5%)	24 (3.6%)	9 (8.2%)	27 (4.1%)
Partial Thromboplastin Time (PTT)	(n=664)	(n=663)	(n=110)	(n=664)
Grade 3	2 (0.3%)	1 (0.2%)	--	--
Grade 4	--	3 (0.5%)	--	--
White Blood Cells (WBC)	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	20 (3.0%)	18 (2.7%)	5 (4.5%)	26 (3.9%)
Grade 4	--	--	--	1 (0.1%)

Studies LBSL02, C1056 and C1057.

Grade 3 or 4 liver function and other chemistry abnormalities were noted in < 2% of subjects, with similar proportions of subjects affected in all treatment groups (Tables 42 and 43). There does not appear to be a belimumab treatment or dose effect on liver function tests or any of the other biochemical parameters evaluated.

Table 42. Grade 3 and 4 Liver Function Toxicities

Worst Grade Observed	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
	(n=674)	(n=668)	(n=110)	(n=672)
Alkaline Phosphatase				
Grade 3	--	--	--	1 (0.1%)
Grade 4	1 (0.1%)	--	--	--
ALT(SGPT)				
Grade 3	2 (0.3%)	3 (0.4%)	--	1 (0.1%)
Grade 4	2 (0.3%)	--	--	--
AST(SGOT)				
Grade 3	2 (0.3%)	1 (0.1%)	--	3 (0.4%)
Grade 4	1 (0.1%)	3 (0.4%)	1 (0.9%)	1 (0.1%)
Gamma-glutamyl-transferase				
Grade 3	18 (2.7%)	16 (2.4%)	2 (1.8%)	21 (3.1%)
Grade 4	10 (1.5%)	3 (0.4%)	3 (2.7%)	4 (0.6%)
Total Bilirubin				
Grade 3	--	--	--	1 (0.1%)
Grade 4	1 (0.1%)	--	--	--

Studies LBSL02, C1056 and C1057

Table 43. Grade 3 and 4 Electrolyte Abnormalities

Worst Grade Observed	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
Hypocalcemia[1]	(n=562)	(n=554)	(n=110)	(n=561)
Grade 3	--	1 (0.2%)	--	1 (0.2%)
Grade 4	--	--	--	--
Hypomagnesemia	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	1 (0.1%)	--	--	--
Grade 4	--	--	--	--
Hypophosphatemia	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	6 (0.9%)	8 (1.2%)	1 (0.9%)	8 (1.2%)
Grade 4	--	--	--	--
Hyperkalemia	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	2 (0.3%)	1 (0.1%)	--	1 (0.1%)
Grade 4	3 (0.4%)	1 (0.1%)	--	1 (0.1%)
Hypernatremia	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	1 (0.1%)	2 (0.3%)	--	--
Grade 4	--	--	--	1 (0.1%)
Hyponatremia	(n=674)	(n=668)	(n=110)	(n=672)
Grade 3	--	1 (0.1%)	--	--
Grade 4	--	1 (0.1%)	--	--

Studies LBSL02, C1056 and C1057.

[1] Hypercalcemia and Hypocalcemia are in studies C1056 and C1057 only since calcium used in C1056 and C1057 is calcium adjusted for albumin while in LBSL02, it was not adjusted. Note: There were no Grade 3 or Grade 4 hypercalcemia, hypermagnesemia, hyperphosphatemia, hypokalemia.

Reductions in immunoglobulin levels are an expected pharmacological effect of belimumab, although Grade 3 or 4 abnormalities were infrequent and occurred at similar rates across all treatment groups (0.2%, 0.6% and 0.2% in the placebo, 1 mg/kg and 10 mg/kg groups, respectively). Across the belimumab groups combined, most subjects (94%) had IgG level which remained within the normal range at any particular scheduled visit. Shifts in IgM from high or normal at baseline to below the lower limit of normal

occurred in more belimumab treated subjects (18%) compared with the control arm (6.0%). This is an expected difference given the mechanism of action of belimumab. However, this serological observation did not correlate with an increased rate of infection.

The incidence of Grade 3 or Grade 4 abnormalities in urinalysis was low and similar in the belimumab treatment groups and the placebo group. There was no apparent treatment effect or dose relationship for any of the urinalysis values.

There appears to be no significant treatment effect (i.e. observed difference) in systolic or diastolic blood pressure changes with time when blood pressure is compared between active treatment and placebo groups. No data on heart rate, respiratory rate or temperature were recorded during the 2 Phase III studies (**C1056** and **C1057**). However, data from the remaining studies did not demonstrate clinically relevant differences in any of these parameters.

Safety in special populations

Effect of gender

The AE profile of belimumab in female patients is represented the overall AE profile of the SLE controlled studies since females constituted 94% of all subjects in the overall trial population. This is not unexpected given the known 90% prevalence of SLE in females.[17] Given the small number of male subjects (n=129), meaningful conclusions concerning differences in the AE profile of male compared to female patients or between the treatment groups within the gender subgroups are not possible.

Pregnancy and lactation

SLE is associated with significant maternal and foetal morbidity, including spontaneous abortion, pre eclampsia, intrauterine growth restriction, foetal death, and pre term delivery[18]. Individuals with SLE testing positive for anti-cardiolipin (aCL) antibodies are at the highest risk of spontaneous abortions and poor foetal outcome[19] with a reported foetal loss rate in the literature of between 15-25% [20], [21], [22], [23]. The presence of anti-phospholipid antibodies has been reported in 30-80% of patients with SLE.[24]

There are no adequate, well controlled studies on the use of belimumab in pregnant women. The long term effects, if any, on surviving infants are unknown. Human IgG is known to cross the placental barrier and belimumab may cause a reduction in the number of foetal B cells. Limited data on the use of belimumab during pregnancy is available from the outcome data for pregnancies in subjects who conceived while receiving belimumab in the clinical studies.

It is not known whether or not belimumab is excreted in human milk or absorbed systemically after ingestion by a nursing infant. However, belimumab has been detected in

[17] Ward MM. Prevalence of physician-diagnosed systemic lupus erythematosus in the United States: Results from the third National Health and Nutrition Examination Survey. J Womens Health (Larchmt) 2004; 13(6):713-8.
[18] Molad Y, Borkowski T, Monselise A, et al. Maternal and fetal outcome of lupus pregnancy: a prospective study of 29 pregnancies. Lupus 2005; 14:145-51.
[19] Cortes-Hernandez J, Ordi-Ros J, Paredes F, et al. Clinical predictors of fetal and maternal outcome in systemic lupus erythematosus: a prospective study of 103 pregnancies. Rheumatology 2002; 41:643-50.
[20] Andrade R, Sanchez ML, Alarcon GS, et al. Adverse pregnancy outcomes in women with systemic lupus erythematosus from a multiethnic US cohort: LUMINA (LUI). Clin and Exp Rheum 2008; 26:268-74.
[21] Clowse MEB, Magder LS, Witter F, et al. The impact of increased lupus activity on obstetric outcomes. Arthritis & Rheum 2005; 52(2):514-21.
[22] Rahman, P., D. D. Gladman, and M. B. Urowitz. Clinical predictors of fetal outcome in systemic lupus erythematosus. J.Rheumatol 1998; 25.8:1526-30.
[23] Yasmeen, S, Wilkins EE, Field NT, et al. Pregnancy outcomes in women with systemic lupus erythematosus. J.Matern.Fetal Med 2001; 10.2: 91-96.
[24] Mecacci F, Bianchi G, Pieralli A, et al. Pregnancy outcome in systemic lupus erythematosus complicated by anti-phospholipid antibodies. Rheumatology 2009; 48:246-249.

the milk of female cynomolgus monkeys administered 150 mg/kg every 2 weeks, indicating that belimumab may be excreted into human milk.

Pregnant women were excluded from belimumab clinical trials and subjects were required to use contraception 1 month prior to the start of receiving belimumab and for 8 weeks after the last dose of belimumab. Pregnancy tests were performed and negative results were ensured before each belimumab infusion. Subjects who became pregnant while enrolled in the clinical studies were required to discontinue treatment with the drug.

As of December 31 2009, a total of 3 partner pregnancies and 47 subject pregnancies have been reported in the Phase II **(LBSL-02**) and III (**C1056** and **C1057**) SLE studies. No pregnancies have been reported in the RA or Phase I studies. Of the 38 subject pregnancies with known outcomes, the rate of adverse outcomes (spontaneous abortion, stillbirth, congenital anomaly) was similar between those who received belimumab or placebo infusions + SOC. The total foetal loss rate in subjects treated with belimumab with known pregnancy outcomes was 31% (10/32 subjects), which is higher than the background rate in patients with SLE (15-25%)[20, 21, 22,23]. For subjects in the control groups in the belimumab SLE studies the rate of foetal loss was also high at 50% (3/6 subjects). The rate of foetal loss can be influenced by lupus activity during pregnancy and by maternal co morbidities (such as renal disease, hypertension, presence of anti-phospholipid antibodies)[19]. For the partner pregnancies, the outcomes have included live birth with no congenital abnormalities (placebo), unknown (belimumab 1 mg/kg), and spontaneous abortion (belimumab 10 mg/kg).

Individuals testing positive for aCL (an anti-phospholipid antibody) are at higher risk of spontaneous abortion and poor foetal outcome[19]. Of the 47 reported pregnancies in the SLE trials, 3/6 (50%) of placebo-treated subjects and 12/41 (29%) of belimumab-treated subjects had positive aCL antibodies. Of the 11 subjects who experienced a spontaneous abortion, 6/9 (67%) of the belimumab subjects and 1/2 (50%) of the placebo subjects had positive aCL antibodies. The 2 subjects who had stillbirths (1 in the placebo arm and 1 in the belimumab 10 mg/kg treatment group) were also positive for aCL. Known outcomes for the other subjects with positive aCL antibodies included elective termination (1 subject each in the placebo, 1 mg/kg and 4 mg/kg treatment groups) and live birth without congenital anomaly (1 subject in the 1 mg/kg treatment group). Given the small numbers of pregnancies overall, it is difficult to know if belimumab treatment has any affect on foetal loss or adverse pregnancy outcomes.

Paediatric population

No studies have been conducted in subjects aged less than 18 years.

Geriatric subjects

No specific geriatric studies have been conducted with belimumab in SLE affected subjects and limited data is currently available from the study dataset. As SLE primarily affects women of childbearing years, a total of only 35 (1.6%) subjects enrolled in the SLE controlled studies (across all treatments) were ≥ 65 years of age or greater (16, 11, 6 patients in the placebo, 1 mg/kg and 10 mg/kg treatment groups, respectively). Given the small numbers of subjects, it is difficult to ascertain if there are any differences in AEs or other safety parameters. The lack of specific geriatric studies has limited influence in the generalisability of the study program findings to clinical practice in Australia as the majority of SLE affected patients are < 65 years of age.

Effect of race

There appears to be no clinically relevant differences in the overall incidences of AEs and SAEs across different races. A slightly higher incidence of SAEs were recorded in the Black/African American population compared with the overall population, however, these

events were also more prevalent in the control treatment group. A slightly lower rate of AEs in the Alaska Native or American Indian subgroup was conversely observed but with similar proportions in the belimumab treatment and control therapy groups.

Baseline prednisone and other immunosuppressant use

There was no difference in the incidence of AEs in subjects taking > or ≤ 7.5mg/day prednisone equivalent. A slightly higher incidence of AEs was seen in subjects taking immunosuppressant therapy compared to those not taking this type of therapy. When AEs were examined by SOC for these subgroups, AEs that occurred most frequently (Infections and infestations, Musculoskeletal and connective tissue disorders and Gastrointestinal disorders) were observed at slightly higher incidences in subjects who used immunosuppressant medications compared with subjects who did not. However, within this subgroup of subjects the incidence of AEs and SAEs was similar in the belimumab and placebo treatment groups.

Immunological events

Anti-drug antibodies (ADA)

In the Phase III IV SLE studies (**C1056** and **C1057**), samples for immunogenicity assessment were drawn on Day 0 and Weeks 8, 24, 52/Exit and Week 76/Exit (in Study **C1056**), as well as after an 8 week follow-up (for subjects discontinuing treatment and not entering the extension period of the study). For subjects who had a positive anti-belimumab antibody response at the 8 week follow-up, a serum sample was obtained if possible at least 6 months after the last dose of study agent or upon completion and/or unblinding of the study, whichever was the later. The anti-drug antibody assays (ADA) appear to have been appropriately developed and validated. However, the presence of belimumab significantly interferes with detection of the ADA. Belimumab treatment at 1 mg/kg leads to belimumab concentrations that do not interfere with the ADA assay. However, treatment with belimumab 10 mg/kg leads to significantly higher belimumab concentrations, into a range where there is significant interference with the ADA assay. Therefore, it is possible that the proportion of subjects with positive ADA in the 10 mg/kg may be significantly underestimated. A significantly higher proportion of subjects in the pooled Phase III study dataset treated with belimumab 1 mg/kg treatment group (13.1%, 73/559) developed ADA, both for transient and persistently positive antibodies compared with placebo (2.0%, 11/562). A smaller proportion of patients in the belimumab 10 mg/kg group developed ADA (0.9%, 5/563) but this is possibly an underestimation of the true proportion. More than two-thirds of ADA patients had a transient positive (single sample only) result. However, 26 patients (4.7% of 559) in the belimumab 1 mg/kg group had a persistent immune response compared with only 10 (1.8% of 562) subjects in the control arm and 4 (0.7% of 563) in the belimumab 10 mg/kg.

One patient with ADA in Study **C1056** had an infusion related AE of recurrent erythema and nausea but in general the detection of ADA had no relationship with reported toxicity events.

In Study **LBSL-99**, 5 of 178 subjects who samples tested had a confirmed positive anti-belimumab antibody response. For all 5 subjects, the positive result was an isolated finding (for 2 subjects the result was negative at the next visit; for another subject ADA was only positive at the last visit; and for the 2 other subjects the positive sample was recorded at their last visit and it was the only sample analysed). No patients experienced concurrent AEs indicative of an allergic or hypersensitivity reaction. Three out of the 5 subjects were tested for neutralisation and the neutralidation assay was not performed in 2 subjects because belimumab drug concentrations exceeded 1 µg/mL. None of the subjects tested had a neutraliding anti-belimumab antibody response.

Effect on vaccination

The effect of belimumab on vaccinations was analysed in a sub-study conducted as part of Study **C1056**. Table 44 outlines the number of subjects that had either pre existing functional antibodies to *streptococcus pneumoniae*, tetanus and influenza or were vaccinated against these organisms during the trial.

Table 44. Vaccination Data

	Placebo	1 mg/kg	10 mg/kg
Total Number of Subjects	**68**	**84**	**71**
Number of subjects in pre-existing functional antibody analysis	**58**	**75**	**61**
S. pneumoniae[1]	24	28	22
Tetanus[2]	29	30	23
Influenza	45	63	39
Number of subjects in vaccine response on study analysis	**26**	**32**	**21**
S. pneumoniae	2	2	3
Tetanus	2	1	1
Influenza	25	32	19

[1] Subject US052-003 had data marked as both pre-existing and on study at different timepoints. This subject was analyzed in the on study aspect of the study only.

[2] Subject US052-003 and US026-010 each had data marked as both pre-existing and on study at different timepoints. These subjects were analyzed in the on study aspect of the study only.

There was no clinically relevant change in the antibody titres in the placebo or belimumab treatment groups for any of the three organisms. Limited data is available to evaluate the effect of belimumab on tetanus and *pneumococcus* immunisations received while on therapy. The overall number of subjects is very small at n=4 for receiving concurrent tetanus immunisation and n=7 for *pneumococcus* vaccine during the study. All the subjects were able to mount a protective response to the vaccines. The results of the antibody response to influenza vaccination were difficult to interpret given that the same influenza strain was present in consecutive seasons. Only 10 subjects in the belimumab treatment groups did not have pre existing antibodies and of those, 7 mounted a protective response after vaccination. Therefore, from the limited evidence that is available, belimumab does not seem interfere with the production of an antibody response to vaccination but few subjects have treated with belimumab thus far to make a clear statement about the effect of belimumab on vaccination response.

Safety related to drug-drug interactions and other interactions

No specific drug-drug interaction studies were been performed. Given that belimumab is unlikely to be metabolised by the cytochrome P450 system, drug interactions with other medications that are metabolised by this system are not expected. No specific studies were conducted to examine for these effects. The 3 controlled clinical trials were conducted in subjects receiving standard care for SLE. Subjects were receiving a wide range of concomitant medications including immunosuppressants (such as methotrexate, azathioprine and mycophenolate mofetil), anti-malarials (such as hydroxychloroquine), corticosteroids, HMG-CoA reductase inhibitors, angiotensin-converting enzyme (ACE) inhibitors, non-steroidal anti-inflammatory drugs and aspirin. Only corticosteroids and ACE-inhibitors had statistically significant effects on any PK parameters. Both caused small increases in central clearance that were not clinically significant. Therefore, of the concomitant medications tested, there were no clinically relevant effects on belimumab pharmacokinetics but as mentioned there were no specific studies assessing safety parameters in relation to drug-drug interactions.

Discontinuation due to adverse events

In the controlled SLE studies (**LBSL-02**, **C1056** and **C1057**), 6.1-6.7% of the subjects in all 3 treatment groups (placebo, and belimumab 1 and 10 mg/kg) discontinued study agent due to an AE. As for other belimumab doses, there was a lower rate of AE-related discontinuation in the 4 mg/kg group (3.6%, 4/111), but the overall numbers in this group are low and derived from a single trial only **(LBSL-02**). The AEs by SOC that most frequently resulted in discontinuation of belimumab were Renal and urinary disorders (22 subjects across all treatment groups), Infections and infestations (17 subjects), Nervous system disorders and Skin and subcutaneous tissue disorders (15 subjects each) and General disorders and administration site conditions (12 subjects). Within these SOC categories, the most common AEs resulting in discontinuation were lupus nephritis, pneumonia, headache, angioedema, SLE rash and infusion related reaction. Only 2 AEs resulted in discontinuation of belimumab for more than 2 subjects in any belimumab treatment group. Lupus nephritis resulted in the discontinuation of 8 subjects (1.2%) in the placebo group, 4 subjects in the belimumab 1 mg/kg group (0.6%) and 6 subjects in the belimumab 10 mg/kg group (0.9%). Also, 1 subject (0.1%) in the placebo group, 2 subjects (0.3%) in the 1 mg/kg group, and 5 subjects (0.7%) in the 10 mg/kg group had their study medication discontinued due to infusion related reactions.

The rate of dosing interruptions (13-14% of subjects) was similar across the placebo and belimumab dose groups (1 and 10 mg/kg groups). There was no apparent belimumab treatment group effect or dose relationship. Adverse events resulting in dosing interruptions were more frequent than AEs causing discontinuation of the study medication. As shown in Table 45, the percentage of subjects who had AEs resulting in dosing interruptions was similar for the placebo group (12.6%) and for the 1 mg/kg and 10 mg/kg groups (12.8% and 13.5%, respectively). The highest incidence of AEs resulting in dosing interruptions occurred in the Infections and infestations SOC, followed by AEs in the General disorders and administration site conditions SOC and then Gastrointestinal AEs. Regarding infections, a higher incidence of AEs resulting in dosing interruptions were noted in the belimumab treatment groups (9-11%) compared with the placebo group (6%). For the remainder of AEs that lead to dose interruption, the rates and types were similar across all 3 treatment groups.

Table 45. Adverse Events Resulting in Dosing Interruption or Study Agent Discontinuation

	Placebo N=675	1 mg/kg N=673	4 mg/kg N=111	10 mg/kg N=674
At least 1 AE resulting in dosing interruption	85 (12.6%)	86 (12.8%)	25 (22.5%)	91 (13.5%)
At least 1 AE resulting in study agent discontinuation	48 (7.1%)	42 (6.2%)	4 (3.6%)	45 (6.7%)

Studies LBSL02, C1056, and C1057

Post marketing experience

At the time of this AusPAR, belimumab was not currently licensed in any market in the world and there was therefore no post marketing experience to consider.

Evaluator's overall conclusions on clinical safety

The data presented in this submission concerning the short term safety profile of belimumab treatment in adult patients with active SLE is of sufficient volume for an interim assessment. In total, 2203 patients have received IV belimumab at any dose in the SLE study program. Just less than half of these subjects (n=946) have received the commercially requested dose of 10 mg/kg for a median drug exposure of 392 days (mean 620 days; range: 28-1933 days). In all studies, the cumulative subject exposure to belimumab approximates 4212 subject-years. For the proposed belimumab dose of 10

mg/kg, a total of 828 subjects (87.5% of 946) had received treatment for at least 6 months and 677 patients (71.6% of 946) had been treated for 12 months. Beyond 18 months of exposure, less than 270 patients have continued to receive belimumab at a dose of 10 mg/kg (refer to Table 28).

Key safety conclusions identified by the entire clinical development program include:

- During the controlled studies (with 52-76 weeks of follow-up), belimumab 1 and 10 mg/kg in conjunction with background SOC treatment was generally well generated with the overall incidence and most types of recorded adverse events being similar in patients receiving placebo infusions and SOC;
- Infections (mainly URTI and UTI) were the most common type of adverse event recorded in the controlled trials and occurred at a slightly higher incidence in those who received belimumab (70-71%) compared with control treatment (67%);
- Serious adverse events occurred at a slightly higher frequency in the belimumab treatment groups (19% in the belimumab 1 mg/kg group and 17% in the 10 mg/kg group) compared to 16% in the placebo + SOC arm;
- Infections (mainly LRTI and UTI) were the most frequent type of SAE and had a similar incidence between belimumab and control treatment arms, however there was a slightly higher incidence of major depression in the belimumab treatment groups (0.4% versus 0.1%);
- Infusion related (and hypersensitivity) reactions were reported for 17% of subjects treated with belimumab (irrespective of dose) which was slightly higher than that seen in patients who were administered placebo infusions (15%). Most of the infusion related events occurred with the first 2 administered infusions;
- Unexpectedly (and of unclear explanation), psychiatric disorders occurred at a higher incidence in belimumab treated subjects (15% versus 12% for control therapy) and this is mainly accounted for by serious depression events and suicide risk;
- Discontinuations due to AEs or dosing interruptions were similar for belimumab and placebo + SOC treatment;
- Foetal loss in association with belimumab treatment appears to be indirectly higher than that reported in the literature but was similar in incidence to that observed with control treatment in the SLE trials;
- Death has been recorded in 24 patients who have received belimumab and the incidence rate is similar to that seen with background SOC treatment in the controlled studies and also within population expectations in published data;
- The incidence and type of malignancies is within cohort expectations and similar to that observed in the placebo + SOC patients in the controlled studies;
- No clinically significantly abnormal laboratory findings have been identified with belimumab treatment (any dose);
- The development of persistently positive anti-drug antibodies is observed in a higher proportion of subjects who received the 1 mg/kg dose (~5%) compared to those who received the higher belimumab dose of 10 mg/kg (<1%) but this result may be influenced by the assay sensitivity to circulating drug;
- Belimumab does not appear to significantly impair vaccination responses in limited numbers of studied patients;
- Data from the continuation trials do not indicate an increased incidence or type of AEs with on-going belimumab treatment.

In summary, the safety data indicates that belimumab treatment is generally well tolerated and has a comparable safety profile in short term follow-up compared to background SOC treatment.

However, some significant potential safety concerns are evident which will require on-going pharmacovigilance. These risks include risk of infection (including serious infection, and mainly involving the respiratory and urinary systems), psychiatric adverse events, infusion related reactions and possible increased risk of malignancy and foetal loss.

No apparent dose response relationship for safety outcomes was evident between the 1 and 10 mg/kg belimumab doses. The limited evaluation of the 4 mg/kg belimumab dose in the Phase II study suggested a possible increased rate of AEs but the overall numbers are small.

List of questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Pharmacodynamics

1. Please clarify the evidence showing that Benlysta® reduces differentiation of B cells into plasma cells?
2. Please outline the evidence supporting BLyS as a critical cytokine for B-cell survival, differentiation and proliferation?
3. Why has no PK-PD relationship analysis of belimumab been performed in the clinical development program?

Efficacy

1. Have any other doses of belimumab between 1 and 10 mg/kg been rigorously studied in clinical trials (other than 4 mg/kg in a very limited patient population)? If not, why has this not been undertaken?
2. Please elaborate further on how the 6 month monkey toxicology (involving belimumab doses of 5, 15 and 50 mg/kg) contributed to the final dose selection in the Phase III studies as none of those doses were actually examined in the Phase III trials?
3. Why was the SELENA version of the SLEDAI chosen for efficacy analysis in the controlled studies as compared with other versions of the SLEDAI such as the 2K version which may be more sensitive to changes to disease activity?
4. Has the SRI been validated as a clinically useful outcome measure in SLE? If not, why?

Safety

1. What are the potential mechanistic explanations for an increased incidence of psychiatric events with belimumab treatment in the Phase III studies and why has this AE not been incorporated as an identifiable potential safety risk in the RMP?

Summary of sponsor's response to questions posed by the clinical evaluator

Note: Pages, figures and tables referred to in this section do not correspond with pages numbers, figures and tables in this AusPAR.**Error! Bookmark not defined.**

Validity of post-hoc subgroup analyses in pivotal studies

Subgroup analyses attempt to identify a subset of patients who derive a greater or lesser benefit from therapies than does the average trial patient. Unless the sponsor is proposing

to amend their indication wording to a more clearly defined patient subgroup with active SLE thought to derive the most benefit from belimumab, it is inappropriate for a subgroup analysis to be considered as part of the original submission indication. In addition, the sponsors should clearly justify the plausibility of an increased treatment effect in patients with high degree of disease activity as defined by positibe anti-dsDNA levels and low complements (the specific levels of each serological marker were not defined in the sponsor response). This particular issue of potential heterogeneity of treatment effect in relation to pathophysiology should be discussed further by the sponsor.

Furthermore, the methodology of the subgroup analysis needs to be scrutinized to ensure the validity of the process, appropriate interpretation, and application to everyday clinical settings. Several prominent authors on analysis of clinical trials (Oxman and Guyatt – see references on page 5)[25] have proposed criteria that should be satisfied before accepting results from subgroup analyses. The criteria are outlined below and are relevant in assessing this particular matter:

- *Clinically significant*: the magnitude of the differences between treatment groups are clinically important and would lead to different decisions for different subgroups.
- *Statistically significant*: the differences remain statistically significant after formally testing for treatment-subgroup interactions using appropriate statistical methods.
- *A priori hypothesis*: the hypothesis of subgroup differences preceded rather than followed the analysis (i.e. a priori hypothesis pre-specified in the trial protocol, not a discovery made from post-hoc analyses).
- *Limited number of comparisons*: the subgroup analysis in question was one of a small number of hypotheses tested to minimize the number of seemingly significant differences (i.e. interactions) that could simply occur by chance.
- *Within study comparisons*: subgroup differences were suggested by comparisons within studies (i.e. direct comparisons) rather than between studies (indirect comparisons)
- *Reproducibility*: the subgroup difference is reproducible in other studies that have adequate power and are of similar design in terms of patient characteristics, co-interventions and outcome measures.
- *Supporting evidence*: the subgroup difference is biologically compelling and consistent with current understanding of biologic mechanisms of disease.

When the additional data presented in the sponsor's response derived from the pivotal phase 3 trials is evaluated against the above criteria, the subgroup analysis arguably satisfies some but clearly not all of the 7 elements. Without doubt the criteria of *apriori* hypothesis and reproducibility have not been met, and these criterion should be fundamental to the scientific strength of the data supporting licensing. It is clear from the medical literature that post-hoc subgroup analyses, in general, are relatively poor options in terms of scinetific rigor and validity. Post-hoc analyses of certain subgroups are potentially fraught with multiple hazards, especially the play of chance and uncontrollable confounders. They are particulary prone to false findings and indeed, the medical literature has numerous examples from randomized trials in which an apparently important differential response to therapy suggested by subgroup analysis generated a hypothesis that was subsequently refuted in a trial designed to test that hypothesis (references such as Parker, Pfeffer, Rothwell and Scott – page 5). In addition, respected authors on the topic of subgroup analysis such as Rothwell report that simulations of randomized controlled trials powered to determine the overall effect of treatment suggest that false subgroup treatment effects occur by chance in 7%-21% of analyses. The same author states "post-hoc observations should be treated with skepticism irrespective of their significance" and that "no test of significance is reliable in this situation."

The sponsor response did not specify the type of statistical analysis utilised to generate the subgroup analysis data so it is impossible to determine if an appropriate statistical test (i.e. to test for a subgroup-treatment effect interaction) has been performed. However, the best test for validity of subgroup-treatment effect interactions is not statistical significance but reproducibility in other trials.

Efficacy dataset comments

In the sponsor response, newly presented post-hoc analyses of the phase 3 trial data has been submitted involving (a) high threshold SRI responses (improvements from baseline in SRI of 5-10 points) and (b) subgroup analysis (in particular, patients with low serum complements and positive anti-dsDNA levels).

(a) Post-hoc analysis of high threshold SRI responses

The sponsor provided 2 figures (1 and 2 on page 7 of their response) examining the proportion of subjects achieving a SRI 5-7 response change from baseline at 52 and 76 weeks of follow-up. Subjects were involved in the 2 phase 3 studies (C1057 and C1056). The statistical analytical plan was not provided, and no confidence intervals for the data presented were available. For the week 52 data, treatment with belimumab at either dose (1 or 10 mg/kg) appeared to be associated with a statistically significant change compared to placebo infusion + SOC for all levels of response except for the proportion of subjects receiving belimumab 1 mg/kg achieving a SRI-7 change involved in Study C1056. No pair-wise statistical comparison for belimumab 1 mg/kg versus 10 mg/kg was provided, and therefore no comment about a dose response effect can be made. For the week 76 data involving patients only in Study C1056, the results were statistically significant for belimumab 10 mg/kg at all levels of SRI change (5-7) but only statistically significant for belimumab 1 mg/kg at the highest level of SRI response (a change of 7 from baseline). This last result is somewhat unexpected given that a higher level of clinical response is only possible (and not lower levels of clinical response) with the low dose of belimumab. Hence, the heterogeneity of the observed treatment effect may be alternatively explained by chance alone for some of the assessed outcomes. Overall, the results of this post-hoc analysis somewhat support (but not strongly) a differential effect of belimumab treatment versus placebo + SOC, but no clear dose response effect is observed. In addition, the results have limited scientific rigour given the nature by which they were derived (post-hoc and multiple subgroup analyses) and the observed heterogeneity of statistically significant responses for the week 76 dataset.

(b) Post-hoc analysis of patients with high baseline disease activity

The sponsor provided an additional 8 pages of data on pages 8-15 of their response (including 3 tables and 5 figures). This new data has also been included in the revised PI document supporting efficacy. In general, the data supports an effect for belimumab treatment when added to the SOC in this patient subgroup with highly active SLE at baseline. The data demonstrates a consistent treatment effect for various outcome measures (at either belimumab dose) for up to 52 weeks of treatment. However, no clear dose response effect with belimumab (1 versus 10 mg/kg) has been demonstrated for most of the outcome measures and the sponsor has not provided statistical pair-wise comparisons of the 2 belimumab treatment groups. For example, the proportion of patients achieving a prednisone dose reduction from baseline of at least 25% between weeks 40-52, a higher absolute response was observed for those who received 1 mg/kg (22.9%) compared to those given 10 mg/kg (18.5%) – refer to Table 2 (page 12) of the sponsor response.

The controlled efficacy data for patients receiving belimumab beyond 52 weeks (i.e. up to 76 weeks of therapy) is less convincing than the the week 52 data and demonstrates mixed efficacy effects. Furthermore the sponsor states (last sentence of page 9) that the effect of belimumab in this SLE patient subgroup was not driven by serological changes

which makes it difficult to understand the biological plausibility of the treatment effect, and why this subgroup was chosen as the subgroup to analyse anyway. Therefore, I speculate that the effect of belimumab has more to do with altering B-cell antigen presentation and B-cell dependent cytokine production, than removal or decreased production of disease associated autoantibodies.

Safety dataset comments

It is pleasing to note that the sponsor is proposing to investigate further a possible association between serious neuropsychiatric adverse events and belimumab, because although patients with SLE have a relatively high background rate for depression and suicide, the incidence of these SAEs was disproportionately observed in patients who received belimumab compared to standard of care only therapy in the clinical studies. I concur with the sponsor in that a biologically plausible mechanism is not readily apparent. Nonetheless, until further information is available on this issue it is my opinion that the sponsor should include this risk into the RMP and PI as a potential consequence of belimumab treatment as such an approach is in accordance with guidelines for optimal pharmacovigilance.

Another safety concern has become apparent in the sponsor response which included an update of the long-term, open-label safety database. In the time period between 1/1/10 and 9/7/10, 4 additional opportunistic infections have been identified which included 2 cases of latent pulmonary tuberculosis (TB), 1 patient experienced extra-pulmonary TB involving a joint and another subject developed an atypical mycobacterial joint infection. In the 3 cases of TB, patients had prolonged exposure to belimumab (> 1 year) and this remains a small but significant risk for patients receiving continuous treatment beyond 52 weeks, for which the efficacy benefit (from controlled data) is not clearly demonstrated. On the assessment of benefit to risk, a restriction to belimumab treatment for up to 52 weeks of therapy may be considered a condition of initial registration.

Conclusion

The additional information provided in the sponsor's response does not alter my intial recommendation of not supporting the licensing of belimumab for the treatment of adult patients with SLE at this stage. The post-hoc subgroup analysis showing a beneficial effect with belimumab in a subset of patients with positive anti-dsDNA levels and low serum complements is noteworthy but contestable in terms of scientific rigour. There remains a considerable lack of clarity in terms of the overall benefit risk analysis and the justification for the commercially requested dose of 10 mg/kg is a sidnificant deficiency.

If belimumab is approved for use in Australia, then I recommend 2 conditions of registration:

1. That the indication wording be further refined to include "add-on treatment to the standard of care in adult patients with autoantibody positive SLE exhibiting high disease activity including elevated levels of anti-dsDNA and low serum complements" as this is the subgroup which appears to have the most justification for therapy; and
2. Therapy should be limited to 52 weeks of treatment as the evidence for a clear and significant efficacy effect beyond that time period is not available, and uncommon but serious adverse events may ensue.

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Clinical summary and conclusions

Pharmacokinetics

The PK of belimumab is well described with a linear 2-compartment model with clearance from the central compartment. PK parameters appear to be dose proportional across the 1 to 20 mg/kg dose range that has been evaluated.

The PK parameters (based upon the population estimates of the PK model) specific to the sponsor requested 10 mg/kg dosing in the Phase III population are as follows:

- Belimumab has a distribution half-life of 1.8 days and an elimination half-life of 19.4 days.
- Belimumab clearance is 215 mL/day (3.2 mL/day/kg based on a median weight of 66.3 kg in the overall study population) and the steady-state volume of distribution is 5.3 L (80 mL/kg based on median weight of 66.3 kg) for the 10 mg/kg dose.

Subject or disease characteristics such as sex, age, race, disease state, hepatic and renal function have no clinically meaningful impact on belimumab PK, whereas body size appears to affect central clearance and volume of distribution. However, these body size effects are addressed by weight based dosing strategy. SLE co-medications evaluated in population PK analyses appear to have no meaningful impact on the PK of belimumab.

Pharmacodynamics

The PD effects of belimumab in the Phase II/III controlled studies in SLE are as follows:

- Compared with placebo, belimumab led to reductions in serum IgG and anti-dsDNA levels (in those individuals with high baseline levels of these markers) and increases in serum complement levels C3 and C4 (in those with low levels at baseline), though the result for a change in C3 levels was only observed in the Phase III studies,
- In subjects who were positive at baseline for anti-dsDNA antibodies, more belimumab-treated patients converted to a negative result at Week 52 compared with placebo,
- Significantly more belimumab treated subjects with low serum complement at baseline had normalised complement levels at Week 52 compared with those receiving placebo,

- Belimumab therapy significantly reduced the numbers of B-cells (CD19+ and CD20+) and B-cell subsets, and plasma cells at Week 52. However, memory B-cells increased initially and slowly declined thereafter to baseline levels; and
- There was no clear, consistent and clinically relevant dose response relationship for belimumab with any of the PD parameters assessed.

Clinical efficacy

Key efficacy data conclusions provided by the 2 pivotal Phase III studies (**C1056** and **C1057)** are:

- Both doses of belimumab (1 and 10 mg/kg) achieved the primary efficacy endpoint of increased rates of SRI compared to placebo + SOC treatment at 52 weeks of follow-up,
- No statistically significant difference in treatment effect was observed between the 2 studied doses of belimumab (1 and 10 mg/kg) for the rates of SRI at 52 weeks,
- By 76 weeks of follow-up in Study **C1056** no statistically significant result was observed for the overall rates of SRI (and each of its individual components) for either dose of belimumab (1 or 10 mg/kg) compared with placebo infusions + SOC,
- Either dose of belimumab demonstrated significantly significant improvements compared with SOC only in the relative proportion of patients showing at least a 4 point reduction in their SELENA-SLEDAI score at 52 weeks compared to baseline,
- Belimumab + SOC treatment inconsistently demonstrated benefit at 52 weeks over placebo + SOC for each of the other individual components comprising the SRI (that is, no worsening of PGA or BILAG score),
- Belimumab treatment (either dose) inconsistently demonstrated benefit over placebo + SOC for the proportion of subjects able to achieve a prednisone reduction between Weeks 40-52 (that is, a statistically significant result for belimumab 1 mg/kg versus control in Study **C1057** only),
- Belimumab treatment (either dose) was able to produce a modest reduction in overall flares (~1 flare per subject-year) between Weeks 24-52 compared to control treatment, and belimumab 10 mg/kg only was able to reduce the frequency of severe flare (~0.3 flare per subject-year) over the same time frame compared to placebo infusions + SOC,
- Neither dose of belimumab was able to demonstrate a statistically improvement in the mean change from baseline in the SF-36 PCS score at 24 weeks compared to SOC, and
- The primary response rate (rate of SRI at 52 weeks) to belimumab in those of Black race and those recruited from within North America was significantly lower than their comparator group (these are the only 2 subgroup analyses of note).

The key efficacy conclusions demonstrated by the supporting studies (the Phase II trial and open label extension studies) are as follows:

- The co-primary efficacy endpoints of Study **LBSL-02** (the mean percent decrease from baseline in the SELENA-SLEDAI score at 24 weeks and the time to first SLE flare) were not achieved with belimumab treatment compared to the SOC,
- Several pre specified secondary outcomes (such as AUC and percent change in SELENA-SLEDAI score to 52 weeks) showed belimumab was not superior to SOC,
- Post hoc analyses of Study **LBSL-02** suggested that belimumab increase the time to first SLE flare and reduce background corticosteroid use in those individuals taking at

least 7.5 mg/day (these results are hypothesis generating for the Phase III studies and should not be considered proof of efficacy), and

- Patients continuing in the open label extension studies showed moderate improvements in some disease measures but this efficacy have limited interpretation with respect to sustained effect as there was no parallel control group.

In summary, the efficacy results of the 3 controlled clinical trial indicate a mixed response to belimumab treatment (which is not clearly and consistently dose related), and that the magnitude of any potential benefit be of modest clinical effect. There is no controlled data to indicate that there is maintenance of clinical effect beyond 52 weeks of therapy. In addition, the dose of belimumab investigated in the Phase III studies and being requested by the sponsor for commercial licensing (10 mg/kg) has not been adequately justified by the trials. This is a major deficiency of the belimumab clinical development program in SLE. The Phase III studies examined only 2 potential doses (1 and 10 mg/kg) and have not clearly explored the belimumab dose range between 1 and 10 mg/kg. No consistent and clear dose response effect has been established for clinically relevant endpoints in any of the belimumab studies.

Clinical safety

The short term safety profile of belimumab treatment in adult patients with active SLE is provided by the data obtained from 2203 patients who received IV belimumab at any dose in the SLE study program. Approximately half of these subjects (n=946) have received the proposed dose of 10 mg/kg for a median drug exposure of 392 days. In all studies, the cumulative subject exposure to belimumab approximates 4212 subject-years. For the proposed belimumab dose of 10 mg/kg, a total of 828 subjects (87.5% of 946) had received treatment for at least 6 months and 677 patients (71.6% of 946) had been treated for 12 months. Beyond 18 months of exposure, less than 270 patients have continued to receive belimumab at a dose of 10 mg/kg.

Key safety conclusions identified by the entire clinical development program include:

- During the controlled studies (with 52-76 weeks of follow-up), belimumab 1 and 10 mg/kg in conjunction with background SOC treatment was generally well generated with the overall incidence and most types of recorded adverse events being similar in patients receiving placebo infusions and SOC;
- Infections (mainly URTI and UTI) were the most common type of adverse event recorded in the controlled trials and occurred at a slightly higher incidence in those who received belimumab (70-71%) compared with control treatment (67%);
- Serious adverse events occurred at a slightly higher frequency in the belimumab treatment groups (19% in the belimumab 1 mg/kg group and 17% in the 10 mg/kg group) compared to 16% in the placebo + SOC arm;
- Infections (mainly LRTI and UTI) were the most frequent type of SAE and had a similar incidence between belimumab and control treatment arms, however there was a slightly higher incidence of major depression in the belimumab treatment groups (0.4% versus 0.1%);
- Infusion related (and hypersensitivity) reactions were reported for 17% of subjects treated with belimumab (irrespective of dose) which was slightly higher than that seen in patients who were administered placebo infusions (15%). Most of the infusion related events occurred with the first 2 administered infusions;
- Unexpectedly (and of unclear explanation), psychiatric disorders occurred at a higher incidence in belimumab treated subjects (15% versus 12% for control therapy) and

this is mainly accounted for by an increased recording of serious depression events (and associated suicide risk);

- Discontinuations due to AEs or dosing interruptions were similar for belimumab and placebo + SOC treatment;
- Foetal loss in association with belimumab treatment appears to be indirectly higher than that reported in the literature but was similar in incidence to that observed with control treatment in the SLE trials;
- Death has been recorded in 24 patients who have received belimumab and the incidence rate is similar to that seen with background SOC treatment in the controlled studies and also within population expectations in published data;
- The incidence and type of malignancies is within cohort expectations and similar to that observed in the placebo + SOC patients in the controlled studies;
- No clinically significantly abnormal laboratory findings have been identified with belimumab treatment (any dose);
- The development of persistently positive anti-drug antibodies is observed in a higher proportion of subjects who received the 1 mg/kg dose (~5%) compared to those who received the higher belimumab dose of 10 mg/kg (<1%) but this result may be influenced by the assay sensitivity to circulating drug;
- Belimumab does not appear to significantly impair vaccination responses in limited numbers of studied patients;
- Data from the continuation trials do not indicate an increased incidence or type of AEs with on-going belimumab treatment.

In summary, the safety data indicates that belimumab treatment is generally well tolerated and has a comparable safety profile in short term follow-up compared to background SOC treatment.

However, some significant potential safety concerns are evident which will require on-going pharmacovigilance. These risks include risk of infection (including serious infection, and mainly involving the respiratory and urinary systems), psychiatric adverse events, infusion related reactions and possible increased risk of malignancy and foetal loss.

No apparent dose response relationship for safety outcomes was evident between the 1 and 10 mg/kg belimumab doses. The limited evaluation of the 4 mg/kg belimumab dose in the Phase II study suggested a possible increased rate of AEs but the overall numbers are small.

Benefit risk assessment

Benefits

The key efficacy results have already been summarized above. In essence, they demonstrate an inconsistent response to belimumab therapy when it is added to the standard of care treatment for adult patients with active SLE.

Although the 2 Phase III studies were statistically positive for belimumab therapy over background control treatment in achieving the primary efficacy outcome, the magnitude of any potential benefit is of modest clinical effect. In addition, there is no controlled data to indicate that there is maintenance of clinical effect beyond 52 weeks of therapy. The Phase II study in SLE patients was negative for the primary and most secondary efficacy endpoints on the pre specified analysis. This probably reflects the sub-optimal patient identification for recruited patients (that is, insufficiently active SLE).

No consistent and clear dose response effect has been established for clinically relevant endpoints in any of the belimumab studies. The sponsor suggests that some comparative biomarker changes support the choice of the higher dose of belimumab (10 mg/kg) for licensing but these are substantially inferior outcomes of purported efficacy in comparison to clinical endpoints. In the clinical evaluator's opinion, the dose of belimumab investigated in the Phase III studies and being requested by the sponsor for licensing (10 mg/kg) has not been adequately justified by the trials. This is a major deficiency of the belimumab clinical development program in SLE. The Phase III studies examined only 2 potential doses (1 and 10 mg/kg) and have not adequately explored the belimumab dose range between 1 and 10 mg/kg.

Risks

The key safety results have already been summarised above. In summary, the data shows that belimumab treatment is generally well tolerated and has a comparable safety profile in short term follow-up compared to background SOC treatment for adult patients with well established and chronic SLE. Several significant potential safety concerns are evident which include risk of infection (including serious infection, and mainly involving the respiratory and urinary systems), psychiatric adverse events, infusion related reactions and possible increased risk of malignancy and foetal loss. Although these adverse events only seem to affect a small proportion of patients overall, their occurrence would be significant in the majority of those individuals affected. Furthermore, no apparent dose response relationship for safety outcomes was evident for the limited dose range of belimumab (1 and 10 mg/kg) examined in the Phase III studies.

Safety specification

The sponsor provided the European Union (EU) Risk Management Plan (dated February 2010). The summary of important identified safety concerns lists most of the potential safety concerns recognized thus far in the belimumab for SLE study program. However, there is no mention of the potential neuropsychiatric effects, which at this stage (in the absence of further long term data in a larger patient cohort) appears to be a deficiency in the safety specification.

Balance

Although there is a significant unmet need for new therapeutic options in patients with active SLE, the benefit-risk assessment of adding belimumab to the current standard of care is unclear. Given there are substantial potential risks for some individuals (actually observed in the clinical studies and putatively considered by the mechanism of action), and the efficacy benefit is modest for the majority of subjects. The clinical evaluator could not recommend the licensing of belimumab at this time point based on the submitted data. The sponsor should be encouraged to perform further clinical trials in well defined SLE patient groups with at least moderately to severely active disease activity at baseline and follow those subjects for an appropriate time period (at least 18 months). Further potential doses of belimumab between 1 and 10 mg/kg could also be more rigorously explored.

The data thus far demonstrates that the drug clearly does not have "substantial" efficacy as one may expect for the intended treatment population. The efficacy data mainly showed benefit in the organ systems mainly involved in influencing a patient's quality of life (such as mucocutaneous system). A lack of efficacy was seen in the organ systems (in particular, kidney) associated with SLE morbidity and mortality. Efficacy trends were inconsistently met during the controlled studies and Black Americans seemed to have deficient responses to belimumab. Furthermore, long term safety outcomes in a significant number of treated patients are still to occur.

Conclusions

The clinical evaluator could *not recommend* acceptance of the sponsor's proposed indication for belimumab in adult patients with active chronic SLE as the overall benefit risk balance is unclear from the current dataset. Belimumab appears to have a modest efficacy benefit (at best) that is only demonstrable in a controlled clinical trial setting up to 52 weeks with some significant potential safety signals (risk of infection, serious depression with suicide attempts, infusion-related reactions and possibly malignancy long term).

Recommended conditions for registration

In the view of the identified concerns in the current belimumab SLE dataset, it is premature to recommend any conditions of registration. However, if marketing approval was granted then significant changes to the proposed PI and Consumer Medicine Information (CMI) documents would be required, as well as wording changes to the proposed indication to more accurately represent subjects included in the trials (those with at least moderately to severely disease activity at baseline). In addition, the sponsor should be asked to provide regular updates (at least annual intervals) to their Risk Management Plan (version 8.0 developed for the EU). The proposed global prospective observational long term safety and pregnancy registries should be a condition of registration.

V. Pharmacovigilance findings

Risk management plan

A summary of the Ongoing Safety Concerns as specified by the sponsor have been included in Table 46 below.

Table 46. Ongoing Safety Concerns

Identified risks	• Infusion Reactions • Hypersensitivity Reactions
Potential risks	• Malignancies • Infections • Immunogenicity • Effects on immunisations, including interactions with live vaccines
Missing information	• Limited data in pregnant and lactating patients • No data in paediatric patients

OPR reviewer comment

Post marketing surveillance of monoclonal antibody therapeutic agents has identified cases of neurological conditions, such as Progressive Multifocal Leuko-encephalopathy and Guillain-Barre syndrome. The sponsor should provide a comment on the risk of these conditions for belimumab, and any plans they have for monitoring or minimising this risk.

With respect to the potential risk of 'infections', the sponsor is requested to comment on the potential for reactivation of hepatitis B, JC virus and latent tuberculosis, and any plans for monitoring or minimising this risk.

Pursuant to the evaluation of the nonclinical and clinical aspects of the Safety Specifications (SS) and an acceptable comment on the risk of neurological conditions, the above summary of the Ongoing Safety Concerns was considered acceptable.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

There is no detailed action plan provided for the pregnant and lactating patient safety concern and so one will be required. The following comments are presented on the PP provided by the sponsor in 2 sections: the evaluation of safety data from ongoing studies, and the 3 planned additional studies. In general, as a large proportion of the ongoing studies outlined will cease once belimumab is registered in the relevant country these will provide little additional pharmacovigilance activity and therefore contribute only modestly to ongoing pharmacovigilance. The planned additional studies have the potential to provide valuable ongoing safety information, however the level of information currently provided is inadequate to assess the value and rigor of these studies. Furthermore, there is the potential for patient overlap between these ongoing and planned additional studies. Additional information is sought on these studies before an informed assessment can be made.

Specific comments are:

1. *Evaluation of safety data from ongoing studies:*

- HGS1006-C1056 is part of the pre-registration development program and has been completed. This study will not contribute to post marketing pharmacovigilance monitoring and it was recommended that it would be removed from the updated PV action plan.
- HGS1006-C1066, HGS1006-C1074 are continuation studies of the pre registration development program and it is stated that these will discontinue once belimumab is commercially available in the countries they are being conducted in. Therefore, these studies will contribute very little to post marketing pharmacovigilance monitoring. While it is noted that some patients are being treated in countries where marketing approval is not being sought at this stage and therefore may contribute to post market safety monitoring data in registered countries, the contribution of this is unclear. The OPR evaluator recommended that the contribution of these studies to post marketing monitoring be clarified. This clarification must also include more detailed information on the proposed reporting dates, planned action if these are not reached and how this information will be incorporated into updated RMP's.
- LBSL99 follow up study will provide some further safety information, however how this will be assessed and evaluated in terms of its contribution to the safety picture is not provided. The evaluator recommended that further information to be provided about how the results will be analysed and interpreted and useful in considering the safety of this drug.
- HGS1006-C1070 trial is assessing belimumab administered SC and therefore safety information arising will not be directly applicable to the IV administration method being applied for. There is also a lack of specificity around the endpoints being measured, proposed dates and how this information will be incorporated into updated RMP's.

2. Additional studies:

- The Paediatric Investigation Plan has been accepted by the EMA, and the assumption is that this will only be conducted in the EU at this stage. Other countries, including Australia, were not mentioned in this plan. Clarity was requested about the role for Australia in this study. Further, for the purposes of registration in Australia where the indication is for SLE in adults, this study will contribute to the pre marketing evaluation of the extension of the indication to children and is therefore not a pharmacovigilance activity.
- Regarding the observational study and pregnancy register the OPR evaluator had some overall concerns about the level of information provided and hence the inability to determine whether these studies will appropriately and effectively provide additional safety information regarding the use of belimumab in adult SLE patients. These concerns are:
  - Where will these studies will be conducted, and how will Australia will be included?
  - Bias concerns: the identification and recruitment of study population, how they will be followed up.
  - Disease frequency measures: what specific further information these will provide, how will this be evaluated and interpreted?
  - Comparison (or baseline population) groups: these are not clearly identified, including the data sources for this information.
  - Sample size calculations: requires the consideration of several of the factors raised above. In particular for the observational safety study, the size of the cohort may be too small to contribute statistically valuable information that would allow the further assessment of malignancy and severe infection.
  - Safety issues: how the information generated will be used, consideration of how concerns will be identified (for example, higher than expected frequencies are identified) and the process by which decisions will be made.
- There is the potential for overlap between the different study population groups. This has potential implications for achieving sample size, reducing patient participation and analysing results.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities for all the important risks and missing information safety concerns. In particular the sponsor considers that no further activities beyond the proposed 'product labelling and patient information' are currently required.

As part of these routine risk minimisation activities, with respect to the 2 Important identified risks of infusion reactions and hypersensitivity reactions, the following statements have been included in the Australian PI:

> *"Benlysta treatment should be initiated and supervised by a healthcare professional experienced in the diagnosis and treatment of SLE", and*
>
> *"Benlysta infusions should be administered by a qualified healthcare professional trained to give infusion therapy".*

No further information is provided regarding these statements, such as what is meant by a 'qualified healthcare professional' or 'healthcare professional experienced in...", how this recommendation will be effected and its effectiveness monitored.

The sponsor further states that the 3 planned studies designed to address the described safety concerns are additional risk minimisation activities:

- Malignancies: Prospective Observational Safety Study in SLE
- Infections: Prospective Observational Safety Study in SLE
- Limited data in pregnant and lactating patients: Pregnancy Registry
- No data in paediatric patients: Paediatric SLE Study.

OPR reviewer comment

To address the 2 Important identified risks the Australian PI will recommend that treatment should be initiated, supervised and administered by qualified and experienced healthcare professionals. However there is insufficient information provided to determine who is considered a qualified healthcare professional (consider experience in treatment of SLE and in the use of specific therapies), how this recommendation will be communicated and implemented, and how it's effectiveness at reducing these adverse events will be monitored. At this stage, without this information, it is difficult to determine whether this is adequate or if additional information in the PI or activities are needed. The OPR evaluator therefore recommends that the sponsor:

- Provide further information as outlined above and considers the adequacy of the current PI statements in light of this information.

For consistency and clarity around pharmacovigilance and risk minimisation activities the OPR evaluator recommended that the sponsor:

- Does not refer to the 3 planned studies (that is the observational study, pregnancy register and paediatric investigational study) as risk minimisation activities. These are pharmacovigilance activities or pre marketing studies for extension of the indication to paediatric populations and should be removed from this section in the updated plan.

Summary of recommendations

It was recommended that once the RMP amendments and additions are agreed to and the RMP is accepted, that a condition of registration be that the sponsor provides at the time of submission of the next Periodic Safety Update Report (PSUR) an updated RMP or an annex to the EU-RMP outlining the Australian specific differences. This updated RMP should include consistent reference to the Australian terminology for product and patient information and an updated PI and CMI reflecting the agreed changes. If there are specific safety related concerns identified from the clinical evaluation of the safety specifications that have not been identified in the RMP, it was recommended that the sponsor include these in the RMP along with sufficient monitoring and risk mitigation strategies.

The following is a summary of specific recommendations to the TGA Delegate.

1. Ongoing Safety Concerns:

- Provide additional information on the risk of neurological conditions (such as PML), and justification for exclusion from further consideration in the RMP.
- Provide additional information the potential for reactivation of hepatitis B, JC virus and latent tuberculosis 'infections' and justify exclusion from further consideration in the RMP.

2. Pharmacovigilance:

- Include a detailed action plan for pregnant and lactating patients in Section 4.4 of the RMP.

- With respect to the safety data from ongoing studies, the sponsor:
  - Acknowledge that HGS1006-C1056, as part of the preregistration development program has been completed and will not contribute to post marketing) pharmacovigilance monitoring. This should be removed from updated RMPs.
  - Acknowledge that HGS1006-C1066 and HGS1006-C1074 are continuation studies of the pre registration development program and will discontinue once belimumab is commercially available and therefore will contribute very little to post marketing pharmacovigilance monitoring. The sponsor was invited to clarify the actual contribution of these studies to post marketing monitoring in countries where registration is not being sought. This clarification should also include more detailed information on the proposed reporting dates, planned action if these are not reached and how this information will be incorporated into updated RMP's
  - Provide additional information on how the results of the LBSL99 follow up study will be analysed, interpreted and used in considering the safety of this drug, and what information will be included in the reports.
  - Acknowledge that the HGS1006-C1070 trial utilises a different administration method and as such safety information arising may not be directly applicable to the current registration. Provide further specific information around the endpoints being measured, proposed dates, and how this information will be incorporated into updated RMP's.
- With respect to the additional studies, the sponsor:
  - Provide further information on where and when the paediatric clinical study will be conducted, with specific information on any plans in Australia. Address the issue that for the purposes of registration in Australia, where the indication is for SLE in adults, this study will contribute to the pre marketing evaluation of the extension of the indication to children and is therefore not a pharmacovigilance activity and should be removed from this section of the updated RMP.
  - Provide further detailed information for both the planned prospective observational study and pregnancy register. Specifically this must include:
    - Where will these studies will be conducted, and how will Australia will be included (justify Australia's role in these studies)?
    - Bias concerns: how will the study population be identified and recruited, how they will be followed up, identify and address any bias issues these raise.
    - Disease frequency measures: what specific further information these will provide, how will this be evaluated and interpreted.
    - Comparison (or baseline population) groups: clearly identified for all outcome measures, including the data sources for this information.
    - Sample size calculations: information and justification for the effect size (such as absolute risk level, relative risk, change in absolute risk) to be determined, the assumptions utilised.
    - Safety: provide a direct link between how the information generated by this study will be used, for example how issues or concerns will be identified during the course of the study and the process by which decisions will be made based on this information.
    - Provide further information regarding the potential for overlap between the different study population groups, specifically addressing the potential implications for achieving sample size, reducing patient participation, and analysing results.

3. Risk Minimisation Activities and Plan:

- With respect to the risk minimisation plan, that the sponsor:
  - Acknowledge that the 3 additional planned studies (observational study, pregnancy register and paediatric investigational study) are pharmacovigilance activities or pre marketing studies for extension of the indication to paediatric populations and in updated RMPs remove reference to them as risk minimisation activities (RMP section 5.1 and 7).
  - Provide further information regarding the routine risk minimisation activity of including the recommendation that treatment should be initiated, supervised and administered by qualified and experienced healthcare professionals in the Australian PI, including who is considered a qualified healthcare professional, how this recommendation will be communicated and implemented and how it's effectiveness at reducing these adverse events will be monitored. The response should also include a consideration of the adequacy of this activity in addressing these 2 safety concerns and whether additional education is required such as pamphlets or treatment protocols are needed.
- Amendments to the PI and CMI were also recommended by the OPR evaluator but these are beyond the scope of the AusPAR.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Belimumab is a recombinant Immunoglobulin G. Its chemical structure has been well characterised. The cell banking processes were considered satisfactory. Viral and prion issues have been addressed including use of animal derived excipients. The manufacturing process is thought to be adequately controlled and product specifications have been negotiated.

Belimumab was presented at the 22 August 2011 meeting of Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). No objections were raised in relation to registration of belimumab.

The quality evaluator(s) pointed out that no information had been provided regarding the potential immunogenicity of various forms of belimumab detected as contaminants. The company was asked to comment and provided response as follows:

'Aggregates, predominately dimers, retain biological activity and thus posses normal or near normal structure. Because of this they are thought not to be strongly immunogenic.

Thioether cross-linked contaminants are also very similar to the native molecule with regard to conformation. Although the hinge region is exposed this is also the case with the native antibody. Sequence variants are possible due to thioether linkages but any immune response would be expected to be specific for the variant and poorly cross reactive with native protein.

The immunogenicity profile of belimumab in clinical trials appears to be low with anti belimumab antibodies detected in < 5% of patients receiving 1 mg belimumab/kg body weight and 0.7% of patients receiving 10 mg belimumab/kg body weight. Neutralising Antibodies were detected in 3 patients receiving 1 mg/kg.

Clinical effects associated with anti-belimumab antibodies included mild infusion reactions, nausea, erythematous rash, pruritus, eyelid oedema, headache and dyspnoea none of which were life threatening.

Thus it is the case that antibodies against belimumab may be induced in patients even at low treatment doses of the drug. However the symptoms induced by antibody formation are not life threatening.'

The proposed shelf life of finished product is 3 years at 5-8 °C and requires protection from light.

Nonclinical

The nonclinical data submission was typical of that for humanised monoclonal antibodies, whereby conventional studies in multiple species are either not appropriate or not required. The extent of the documentation complied with relevant regulatory standards and guidelines and was considered adequate. Some conclusions of the nonclinical reviewers are reproduced below for reference:

In vitro, belimumab was shown to inhibit soluble BLyS. *In vivo*, it offsets exogenous BLyS-induced proliferation of mouse B slenocytes. Belimumab is associated with slow-onset, moderate and prolonged depression of peripheral B lymphocytes in monkeys.

The effect of belimumab on endogenous BLyS was investigated only after treatment ceased in a reproductive toxicity study in monkeys, where overshoot of baseline BLyS levels occurred once serum belimumab levels had dropped.

There were no studies of efficacy in animal models of SLE. The antibody is fatally toxic after 1-2 doses in mouse model. A dose response curve for the effect of belimumab on B lymphocytes has not been characterised.

Toxicology studies were conducted in cynomolgus monkeys. Belimumab exposure multiples (AUC, C_{max}) and treatment duration (up to 6 months) were adequate. There were few findings other than partial depression of B cell numbers, which reversed gradually after the cessation of treatment. Antibody responses against belimumab were relatively low. IgG levels remained normal in the toxicity studies but no studies examined primary immune responses to infection.

Findings of uncertain significance include thyroid gland enlargement, follicular epithelial degeneration, renal tubular epithelial regeneration and mesangial thickening of the renal glomerulus. The nonclinical evaluator commented that these may warrant consideration in post market studies should belimumab be approved for registration.

No carcinogenicity studies were conducted and will require on-going clinical surveillance.

The reproductive toxicity studies showed transfer of belimumab to foetus and depression of B cell numbers as well as altered immunoglobulin levels in offspring. A higher incidence of early neonatal deaths in offsprings of treated mothers was found.

The sponsor has subsequently also provided response to these nonclinical observations. This has been reviewed by the nonclinical evaluator and considered satisfactory.

Pregnancy category C was proposed for belimumab.

Clinical

The clinical data submission comprised of 5 clinical studies; one pharmacokinetic (PK) study in healthy volunteers (Study C1058: C_{max} 36.7mcg/mL; CL[25] 3.3mL/kg/day; $t_{1/2}$ 13.5 days), one PK study in SLE patients (Study LBSL-01: $t_{1/2}$ 8.5-11.3 days; CL 6.9-7.3 mL/kg/day; dose proportionality in the range 1-20mg/kg), one dose-ranging study (Study LBSL-02: 1, 4 and 10 mg/kg doses tested against placebo; lack of effect and dose response; 1 and 10 mg/kg doses selected for Phase III testing) and two Phase III clinical trials (Studies C1056 & C1057: high placebo effect; moderate and variable clinical response; lack of discrimination between 1 and 10 mg/kg doses; 10 mg/kg proposed for registration).

The studies LBSL-02/C1056/C1057 were also used to collect sparse PK data and estimate population PK parameters. The data indicate terminal elimination $t_{1/2}$ of 12.5 & 19.4 days, Vd_{ss}[26] of 3.7 and 5.3L and CL of 215 mL/day for the 1 and 10 mg/kg doses respectively. The proposed body weight based dosing regimen appears to be appropriate. No other covariates with clinically important influence were found.

The pharmacodynamic (PD) outcomes in these clinical studies (B cell populations, complement activity, autoantibodies, immunoglobulins) supported the proposed mechanism of action but were of variable magnitude with respect to the 2 active dose groups. A total of 94% subjects maintained IgG level above the lower level of normal range.

The submission did not include any PK-PD modelling data.

Although the Phase II study LBSL-02 failed to show a linear dose response, the estimates of magnitude of effect and variability obtained in this study usefully contributed to the trial specifications in the subsequent Phase III trials in collaboration with the European and the US regulators.

Clinical efficacy

The two Phase III studies contain pivotal clinical data. Further discussion in this overview is therefore limited to these 2 studies.

For further details, please also see the clinical evaluation report (CER), the sponsor's response to the CER and the evaluator's review of this response.

Studies C1056 & C1057

The study population, trial structure, drug exposure and outcomes in both studies were identical.

The study population consisted of patients with clinical diagnosis of SLE according to the ACR criteria. Furthermore, the patients were autoantibodies positive (ANA titre ≥ 1:80 and/or anti-dsDNA ≥ 30 IU/mL) and had active disease (SELENA SLEDAI score ≥ 6) at baseline despite stable standard treatment for 30 days prior to enrolment. Key exclusions included active lupus nephritis within preceding 90 days and active CNS lupus in preceding 60 days.

The trials were randomised, double blind, placebo controlled on background of standard therapy. Belimumab (1 mg/kg or 10 mg/kg) or placebo was given by IV infusion on Days 0, 14 and 28 followed by (every) 4 weekly infusions for 48 weeks. The primary efficacy assessment was at 52 weeks. In Study C1056, the controlled treatment continued to 76 weeks.

[25] Total Body Clearance
[26] Steady-state volume of distribution

Study C1056 was carried in North America, Central America and Europe. Study C1057 was carried out in Asia Pacific (including Australia), South America and Eastern Europe.

The primary efficacy outcome was a composite endpoint called SRI response[27]. A response with respect to SRI at 52 weeks was defined as (i) at least 4 point reduction from in SELENA-SLEDAI score from baseline, and (ii) no worsening (increase < 0.30 points) in PGA compared to baseline, and (iii) no new BILAG-A organ domain score or 2 new BILAG-B organ domain score compared to baseline.

The S-S score (6-9 or ≥ 10), proteinuria (< or ≥ 2g/24h) and race (Black or any other) were stratification factors in randomisation which was carried out in blocks to keeps the 3 treatment groups balanced.

The sample size was based on being able to detect 14% placebo corrected treatment difference in SRI. The primary efficacy analysis was based on modified ITT population, that is, patients who received at least one dose of study drugs. Premature withdrawals were treated as failures in the primary analysis (logistic regression with stratification factors as covariates).

A step-down procedure was adopted with respect to the primary outcome to control Type 1 error (multiplicity). First, 10 mg/kg group was compared with placebo at 2-sided alpha of 5%. If statistically significant, then 1 mg/kg group was to be compared with placebo at 2-sided alpha of 5%.

The groups were well balanced within both within each study regarding demographic characteristics. As expected, based on epidemiology of SLE the participants were predominantly (> 90%) female. In Study C1056, 14% participants were Black and 70% were Caucasians. The population was more diverse in Study C1057 but groups were still balanced. The mean age was 40 years in C1056 and 35 years in C1057.

The groups were also well balanced within each study with respect to baseline disease characteristics. Notable imbalance included relatively more patients in SELENA-SLEDAI **(**S-S) score category 4-9 (50.3%) and relatively fewer patients in S-S score category 10-11 (18.4%) in the 1 mg/kg treatment group compared to the placebo and the 10 mg/kg treatment groups in Study C1057 (Table 19).

The results are shown in Table 47 below.

The statistical comparison between the two active groups (1 mg/kg and 10 mg/kg) was not formally conducted but given that the treatment differences between the 2 dose groups were small (about 3% and 6% in Studies C1056 and C1057 respectively), these are not likely to have been statistically significant.

[27] SLE Response Index: The 3 components of the composite were SELENA-SLEDAI (S-S) score, Physician Global Assessment (PGA on visual analogue scale) and BILAG (no clinically relevant deterioration i.e. no 1 new A or 2 new B).

Table 47. Results for Studies C1056a nd C1057. Table continued across three pages.

Studies C1056/C1057		C1056 (aka BLISS 76)			C1057 (aka BLISS 52)		
		Placebo	1 mg/kg	10 mg/kg	Placebo	1 mg/kg	10 mg/kg
Primary variable							
(1)	N	275	271	273	287	288	290
	SRI response at 52 weeks	93	110	118	125	148	167
		33.8%	40.6%	43.2%	43.6%	51.4%	57.6%
	Rx difference vs Placebo	-	6.77%	9.41%	-	7.83%	14.03%
	Odds Ratio (OR)	-	1.34	1.52	-	1.55	1.83
	95% CI	-	0.94, 1.91	1.07, 2.15	-	1.10, 2.19	1.30, 2.59
	p value	-	0.1041	0.0207	-	0.0129	0.0006
components of SRI index							
(i)	At least 4 point reduction in S-S	98	116	128	132	153	169
		35.6%	42.8%	46.9%	46.0%	53.1%	58.3%
	Rx difference vs Placebo	-	7.17%	11.25%	-	7.13%	12.28%
	OR	-	1.36	1.63	-	1.51	1.71
	95% CI	-	0.96, 1.93	1.15, 2.32	-	1.07, 2.14	1.21, 2.41
	p value	-	0.0869	0.0062	-	0.0189	0.0024

Table 47 continued. Results for Studies C1056a nd C1057.

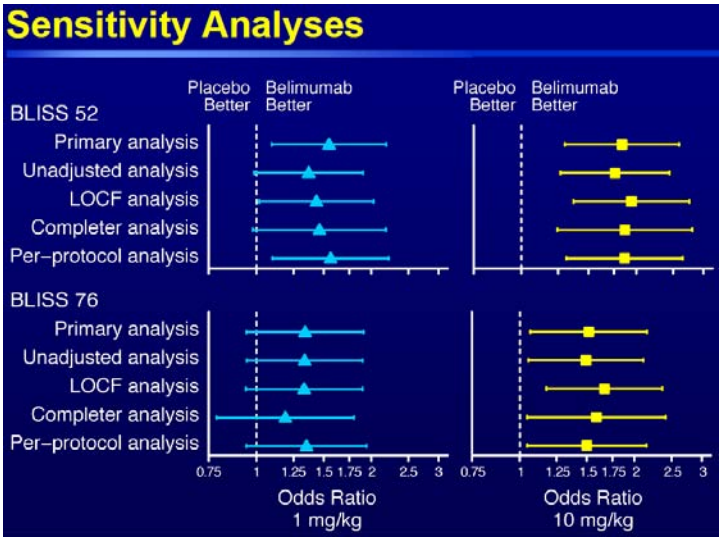
(ii)	no worsening in PGA	173	197	189	199	227	231
		62.90%	72.70%	69.20%	69.30%	78.80%	79.70%
	OR	-	1.6	1.32	-	1.68	1.74
	95% CI	-	1.11, 2.30	0.92, 1.90	-	1.15, 2.47	1.18, 2.55
	p value	-	0.012	0.1258	-	0.0078	0.0048
(iii)	no new 1A/2B BILAG	179	203	189	210	226	236
		65.1%	74.9%	69.2%	73.20%	78.50%	81.40%
	OR	-	1.63	1.2	-	1.38	1.62
	95% CI	-	1.12, 2.37	0.84, 1.73	-	0.93, 2.04	1.09, 2.42
	p value	-	0.0108	0.3193	-	0.1064	0.0181
Other outcomes							
(2)	mean (se) S-S change from baseline at 52 weeks	-2.77 (0.25)	-3.58 (0.26)	-3.70 (0.27)	-3.57 (0.24)	-4.04 (0.25)	-4.97 (0.27)
	p value	-	0.0224	0.0063	-	0.0297	< 0.0001
(3)	mean (se) PGA change from baseline at 24 weeks	-0.49 (0.04)	-0.47 (0.04)	-0.44 (0.03)	-0.39 (0.03)	-0.44 (0.03)	-0.54 (0.03)
	Rx difference vs Placebo	-	-0.00	0.01	-	-0.05	-0.15
	95% CI	-	-0.09, 0.09	-0.08, 0.10	-	-0.13, 0.04	-0.23, -0.07
	p value	-	0.9545	0.7987	-	0.2712	0.0003
(4)	mean (se) SF-36 score change from baseline to week 24	3.36 (0.51)	3.78 (0.46)	3.22 (0.43)	3.64 (0.42)	3.65 (0.43)	3.58 (0.46)
	Rx difference versus Placebo	-	0.53	-0.27	-	0.13	0.08

	95% CI	-	-0.67, 1.74	-1.48, 0.94	-	-0.95, 1.21	-1.00, 1.15
	p value	-	0.3848	0.6601	-	0.8127	0.887
(5)	prednisone reduction by ≥ 25% from baseline to ≤ 7.5mg/day during week 40 through 52	16/126	25/130	20/120	23/192	42/204	38/204
		12.7%	19.2%	16.7%	12.00%	20.60%	18.60%
	Rx difference vs Placebo	-	6.53%	3.97%	-	8.61%	6.65%
	p value	-	0.2034	0.5323	-	0.0252	0.0526
(6)	mean (se) flares per Subject-Year from week 0 to 52	3.81 (0.18)	3.33 (0.18)	3.42 (0.19)	3.22 (0.17)	2.50 (0.17)	2.37 (0.16)
	p value	-	0.0632	0.1276	-	0.0012	0.0002
(7)	**SRI response at 76 weeks**	88/275	106/271	105/273	-	-	-
		32.4%	39.1%	38.5%	-	-	-
	p value	-	0.1050	0.1323	-	-	-

se = standard error

The robustness of the primary analysis for SRI index at 52 weeks was checked using a number of additional samples populations which included (1) unadjusted analysis (2) Last Observation Carried Forward analysis (3) Completer analysis and (4) Per Protocol analysis. All were consistent with the primary analysis as shown in Figure 4 below.

Figure 4. Sensitivity Analyses



The treatment effect was not uniformly significant across the three components of SRI. Also note nearly 70% patients in each group were classified as 'no worsening on PGA' defined as 'change < 0.3'. However, the overall mean change in PGA in all groups as a secondary outcome was shown to have been greater than this cut-off limit.

The SRI index was statistically not significant at 76 weeks follow up compared to baseline in the study C1056.

A number of pre-specified subgroup analyses were also carried out. Important effect modification was shown for race in Study C1056 (Tables 48 and 49).

Table 48. Subgroup analyses

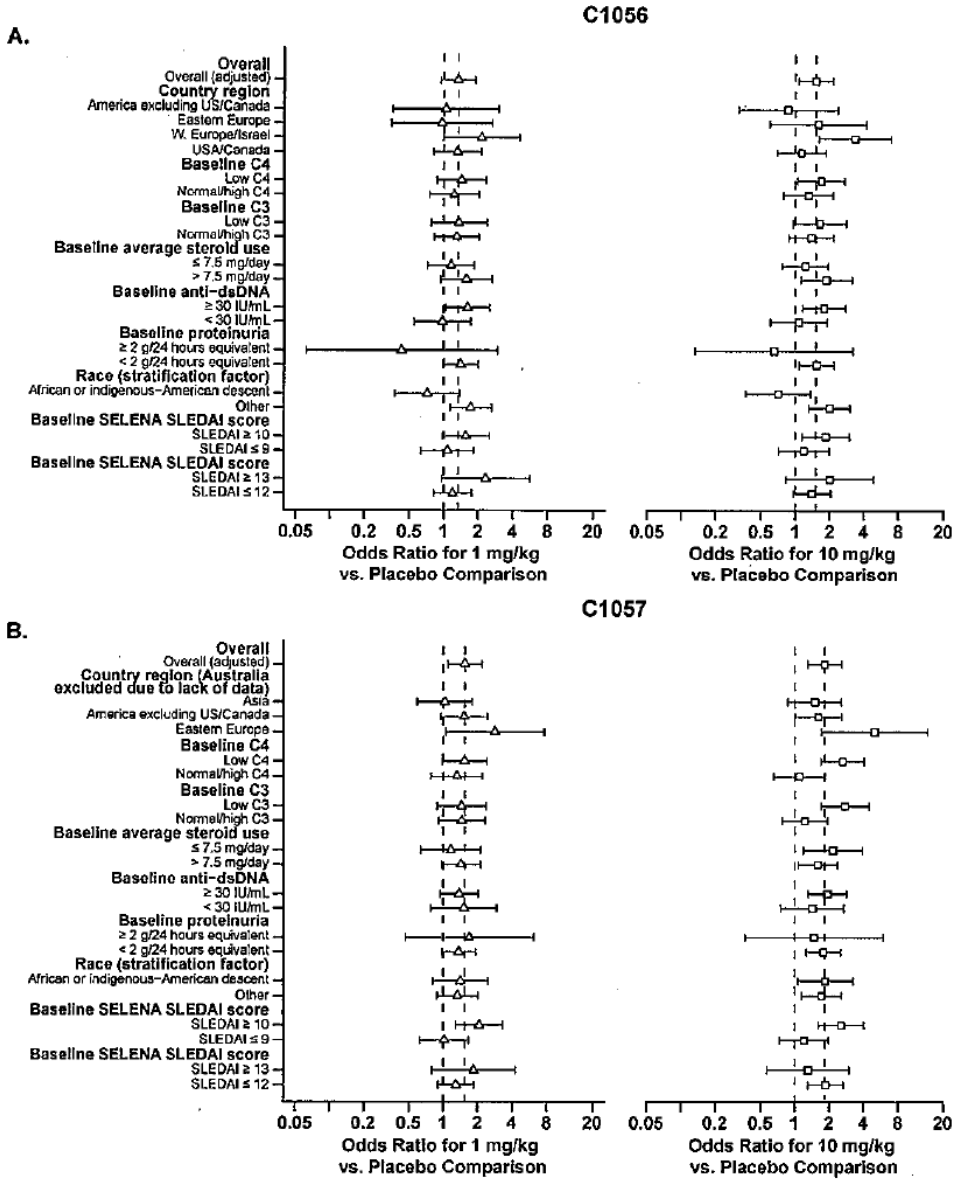
	C1056			C1057		
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290
Overall	93 (33.8%)	110 (40.6%)	118 (43.2%)	125 (43.6%)	148 (51.4%)	167 (57.6%)
Region						
US/Canada	46/145 (31.7%)	59/155 (38.1%)	47/136 (34.6%)	-	-	-
W Europe/Israel	15/64 (23.4%)	25/63 (39.7%)	38/75 (50.7%)	-	-	-
E Europe	15/36 (41.7%)	11/27 (40.7%)	16/30 (53.3%)	12/33 (36.4%)	21/34 (61.8%)	23/31 (74.2%)
Americas (excl US/Canada)	17/30 (56.7%)	15/26 (57.7%)	17/32 (53.1%)	71/145 (49.0%)	85/143 (59.4%)	85/140 (60.7%)
Asia	-	-	-	40/103 (38.8%)	42/106 (39.6%)	56/115 (48.7%)
Interaction P-value[1]	-	0.5597	0.0727	-	0.3605	0.1800
Baseline C4						
Normal/high C4	49/132 (37.1%)	55/130 (42.3%)	55/126 (43.7%)	71/127 (55.9%)	72/115 (62.6%)	64/110 (58.2%)
Low C4	44/143 (30.8%)	55/141 (39.0%)	63/147 (42.9%)	54/160 (33.8%)	76/173 (43.9%)	103/180 (57.2%)
Interaction P-value[1]	-	0.6795	0.4774	-	0.6609	0.0118
Baseline C3						
Normal/high C3	57/159 (35.8%)	72/171 (42.1%)	69/158 (43.7%)	82/155 (52.9%)	87/140 (62.1%)	83/143 (58.0%)
Low C3	36/116 (31.0%)	38/100 (38.0%)	49/115 (42.6%)	43/132 (32.6%)	61/148 (41.2%)	84/147 (57.1%)
Interaction P-value[1]	-	0.9012	0.6295	-	0.9836	0.0183
Baseline average steroid use						
0 - ≤7.5 mg/day	54/149 (36.2%)	56/141 (39.7%)	63/153 (41.2%)	35/95 (36.8%)	34/84 (40.5%)	48/86 (55.8%)
> 7.5 mg/day	39/126 (31.0%)	54/130 (41.5%)	55/120 (45.8%)	90/192 (46.9%)	114/204 (55.9%)	119/204 (58.3%)
Interaction P-value[1]	-	0.3808	0.2303	-	0.5715	0.3947
Baseline steroid use[2]						
No	*24/63 (38.1%)*	*27/60 (45.0%)*	*24/73 (39.9%)*	*5/11 (45.5%)*	*6/12 (50.0%)*	*7/12 (58.3%)*
Yes	*69/212 (32.5%)*	*83/211 (39.3%)*	*94/200 (47.0%)*	*120/276 (43.5%)*	*142/276 (51.4%)*	*160/278 (57.6%)*
Interaction P-value[1]		*0.9797*	*0.0430*		*0.8716*	*0.9554*
Baseline anti-dsDNA						
< 30 IU/mL	39/101 (38.6%)	38/100 (38.0%)	38/94 (40.4%)	43/82 (52.4%)	42/67 (62.7%)	44/72 (61.1%)
≥30 IU/mL	54/174 (31.0%)	72/171 (42.1%)	80/179 (44.7%)	82/205 (40.0%)	106/221 (48.0%)	123/218 (56.4%)
Interaction P-value[1]	-	0.1686	0.1661	-	0.8026	0.4186

Table 48 continued. Subgroup analyses

	C1056			C1057		
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290
Baseline proteinuria level (stratification factor)						
< 2 g/24 hours equivalent	86/264 (32.6%)	107/264 (40.5%)	110/258 (42.6%)	120/266 (45.1%)	139/262 (53.1%)	161/271 (59.4%)
≥2 g/24 hours equivalent	7/11 (63.6%)	3/7 (42.9%)	8/15 (53.3%)	5/21 (23.8%)	9/26 (34.6%)	6/19 (31.6%)
Interaction P-value[1]	-	0.2357	0.3037	-	0.7590	0.7984
Race (stratification factor)						
African descent or indigenous-American descent	36/74 (48.6%)	30/74 (40.5%)	29/72 (40.3%)	47/100 (47.0%)	59/106 (55.7%)	64/103 (62.1%)
Other	57/201 (28.4%)	80/197 (40.6%)	89/201 (44.3%)	78/187 (41.7%)	89/182 (48.9%)	103/187 (55.1%)
Interaction P-value[1]	-	0.0265	0.0088	-	0.8709	0.8278
Race (exploratory subgroup)						
Black	*15/39 (38.5%)*	*12/40 (30.0%)*	*13/39 (33.3%)*	*7/11 (63.6%)*	*3/8 (37.5%)*	*5/11 (45.5%)*
Other	*78/236 (33.1%)*	*98/231 (42.4%)*	*105/234 (44.9%)*	*118/276 (42.8%)*	*145/280 (51.8%)*	*162/279 (58.1%)*
Interaction P-value[1]	-	*0.1429*	*0.1809*	-	*0.4314*	*0.4110*
Baseline SELENA SLEDAI score (stratification factor)						
≤9 points	39/134 (29.1%)	39/127 (30.7%)	45/137 (32.8%)	47/129 (36.4%)	55/149 (36.9%)	53/130 (40.8%)
≥10 points	54/141 (38.3%)	71/144 (49.3%)	73/136 (53.7%)	78/158 (49.4%)	93/139 (66.9%)	114/160 (71.3%)
Interaction P-value[1]	-	0.3031	0.2108	-	0.0409	0.0312

[1] For treatment by subgroup interaction effect from logistic regression.

Table 49. Subgroup analyses Forest plot



In response to the negative recommendation in the CER, the sponsor also provided further post hoc subgroup analyses based on patients with high disease activity at baseline, that is, elevated anti-dsDNA antibodies and low complement (C3/C4) levels using pooled C1056/C1057 data (Tables 50 and 51).

Table 50. Post hoc.

Efficacy of belimumab in Subjects positive for Anti-dsDNA and Low C3/C4 at baseline

C1056/C1057 (pooled)	Placebo (N=287)	1mg/kg (N=284)	10mg/kg (N=305)
SRI response at Week 52 p-value	91 (31.7%)	118 (41.5%) p=0.0020	157 (51.5%) p<0.0001
Prednisone reduction of ≥25% to ≤7.5mg/day, weeks 40-52 p-value	N=173 21 (12.1%)	N=188 43 (22.9%) p=0.0085	N=195 36 (18.5%) p=0.0964
Mean FACIT fatigue score improvement Week 52 p-value	1.92	5.16 p=0.0003	4.50 p=0.0048
C1056	**N=131**	**N=125**	**N=134**
SRI response at Week 52 p-value	37 (28.2%)	50 (40.0%) p=0.0232	61 (45.5%) p=0.0006
SRI response at Week 76 p-value	36 (27.5%)	45 (36.0%) p=0.0997	53 (39.6%) p=0.0160

Table 51. Post hoc.

Efficacy Responses for belimumab 10mg/kg dose in Phase 3 (BLISS52, BLISS76)

Type of response	Overall Population (N=1684)	Anti-dsDNA+ and Low C3/C4[2] (N=876)
SRI at Week 52 (pooled) Observed diff vs placebo Odds Ratio (95% CI)	11.8% **1.7 (1.3, 2.2)**	19.8% **2.7 (1.9, 3.9)**
SRI at Week 52 (BLISS-76) Observed diff vs placebo Odds Ratio (95% CI)	N=819 9.8% **1.5 (1.1, 2.2)**	N=390 17.3% **2.6 (1.5, 4.4)**
SRI at Week 76 (BLISS-76) Observed diff vs placebo Odds Ratio (95% CI)	N=819 6.1% **1.3 (0.9, 1.9)**	N=390 12.1% **1.9 (1.1, 3.3)**
SRI6 at Week 52 (pooled)[1] Observed diff vs placebo Odds Ratio (95% CI)	13.8 **2.1 (1.6, 2.8)**	17.2% **3.1 (2.1, 4.6)**
SELENA SLEDAI 4-point reduction (pooled) Observed diff vs placebo Odds Ratio (95% CI)	11.8% **1.7 (1.3, 2.2)**	18.6% **2.6 (1.8, 3.7)**
No new BILAG 1A/2B at Week 52 (pooled) Observed diff vs placebo Odds Ratio (95% CI)	6.27% **1.4 (1.1, 1.8)**	12.3% **1.8 (1.3, 2.6)**
No worsening of PGA at Week 52 (pooled) Observed diff vs placebo Odds Ratio (95% CI)	8.4% **1.5 (1.2, 2.0)**	14.1% **1.9 (1.3, 2.7)**
Prednisone reduction ≥25% to ≤7.5mg/d during Weeks 40-52 among patients with baseline prednisone>7.5mg/d Observed diff vs placebo Odds Ratio (95% CI)	N=976 5.6% **1.6 (1.0, 2.5)**	N=556 6.3% **1.6 (0.9, 2.9)**
Prednisone reduced to ≤7.5mg/d with baseline prednisone >7.5mg/d Observed diff vs placebo Odds Ratio (95% CI)	N=976 7.5% **1.7 (1.1, 2.5)**	N=556 9.6% **1.8 (1.0, 3.1)**
Prednisone increased to >7.5mg/d with baseline prednisone ≤7.5mg/d Observed diff vs placebo Odds Ratio (95% CI)	-7.2% **0.58 (0.34, 0.98)**	-12.1% **0.60 (0.34, 1.06)**
Severe Flare over 52 Weeks Patients experiencing a severe flare (% pla vs 10mg/kg) Time to 1st severe flare [Hazard ratio (95% CI)]	23.7% vs 15.6% **0.64 (0.49,0.84)**	29.6% vs 19.0% **0.61 (0.44, 0.85)**
Mean FACIT fatigue score improvement Week 52 Mean treatment difference vs placebo (95% CI)	1.92 (0.82, 3.02)	2.92 (1.47, 4.37)

1. Requires 6 pt improvement in SELENA-SLEDAI
2. The Anti-dsDNA+ and Low C3/C4 group analysis was run against the pooled dataset using the final BLISS-76 dataset.

Clinical Safety

The primary safety population for this submission is 2133 subjects who received any dose of belimumab/placebo by IV infusion in SLE trials. Of these 1546 were belimumab recipients representing 3976 Patient-Years (PY) of exposure. The median number of days of exposure with the 1 mg and 10 mg/kg doses was 370 days (range 28 to 625 days) and 392 days (28 to 1933 days) respectively (Table 28).

The overall incidence of (any) AEs in Phase II/III SLE studies was 93.0%, 96.4% and 92.7% for the 1, 4 and 10 mg/kg groups respectively compared to 92.4% in placebo patients (Table 29).

The overall incidence of any AE in Phase II/III SLE studies leading to discontinuation was 6.2%, 3.6% and 6.7% for the 1, 4 and 10 mg/kg groups respectively compared to 7.1% in placebo patients. The overall incidence of SAEs in Phase II/III SLE studies was 18.6%, 13.5% and 17.4% for the 1, 4 and 10 mg/kg groups respectively compared to 15.9% in placebo patients (Table 29).

There was generally higher incidence of AEs with the 4 mg/kg dose (based on a single Phase II study) and similar rates among other groups (based on two additional Phase III studies).

The most commonly affect system organ classes and the incidences of selected AEs have been summarised in Tables 30 and 31 above.

The incidence of hypersensitivity and infusion reactions was 14.7%, 16.6%, 23.4% and 16.8% for placebo, 1, 4 and 10 mg/kg groups respectively. The incidence of serious hypersensitivity and infusion reactions was 0.4%, 0.9% and 0.9% for placebo, 1 and 10 mg/kg groups respectively. The majority of infusion and hypersensitivity reactions occurred during the first 6 months of treatment and the overall rates were 24.9, 25.2, and 29.1 per 100 PY for placebo, 1 and 10 mg/kg groups respectively, with the highest incidence occurring with the first infusion (4.1%, 5.8% & 7.3% for placebo, 1 and 10 mg/kg groups respectively). Anaphylactic reaction was reported in 2 patients in 1 mg/kg group and 1 patient in the 10 mg/kg group. Angioedema was reported in 1 patient in each belimumab group. Hypersensitivity and infusions related events leading to study drug discontinuation included anaphylactic reaction, angioedema, bradycardia, drug hypersensitivity (not otherwise specified), dyspnoea, and generalised pruritus. Four patients suffered serious and/or severe hypersensitivity reactions that occurred on the day of infusion. No fatal hypersensitivity and infusions related AEs were reported.

The incidence of serious infection was 5.2%, 6.8% and 5.2% for placebo, 1 mg/kg and 10 mg/kg groups respectively. The reported serious infections included pneumonia, UTI, cellulitis, bronchitis and pyelonephritis. The incidence of pre defined infectious AEs of special interest were as described in Table 52 below.

Subsequent data indicate occurrence of 1 case of opportunistic infection (*Acinebacter Pneumonia*) in 1 mg/kg group. The incidence reported above in 10 mg/kg group was based on 2 cases (*Acinebacter bacteraemia* and disseminated cytomegalovirus). Longer term data (2425 PY) further indicate 6 cases of opportunistic infection (1 cytomegalovirus pneumonia, 2 pulmonary tuberculosis, 2 extrapulmonary tuberculosis and 1 coccidioidomycosis). A case of mycobacterium avium pulmonary infection was reported in long term RA trials. The reported incidence rate of opportunistic infections as of 9 July 2010 has been summarised in Table 53 below.

Table 52. Infectious AEs of special interest

	placebo	1 mg/kg	4 mg/kg	10 mg/kg
Cellulitis	6.4%	8.2%	8.1%	6.4%
Cellulitis (serious)	0.7%	1.3%	0.9%	0.4%
Fungal infections	3.3%	3.0%	3.6%	2.5%
Fungal infections (serious)	0.1%	-	-	-
Herpes viral infections	8.0%	7.6%	4.5%	6.5%
Herpes viral infections (serious)	0.4%	0.6%	-	0.7%
Sepsis	0.4%	0.6%	0.9%	0.7%
Upper Respiratory Infections	43.3%	43.7%	55.0%	44.8%
URI (serious)	0.1%	-	-	0.3%
Lower Respiratory Infections	8.6%	11.3%	11.7%	12.0%
LRI (serious)	1.6%	1.8%	2.7%	1.3%
Pneumonia	2.5%	3.1%	1.8%	2.4%
Pneumonia (serious)	1.5%	1.3%	1.8%	1.0%
Opportunistic infections	-	-	-	0.3%

Table 53. Opportunistic infections reported

	Belimumab Studies			
	IV SLE CRD		All SLE Studies	
	Placebo	All Active	Placebo	All Active
No. Patients	675	1458	688	1982
Patient years	692	1516	702	3,976
Opportunisitic Infections	0	3[1]	0	9[1, 2]
Opportunistic Infection rate / 100 patient years	0	0.20	0	0.23
95% Confidence interval	(0.00, 0.43)	(0.04, 0.58)	(0.00, 0.43)	(0.10, 0.43)

Source: Table TA194 and TA195, m5.3.5.3
1 Includes one event reported on Day 0 and therefore unlikely to be related to belimumab.
2 Includes 4 events reported in the MAA (3 in the primary safety population and 2 in LBSL99) and an additional 5 events reported through 09July2010 in long-term continuation studies.

An association with adverse neuropsychiatric outcomes was also found in the clinical studies. The reported psychiatric disorders were primarily insomnia (5.3%, 5.5%, 6.5%), depression (3.7%, 6.1%, 5.2%) and anxiety (2.5%, 4.5%, 2.2%) for placebo, 1 mg and 10 mg/kg groups respectively. The incidence of serious psychiatric disorders was 0.6% and 1.2% for 1 mg and 10 mg/kg groups respectively compared with 0.4% with placebo, accounted for mainly by 6 events of depression (3 each in 1 and 10 mg/kg groups and 1 event in placebo). Five cases of suicidal behaviour or suicidal ideation were reported during the 3 Phase II/III trials including 2 completed suicides (1 each in 1 mg and 10

mg/kg groups). Further 7 cases are reported in the longer term data based on 2425 PY of exposure including one completed suicide.

The reported rates of malignancies as of 9 July 2010 are shown in Table 54 below.

Table 54. Rate of malignancies

	Background Rate	Belimumab Studies			
		IV SLE CRD[1]		All SLE Studies[2]	
	Bernatsky et al, 2005	Placebo	All Active	Placebo	All Active
No. Patients	9547	675	1458	688	1,982
Patient years	76,948	692	1516	702	3,976
All malignancies	410	2	3	2	18
Malignancy rate / 100 subject years	0.53	0.29	0.20	0.28	0.45
95% Confidence interval	(0.48, 0.59)	(0.04, 1.04)	(0.04, 0.58)	(0.03, 1.03)	(0.27, 0.72)
Hematological malignancies	67	0	0	0	3
Hematological malignancy rate / 100 subject years	0.087	0.000	0.000	0.000	0.075
95% Confidence interval	(0.067, 0.111)	NP[4]	NP[4]	(0.000, 0.427)	(0.016, 0.221)

1. Includes Studies LBSL02, C1056, and C1057 as updated and reported in 120-Day Safety Update
2. Includes Studies LBSL01, LBSL02, C1056, C1066, C1074, C1070, and LBSL99 as updated and reported in the 120-day Safety Update. Note that placebo subjects were followed for up to 18 months while belimumab subjects were followed for up to 5 years.
3. Includes b cell lymphoma (n=2) and multiple myeloma (n=1)
4. Not provided

Source: Tables 25.01 and 25.02, m 5.3.5.3 and Day120 safety update, m5.3.5.3

The reported mortality rates as of 9 July 2010 are shown in Table 55.

Table 55. Mortality rate.

	Background Rate	All SLE Studies[1]	
	Bernatsky et al 2006	Placebo	All Active
No.Subjects	9,547	688	1,982
Subject years	76,948	702	3,976
Deaths	1,255	3	22
Death rate / 100 subject years	1.63	0.43	0.55
95% Confidence interval	(1.54, 1.72)	(0.09, 1.25)	(0.35, 0.84)

[1] Includes LBSL01, LBSL02, LBSL99, C1056, C1057, C1066, C1074, C1070 ;SOURCE = US 120 Day Safety Update

Although not confirmed in the current dataset, there is a safety signal for (1) serious infections including opportunistic infections (2) neuropsychiatric adverse outcomes including suicidal behaviour (3) malignancies including non-haematological and (4) overall mortality in association with belimumab treatment which requires further data such as by active surveillance in post-market setting.

A total of 47 subject pregnancies and 3 partner pregnancies have been reported in Phase II/III SLE studies. The foetal loss rate in subjects treated with belimumab with known pregnancy outcomes was 31% (10/32), which stated to be higher than the background rate in patients with SLE (15-25%) based on published literature. For patients placebo group the rate of foetal loss was 50% (3/6 subjects). For the partner pregnancies, the outcomes were a live birth with no congenital abnormalities (placebo), unknown (1 mg/kg) and a spontaneous abortion (10 mg/kg). The sponsor has proposed to set up a pregnancy registry.

No studies have been conducted in patients < 18 years old or elderly (17 patients > 65 years old were exposed to any belimumab in SLE studies). No specific drug interaction studies were performed.

No clinically significantly laboratory (chemistry) abnormalities were identified with belimumab treatment.

The proportion of belimumab treated patients who tested anti-belimumab antibody (ADA) positive in the two Phase III studies was 13.1%, 0.9% and 2.0% for 1 mg, 10 mg/kg and placebo respectively. The result for the 10 mg/kg was likely an underestimation due to interference with the assay. Over 2/3 of ADA+ patients had a transient (single sample only) result. However, 4.7% patients in 1 mg/kg group had a persistent immune response compared with 1.8% placebo patients and 0.7% 10 mg/kg patients.

The effect of belimumab on vaccinations was analysed in a sub-study (Table 44) within Study C1056 comprising participants with pre existing functional antibodies to *streptococcus pneumoniae*, tetanus or influenza or participants who were vaccinated against these organisms during the study. The belimumab treatment was not associated with clinically relevant change in the antibody titres in any group. Although effective immune response was mounted, the data were very limited for tetanus (n = 4) and *streptococcus pneumoniae* (n = 7) vaccination during belimumab treatment. For influenza vaccination, 7 out of 10 patients in belimumab treatment groups who did not have pre-existing antibodies mounted a protective response following vaccination.

Risk Management Plan

The evaluation of the RMP (version 03) by TGA's OPR (see *Pharmacovigilance Findings* above) was included for the ACPM's information.

Risk-Benefit Analysis

Delegate Considerations

The Delegate agreed with the clinical evaluator's critique of the data both in the CER and in reviewing the sponsor's response to the CER. These include (1) insufficient investigation of doses between 1 and 10 mg/kg (2) modest and variable efficacy in the two Phase III studies, and (3) limitations of post hoc analyses provided subsequently.

The lack of dose response and presence of variable effect was seen across pharmacodynamic endpoints as well as clinical efficacy outcomes.

However, the Delegate noted that the construction of a composite SRI index and both Phase III studies were well planned and implemented. This latter point is borne out by the consistency of the primary outcome in a number of sensitivity analyses using various sample populations.

It may therefore be argued that the variability in response seen here is inherent in the nature of this heterogeneous disease rather than a consequence of poor trial design, execution or analysis.

With respect to discrimination between 1 mg and 10 mg/kg doses against placebo, the only clinically meaningful magnitude of treatment effect (14%) with respect to SRI at 52 weeks was obtained with the 10 mg/kg dose in Study C1057 (Odds Ratio 1.8; 95% CI 1.3 to 2.6). Even though 14% placebo corrected difference is only a modest gain and is based on the fact that this was used as a minimum clinically useful difference to be detected in sample size calculations, the Delegate accepted that this is a clinically useful magnitude especially as it is achieved on the background of standard care which includes immune

modulatory drugs. In general, the current standard of care therapies in the management of SLE are not evidence based.

As noted elsewhere the effect was not maintained to 76 weeks despite continuing controlled treatment in study C1056.

With respect to the post hoc analysis showing enhanced efficacy in anti-dsDNA positive/low complement patients at baseline, the Delegate was of the view that the estimates obtained in the overall sample population are likely to be better guide to the true clinical effect and any approval usage should reflect the overall trial population such as patients with active disease defined as SELENA-SLEDAI score ≥ 6 who are autoantibodies positive defined as ANA titer ≥ 1:80 and/or anti-dsDNA titer ≥ 30 IU/mL.

With respect to safety, although the drug has a very specific target and has high affinity for its target so that off-target effects are not expected, the final immune modulation of B cells has expected and diverse consequences namely risk of serious infection and malignancies. There was signal in the data requiring further confirmation with larger data. Similarly, overall mortality rate was nominally higher (0.55 versus 043 per 100 PY for belimumab vs. placebo) which would require ongoing surveillance. The unexpected findings included risk of serious neuropsychiatric effects. Adverse effect on pregnancy outcomes was also demonstrated. The data are too limited at this stage to be able to declare lack of effect on immune response to prophylactic vaccines.

Given these findings, the Delegate was of the view that there is sufficient evidence has to recommend approval of 10 mg/kg dose in the treatment of SLE. However, the risk/benefit balance can only be captured in favour of benefit provided the trial population is correctly reflected in the indication, duration of treatment is specified and a well defined post market surveillance plan is put in place. This latter should aim to captures all patients who receive belimumab for the approved indication with a view to revisiting of efficacy and safety at specified timepoints such as 1, 3 and 5 years post market availability, effectively a conditional registration.

Issues for which Committees advice was specifically requested

In addition to the Committee' overall advice regarding adequacy of data to support approval, the Committee was also requested to specifically address the following:

- 1 mg/kg versus 10 mg/kg dosing: Arguably 1 mg/kg can be recommended instead of 10 mg/kg on this data.
- Duration of treatment: Is withdrawal of treatment at 52 weeks in responders reasonable given lack of significant effect at 76 weeks and the associated risks of immune suppression in indefinitely ongoing treatment?
- Early withdrawal of treatment in non-responders: The data did not indicate any suitable measure whereby non-responders could be identified early. There was also the indication that the clinical effect begins to appear after 24 weeks. Early identification of non-responders is important missing information at present.
- Post market surveillance: Committee's advice in setting up appropriate risk management plan in regard to both efficacy and safety.

Delegate's proposed recommendation

Based on the foregone comments and pending advice from the ACPM, the Delegate was of the view that belimumab may be approved for the following indication:

> *Belimumab is indicated as add-on therapy for reducing disease activity in adult SLE patients who have active disease (SELENA SLEDAI score ≥ 6) and are autoantibodies*

positive (ANA titer ≥ 1:80 and/or anti-dsDNA titer ≥ 30 IU/mL) at baseline who are receiving standard therapy. The benefit or durability of treatment beyond 52 weeks has not been demonstrated.

The recommended dose is 10 mg/kg by IV infusion every 2 weeks for 3 doses, followed by once every 4 weeks for 52 weeks.

Response from Sponsor (dated 7 September 2011)

Purpose of Application: To register the product as a new chemical entity for the treatment of Systemic Lupus Erythematosus (SLE).

It is important to highlight that the patient population for whom Benlysta is intended, have a disease which is complex and varied in its manifestation, have high risk factors for comorbidities and have not responded to the currently available standards of care. Belimumab offers an important additional treatment option for these patients.

Based on the review of all submitted information the Delegate has recommended approval of Benlysta for reducing disease activity in adult SLE patients at a dose of 10 mg/kg by IV infusion. This recommendation is consistent with the approvals for Benlysta in the USA, EU and Canada.

GSK believes that adequate data have been submitted that support the following:

- The data demonstrate that the only statistically and clinically meaningful magnitude of treatment effect was achieved with the 10 mg/kg dose at 52 weeks, as confirmed by the Delegate.
- The available data do not support a restriction of treatment to 52 weeks in patients who are responding to treatment; the decision for continuing with ongoing treatment should be managed by the treating physician, based on their assessment
- The available data support restriction on the duration of treatment to 6 months for non-responders.
- The available risk management plan will enable adequate management of the known and potential risks associated with belimumab. In addition GSK agrees to submit the synopsis and protocol of the post marketing efficacy and safety study to the TGA, Office of Medicine Safety Monitoring (OMSM) and undertake a local audit of the effectiveness of the risk mitigation strategy for potential hypersensitivity reactions.

GSK have provided pivotal evidence to demonstrate statistically significant and clinically relevant improvement over and above standard of care. Clinical opinion has been sought from a leading expert in SLE with respect to the specific questions raised by the Delegate.

1. 1 mg/kg versus 10 mg/kg dosing: Arguably 1 mg/kg can be recommended instead of 10 mg/kg on this data.

The Delegate indicates that there is sufficient evidence to recommend approval of the 10mg/kg dose in the treatment of SLE and GSK agrees that this is the appropriate dose as demonstrated by the available pivotal clinical evidence from the Phase III clinical studies and supported by the Phase II studies.

In the Phase III SLE studies, C1056 and C1057, both the 1 mg/kg and 10 mg/kg belimumab doses were associated with positive effects on efficacy and biomarker parameters. However for several endpoints the effect observed with the 10 mg/kg belimumab dose was more robust than was observed with 1 mg/kg. Only the 10 mg/kg dose met the primary endpoint in both Phase III trials, whereas the 1 mg/kg dose only met the primary endpoint in one study. A similar pattern was observed in sensitivity analyses of these studies. Moreover, several other clinical measures of improvement including severe flare risk reduction and complement normalisation generally favoured the 10 mg/kg dose.

While steroid reductions tended to favour 1 mg/kg belimumab, fewer patients receiving 10 mg/kg belimumab required increases in steroids over time. As requested by the clinical evaluator, the effect on a number of endpoints for both doses is now presented in the Clinical Trials section of the Product Information.

In the Phase II trial in SLE (LBSL02), the co-primary endpoint was percent change in SELENA SLEDAI score at Week 24. The mean percent decrease in SELENA SLEDAI score was numerically better than placebo for the 1 and 10 mg/kg groups with an average of approximately 23% each compared with 17% in the placebo group and these trends continued through Week 52/56. However, the 10 mg/kg dose showed evidence of faster onset of effect as evidenced by earlier reductions in SELENA SLEDAI score in autoantibody positive subjects. In addition, the 10 mg/kg dose was associated with trends toward greater reductions (and fewer increases) in steroid use. As requested by the clinical evaluator, a summary of Phase II study LBSLO2 has been included in the Clinical Efficacy section of the Product Information.

BLyS, the target of belimumab, is secreted as a soluble trimer by innate immune cells including macrophages, dendritic cells, neutrophils, mast cells and monocytes. Belimumab-BLyS complexes accumulate, so it is important that excess belimumab be present to maintain an equilibrium that favours formation of the complex. As measured in the Phase III studies, steady-state trough belimumab levels for a 10 mg/kg dose were 30-150 times greater on a molar basis than the highest BLyS level observed in the Phase III studies. Steady-state trough belimumab levels for a 1 mg/kg dose were 2-7 times greater on a molar basis than the highest BLyS level observed in the Phase III studies. Corresponding to this, BLyS-belimumab reached stable levels that were higher in the 10 mg/kg group than in the 1 mg/kg group but did not increase over time, which is consistent with BLyS being produced at a constant rate. The fact that complex levels are higher in the 10 mg/kg group suggests that circulating levels of belimumab attained with the 1 mg/kg dose may not be sufficient to completely bind BLyS.

Additionally, and importantly, there was no apparent dose-response in the safety profile of belimumab, with both doses being generally well tolerated.

The long term continuation trial LBSL99 further supports a sustained disease improvement and safety profile with the 10 mg/kg dose over a 6 year period.

2. Duration of treatment: Is withdrawal of treatment at 52 weeks in responders reasonable given lack of significant effect at 76 weeks and the associated risks of immune suppression in indefinitely ongoing treatment?

A comment on this question has been sought from a leading physician in SLE in Australia, and an expert statement was included with this response.

As noted by the Delegate and confirmed by the sponsor's expert;

"The standard of care of SLE is based on 'Off-label' use of drugs for which a sound evidence base is lacking. Nonetheless, it is common practice to continue treatment long term once SLE patients achieve good disease control, albeit with the parallel goal to minimise total drug exposure, especially corticosteroids dosing."

Long term data from the continuation trials provide evidence that the 10 mg/kg dose is safe and effective for chronic use. In Phase II after 76 weeks of treatment all patients (placebo, 1, 4 and 10 mg/kg) were put on 10 mg/kg dose in the long term continuation trial LBSL99. In Phase III long term continuation studies patients on belimumab remained on the originally assigned dose (1 or 10 mg/kg) and placebo patients were placed on 10 mg/kg dose. Our data suggest that improvements accumulate over time on a long term dose of 10 mg/kg, while maintaining a favourable safety profile. Data from the Phase II long term continuation trial suggest continuing benefit with 10 mg/kg belimumab treatment through at least 5 years. Data available to 6 years indicate that the SRI rate with

belimumab was 46% at wk 52 (versus 29% with placebo; p <0.05), increasing to 55% to61% through 6 years of open label treatment. The frequency of new BILAG 1A or 2B flares with belimumab was 38% at 1 year versus 44% with placebo, decreasing to 11% at 6 years of open label treatment. The frequency of all SFI flares with belimumab was 84% (severe 17%) at 1 year versus 85% (severe 19%) with placebo, decreasing to 42% (severe 5%) at 6 years. Patients on belimumab had increases in complement (C3 or C4) levels over 6 years. Autoantibody levels (anti-Smith, anti-double-stranded DNA, anticardiolipin-immunoglobulin-G) generally decreased over time. In 283 patients taking corticosteroids at baseline, corticosteroid use decreased over time with a mean reduction of 34% and an absolute reduction of 4.7 mg/day at 6 years versus baseline. Although there is no control group in this tria, and therefore data should be interpreted in that context, these data suggest that effects on disease activity, flares and serologic activity are maintained over time or improve.

In addition to the long term continuation data, the randomised, placebo controlled portions of the Phase III trials also support continued efficacy over and above standard of care beyond 52 weeks. When looking at more stringent thresholds of response (minimum SELENA SLEDAI improvements of 5 to 10 points to define a responder), statistical significance of belimumab over placebo out to 76 weeks in BLISS 76 was maintained. In addition, in the immunologically highly active subgroup of patients with anti-dsDNA and low complement (a group at high risk of flares and renal disease) a statistically significant treatment benefit was maintained out to 76 weeks in BLISS 76.

Given these data, an optimal duration of treatment cannot be determined for patients who continue to benefit over the long term.

From a safety perspective, the available long term data up to 6 years do not indicate an increased risk of specific immunosuppressive consequences not observed with treatment up to 52 weeks. A robust RMP will continue to monitor the identified safety risks to ensure that any long term safety effects are appropriately communicated and managed by the Health Care Professional (HCP)

For all the reasons discussed above, GSK believes that discontinuing belimumab at 52 weeks in a patient who has responded presents an ethical dilemma to the physician and is not supported by the clinical data. This is supported by the sponsor's expert's assessment of this issue,

"I support physicians being advised that efficacy has not been proven beyond 52 weeks, but would strenuously oppose therapy being limited to that duration. It is certainly conceivable that some patients who do extremely well could be considered for treatment withdrawal, but also that many patients who demonstrate a response would be best served by continuing a treatment that has given them that response rather than return to sickness".

GSK therefore believed it was not appropriate to include a restriction to 52 weeks treatment in the Indication or dosing section of the PI. GSK would instead propose the following language to provide guidance to the physician:

"*The recommended dose is 10 mg/kg by IV every 2 weeks for 3 doses, followed by once every 4 weeks thereafter. Discontinuation of treatment with Benlysta should be considered if there is no improvement in disease control after 6 months of treatment. Beyond 52 weeks of treatment the physician should regularly monitor the patient to ensure benefit and durability of treatment are maintained (see Clinical Trials sections)."*

3. **Early withdrawal of treatment in non-responders: the data did not indicate any suitable measure whereby non responders could be identified early. There was also the indication that the clinical effect begins to appear after 24 weeks. Early indication of non responders is important missing information at present.**

While data from the Phase III trials demonstrate that, on an individual basis, responses continue to occur throughout the 52 weeks of the trial, when responses to belimumab are viewed on a population basis, it appears that responses appear to plateau at or around the 6 month time point. After 6 months there appears to be a greater separation between belimumab and placebo primarily due to a decreasing efficacy of the placebo arm most likely due to progressive restrictions on steroid use. This is not to say that maximal responses are reached at 6 months but that when looking across the population of patients, peak rates of response are reached by 6 months.

Belimumab demonstrated a variety of potential benefits to patients at different time points during the trial. Biological response can be seen in the first few months in improvement in serological activity and reduction of selective B-cell subsets but these effects continue to increase over 52-76 weeks. Belimumab can reduce steroid use by decreasing steroid dose or require less increase over 52-76 weeks. In addition, reduction of risk of severe flares can occur over 52 weeks and is often seen in patients who have not achieved an SRI. Improvements in quality of life and fatigue can be observed early but become more apparent after 24 -52 weeks. Therefore, based on a variety of potential benefits we would propose that if after 6 months of treatment the patient has not experienced improvement of one or more of her/his manifestations of lupus, (including serologies, reduced flare, improvement in QOL or reduction of steroid use) in the physician's clinical judgement, the patient should have their course of belimumab discontinued. This view is supported by the sponsor's assessment of this question.

To this point, GSK proposes to amend the recommended dosage statement in Dosage and Administration section of the Product Information as follows:

The recommended dose is 10mg/kg by IV every 2 weeks for 3 doses, followed by once every 4 wks thereafter. ***Discontinuation of treatment with Benlysta should be considered if there is no improvement in disease control after 6 months of treatment.*** *Beyond 52 weeks of treatment the physician should regularly monitor the patient to ensure benefit and durability of treatment are maintained (see clinical trials sections).*

The statement in bold is consistent with the statement included in the approved EU SPC for Benlysta.

4. **Post market surveillance: Committee's advice in setting up appropriate risk management plan in regard to both efficacy and safety.**

GSK have a comprehensive RMP for Benlysta to address the important identified and potential risks. The identified risks for belimumab are infusion reactions, hypersensitivity reactions and infections. The potential risks for belimumab include malignancies, immunogenicity, diminished response to live or attenuated vaccines and secondary transmission of infection with live vaccines and psychiatric events including depression and suicide. As requested in the RMP and clinical evaluation reports, GSK have included additional precautionary text to the Product Information to further highlight these risks to the treating physician.

The pharmacovigilance plan includes routine Pharmacovigilance and significant long-term safety follow-up from long term continuation studies, including Phase II, LBSL99 for up to 10 years, Phase III C1066 for up to 5 years and Phase III C1074 up to MA approval in each clinical trial country (The mean subject years of exposure currently available (July 2011 cut-off) is 2.2 and 4.1 years of treatment in Phase III and II respectively, with a range up to 4.3 and 7.3 years, respectively; 1064, 746, 251, 298, 157 and 87 subjects have received

over 2, 3, 4, 5, 6, and 7 years of treatment, respectively). This will increase substantially as Phase III continuation patients are treated longer. The company also proposes a large randomised controlled post authorisation safety study of approximately 5000 patients and in addition a pregnancy registry and a proposed post registration vaccine study. Safety endpoints in continuation studies will include but not be limited to, analysis of pre specified adverse events of special interest: infusion-related reactions and hypersensitivity reactions (those occurring on the day of infusion), infections, and malignant neoplasms. Anti-belimumab antibody response and association with adverse events will also be analysed. In addition in Study C1066, B cells will be evaluated every 24 weeks.

The large randomised controlled safety study was previously proposed as being a 5 year study, where the first year would be a randomised double-blind controlled study, followed by years 2-5 being an open labelled controlled study. The FDA have recently requested that the company (our alliance partner) consider limiting the duration of the trial to 1 year only, that is, the double blind controlled phase only. This request is linked to the concern the FDA have with potential bias in the open label randomised phase of the study, years 2-5 (current trial design: Year 1: belimumab + SOC versus SOC, Year 2 to 5: belimumab patients stay on belimumab, SOC arm stay on SOC which can include belimumab) . GSK propose to revise the company RMP to propose a 1 year large safety study.

The company would therefore like to propose to submit to the TGA by end of October 2011 a synopsis for the 1 year large safety study and a revision to the RMP regarding proposals for risk management for the identified and potential risks to account for this amendment.

The OPM evaluator has also recommended that GSK propose a plan to monitor the effectiveness of the risk minimisation activity for infusion and hypersensitivity reactions (requirement in PI for treatment to be undertaken in a facility with appropriate resuscitation facilities). To this end the company agrees to develop a plan locally to provide relevant educational material to the treating healthcare professionals and to surveying the adherence to these materials via the known treatment centres over a period of 12 months post product launch. The results of the surveys will be submitted with a PSUR at a timepoint agreed with the TGA.

In addition to the safety studies discussed above, several additional efficacy studies are planned, which will validate the benefits of belimumab observed in the pivotal studies 1056 and 1057. These include the ongoing SC Phase II study (N = ~33); an ongoing study in SLE patients in East Asia (same design as the Phase III IV trial C1057, N = ~630); a proposed study in SLE patients of Black race (N = ~815); a proposed pivotal SC study (N = ~815), a proposed lupus nephritis study (N = ~464); and a proposed study in vasculitis (N = ~400). The completed, ongoing, and planned studies would provide data on ~3,400 patients receiving belimumab and ~1,860 receiving placebo and are projected to mature before the 1 year data are available from the large safety trial (which is projected to be available ~8 years from now).

A summary of the ongoing studies, with reporting timeframes was included in the sponsor's response and provided a guide as to when data will be available for submission to regulatory authorities if required.

Proposed indication

The indication proposed by the Delegate is noted and the sponsor agreed to the following indication:

> *Benlysta is indicated as **add-on therapy** for reducing disease activity in adult **systemic lupus erythematosus (SLE)** patients **who have active disease, are autoantibody positive and** who are receiving standard therapy.*

Given the complexity of the disease and the range in clinical assessment practice, GSK does not believe that it is appropriate to include specific clinical parameters in the indication. Notably, by directing the treating physician to a formal SLEDAI assessment prior to prescribing Benlysta, a significant and unnecessary barrier would be placed in many clinics, especially given that not all clinicians use this instrument routinely in clinical practice. The inclusion criteria including SLEDAI score and autoantibody titre is detailed in the Clinical Trial section of the PI and therefore all necessary information for the treating physician is available to make an informed decision as to the appropriateness of Benlysta treatment for a patient with SLE.

In addition, GSK contends that the qualification statement "The benefit or durability of treatment beyond 52 weeks has not been demonstrated" does not belong in the "Indications" section of the Product Information. GSK recognises the limitation of the benefit and durability of data on Benlysta treatment past 52 weeks at this stage; however as justified in responses to Questions 2 and 3 raised by the Delegate, GSK believes that the treatment duration for a chronic therapy should not be limited to 52 weeks. As suggested by the sponsor's expert, this decision should be the responsibility of the treating physician to assess from both a response and safety perspective, in the knowledge of the available clinical data. To suggest limiting the treatment duration to 52 weeks would present an unethical dilemma for physicians.

Taken together, GSK proposes that in addition to the statement included in the Clinical trials section of the PI ("At Week 76 in Study 2, the SRI response rate with belimumab was not significantly different from that of placebo (39% and 32% respectively)") a further statement would be more appropriately placed in the "Dosage and Administration" sections of the Product Information as shown below:

Dosage and administration

The recommended dose is 10 mg/kg by IV every 2 weeks for 3 doses, followed by once every 4 weeks thereafter. ***Discontinuation of treatment with Benlysta should be considered if there is no improvement in disease control after 6 months of treatment. Beyond 52 weeks of treatment the physician should regularly monitor the patient to ensure benefit and durability of treatment are maintained (see clinical trials sections).***

Response from Sponsor: Reconsideration for February 3, 2012 ACPM

GSK wishes to add to the Delegate's reconsideration to the ACPM on this important medicine.

Key points

SLE is a chronic autoimmune, multisystem disorder; with varying manifestations. There is a need for specific SLE treatments, that can be safely administered with standard of care SLE therapies, and that will reduce disease activity and flares, both of which have been shown to predict irreversible organ damage. A treatment which minimises the requirement for steroids is also required.

At the FDA Arthritis Advisory Committee (AdCom), an external expert summarised the physicians' perspective well*, "The SLE community has persevered through a decade of failed trials to arrive here today. A targeted biologic in SLE needs to have efficacy with an acceptable safety profile. The belimumab Phase 3 trials have demonstrated compelling efficacy in moderate to severe SLE, with a favourable safety profile".*

The Delegate and sponsor's expert have noted that the standard of care in SLE in Australia is currently based on "off-label" use of drugs for which a sound evidence base is lacking. The sponsor's expert was quoted: "*There is no specific therapy for SLE approved in*

Australia, and therefore patients are treated with non-specific and highly toxic drugs used since the 1950s."

The regulatory approvals in the USA, EU and Canada followed considerable debate on similar issues which have been raised by the TGA. On overall approvability, the FDA AdCom meeting voted 13 to 2 in favour and at the CHMP Ad-Hoc Expert Meeting; the lupus experts agreed that a moderate effect of belimumab has been demonstrated on top of other therapies in a patient population that represents the majority of cases in clinical practice.

- The ACPM Resolution No. 9570 advised that the risk-benefit of Benlysta was not favourable to support registration notwithstanding the Delegate's recommended approval for the 10 mg/kg dose subject to conditions. GSK submits that the evidence clearly supports approval given the demonstrated efficacy (which may be viewed as modest) benefits over Standard of Care (SOC), thus providing a unique advance in SLE treatment.
  - The 2 Phase III pivotal clinical trials clearly met their primary efficacy endpoints for a 10mg/kg dose, which by definition is clinically relevant and therefore the statutory test has been satisfied;
  - The current safety profile for Benlysta contributes to a favourable benefit:risk. GSK has an updated EU-RMP in place to reflect EMA comments and includes a comprehensive set of CHMP agreed post approval commitments/studies with due dates. This provides for long term follow-up in a large data set for each of the adverse events of special interest, including neuropsychiatric adverse events that are relatively common in an SLE population.

Indication and Product Information

GSK agreed with the Delegate that the indication should reflect the clinical trial population and offered to amend the Delegate's proposed indication as follows:

Belimumab is indicated as add-on therapy for reducing disease activity in adult *systemic lupus erythematosus* ***(SLE) patients who have active disease (SELENA SLEDAI score ≥6*** *Refer to Clinical Trial Section****) and are autoantibodyies positive (ANA titer ≥1:80 and/or anti-dsDNA titer ≥30 IU/mL) at baseline, who are receiving standard therapy.*** *The efficacy of Benlysta has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.* ***The benefit or durability of treatment beyond 52 weeks has not been demonstrated.***

To address the need for information regarding efficacy and duration of treatment past 52 weeks

In the Pre-ACPM response (October 2011, ACPM), the statement "*At Week 76 in Study 2, the SRI response rate with belimumab was not significantly different from that of placebo (39% and 32% respectively)* was proposed for the Clinical Trials section. The statement *"Beyond 52 weeks of treatment the physician should regularly monitor the patient to ensure benefit and durability of treatment are maintained (see clinical trials sections)"* was also proposed for the Dosage and Administration section.

Background

Patient testimonies (FDA AdCom transcript) vividly describe the impact of SLE (and the inevitable long term steroid use) and how the life-altering consequences are unavoidable due to lack of treatment options targeting the disease.

It is unsurprising given the complexity of SLE and the lack of established regulatory tools for evaluating products in development for treating SLE, that the FDA, EMA, Health Canada and the TGA challenged the relevance of the efficacy and safety results from the pivotal

trials investigating the benefits of Benlysta. However, as a result of face to face consultations between the regulatory bodies and leading lupus experts (FDA AdCom, EMA Ad-Hoc Expert Meeting, Health Canada) the overall appropriateness for the registration of Benlysta was confirmed. A face to face meeting involving GSK, the TGA and the sponsor's expert was held where the latter offered an independent clinical opinion on the interpretation of the clinical data and summarised current Australian clinical practice for the treatment of SLE. Following this, the Delegate's Overview concluded that there was a potential benefit for a group of patients which could be accurately identified in the product information available to the prescriber and in the context of implementing a robust risk management plan.

In summary, despite two negative clinical evaluation reports, the Delegate's Overview included a *proposed recommendation to approve the application for a 10 mg/kg dose of Benlysta.*

ACPM resolution

The ACPM Resolution No. 9570 states "*the treated patients in the 2 Phase III trials had a modest and variable improvement in disease parameters compared to the placebo group*" and that, "*Belimumab was well tolerated at the doses studied and adverse events (AEs) and serious AEs were generally of similar frequency in placebo and active drug groups*". This acknowledgement of efficacy (although viewed as modest) and an acceptable safety profile, makes it difficult to reconcile these statements with the view that the risk-benefit for Benlysta was considered not favourable.

The following paragraphs address the issues raised by the ACPM. GSK believe these issues do not preclude an overall favourable benefit:risk of Benlysta.

Efficacy

The clinical efficacy (which may be viewed as modest) demonstrated for the 2 Phase III pivotal clinical trials (10mg/kg dose of Benlysta) is highly relevant for SLE treatment, given the limited benefits of SOC that was being co-administered. A sponsor expert states: "*There are no modest results when it comes to the treatment of lupus in a world where there is zero cure for the disease and only seriously toxic treatments replacing one pain with another, with considerable associated risks."*

The Delegate acknowledged the 14% placebo-corrected difference for C1057 as being clinically significant above SOC and noted that in general the SOC therapies in the management of SLE are not evidence based. The latter view was reinforced by the sponsor's expert who highlighted to the TGA that Benlysta is the only treatment ever to be proven effective and superior in randomised trials in comparison to placebo plus SOC. The sponsor's expert also noted that it was difficult to assess the full clinical benefit due to the extent of background treatment, hence probably masking the full efficacy benefit. This view was also expressed by another expert.

Although the ACPM Resolution cites "*about a 7% greater response rate in the actively treated groups*", it is unequivocal that Benlysta 10 mg/kg response rates were statistically superior to placebo in both C1056 and C1057, with absolute treatment differences versus placebo of 9% (C1056) and 14% (C1057) at Week 52. Even though the absolute treatment difference was not as great in C1056, the relative treatment difference observed was similar to what would be expected based on the sample size assumptions. Response rate estimates of 43% for placebo and 57% for Benlysta were chosen for the study sample size calculation as these estimates result in the largest, most conservative sample size required to detect a minimum of a 14% absolute difference in the response rates. These estimates result in a relative treatment difference of ~32% [(57% - 43%) /43%]. The observed relative treatment differences

for Benlysta 10 mg/kg versus placebo were 28% (C1056) and 32% (C1057), both of which are clinically meaningful improvements.

1. GSK believes that the observed and statistically valid efficacy result achieved in both C1056 and C1057 are clinically meaningful for the below reasons:
2. Those 1 in 10 patients with active SLE who are symptomatic despite optimised background therapy (corticosteroids, anti-malarials and immunosuppressives) were able to achieve significant efficacy by the addition of Benlysta to that background, which indicates a unique advance in SLE treatment. Of note, the trial design allowed some optimisation in the first 16-24 weeks of the studies.
3. The endpoint, achieving an SRI response is a high hurdle and a very clinically meaningful result. This included resolutions of disease manifestations such as rash, oral ulcers, alopecia, immunological serology, arthritis, vasculitis and lupus headache. Skin and joint lupus can be disfiguring and disabling respectively and both drive an ongoing need for steroids.
4. Importantly, the primary endpoint is not the only data supporting the overall efficacy of belimumab; the totality of the data support a favourable benefit:risk. Specifically, treatment with belimumab resulted in:
   - Steroid sparing: fewer belimumab patients increased steroids to 7.5 mg/day and a greater proportion decreased steroid use to ≤ 7.5 mg/day. Steroid use has a significant impact on the likelihood of permanent organ damage which often results from long term use of corticosteroids.There was broad agreement amongst the lupus experts at the CHMP Ad Hoc Expert Meeting that a steroid sparing effect is of great importance and has a significant impact on the patient's quality of life.
   - 30-40% reduction in severe SLE flares, which are known to be associated with long term outcomes.
   - Less fatigue as measured by the FACIT-Fatigue index and by the vitality domain in the SF-36.
   - Greater proportion of patients with reduced autoAbs and those who become autoAb negative.
   - Normalisation of low C3/C4 or hypergammglobulinemia and greater B-cell and plasma cell reduction including SLE subset associated with SLE disease activity.

Long term efficacy was not demonstrated at 76 weeks

The recent publication of the BLISS-76 data[28] highlighted the following points:

- It is likely that the ability to discriminate between doses was compromised at Week 76 because of an additional 7% dropout rate that occurred in each group between weeks 52 (23%) and 76 (30%).
- The more liberal use of prednisone in the placebo group over 76 weeks could have reduced disease activity more than in the belimumab groups.
- The duration of SRI response in Week 52 responders was significantly greater with 10 mg/kg belimumab than with placebo for 1–6 months before or after the Week 52 visit (Figure 5).

[28] Furie R. et al (2011). A Phase III, Randomized, Placebo-Controlled Study of Belimumab, a Monoclonal Antibody That Inhibits B Lymphocyte Stimulator, in Patients With Systemic Lupus Erythematosus, Arthritis & Rheumatism 63:3918–3930

- The SRI response rates were numerically greater with 10 mg/kg belimumab (38.5%) (P =0.13) and 1 mg/kg belimumab (39.1%) (P = 0.11) than with placebo (32.4%) at Week 76 (Table 2, Figure 2A).
- The effect of belimumab using a modified SRI that required higher thresholds for the SELENA–SLEDAI component (that is, starting from a ≥5 point reduction to a ≥10 point reduction). These more stringent response criteria increased the differentiation of belimumab treatment from placebo at both Weeks 52 and 76, with 10 mg/kg belimumab achieving a significant difference from placebo for every SELENA–SLEDAI threshold at Week 76 (all P <0.05) (Table 56 and Figure 5C).

Table 56. Clinical and biomarker outcomes*.

Efficacy parameter	Placebo (n = 275)	Belimumab 1 mg/kg (n = 271)	Belimumab 10 mg/kg (n = 273)
SRI response rate at week 52†	92 (33.5)	110 (40.6)	118 (43.2)‡
≥4-point reduction in SELENA–SLEDAI score§	97 (35.3)	116 (42.8)	127 (46.5)¶
No worsening by BILAG#	180 (65.5)	203 (74.9)‡	189 (69.2)
No worsening by PGA	173 (62.9)	197 (72.7)‡	190 (69.6)
SRI modified by SELENA–SLEDAI score reduction at week 52			
≥5-point reduction**	56 (20.4)	84 (31.0)¶	89 (32.6)††
≥6-point reduction**	52 (18.9)	78 (28.8)¶	84 (30.8)¶
≥7-point reduction‡‡	29/216 (13.4)	42/217 (19.4)	46/216 (21.3)‡
≥8-point reduction‡‡	28/210 (13.3)	39/211 (18.5)	45/210 (21.4)‡
≥9-point reduction‡‡	12/147 (8.2)	21/150 (14.0)	22/143 (15.4)
≥10-point reduction‡‡	12/140 (8.6)	20/144 (13.9)	21/136 (15.4)
SRI response rate at week 76†§	89 (32.4)	106 (39.1)	105 (38.5)
≥4-point reduction in SELENA–SLEDAI score§	93 (33.8)	114 (42.1)‡	113 (41.4)
No worsening by BILAG#	162 (58.9)	187 (69.0)‡	173 (63.4)
No worsening by PGA	160 (58.2)	178 (65.7)	172 (63.0)
SRI modified by SELENA–SLEDAI score reduction at week 76			
≥5-point reduction**	60 (21.8)	77 (28.4)	84 (30.8)‡
≥6-point reduction**	56 (20.4)	73 (26.9)	79 (28.9)‡
≥7-point reduction‡‡	30/216 (13.9)	47/217 (21.7)‡	47/216 (21.8)‡
≥8-point reduction‡‡	27/210 (12.9)	42/211 (19.9)‡	46/210 (21.9)¶
≥9-point reduction‡‡	7/147 (4.8)	22/150 (14.7)¶	22/143 (15.4)¶
≥10-point reduction‡‡	7/140 (5.0)	21/144 (14.6)¶	19/136 (14.0)‡
Corticosteroid-sparing activity			
Prednisone reduced by ≥25% to ≤7.5 mg/day during weeks 40–52§	16/126 (12.7)	25/130 (19.2)	21/120 (17.5)
Prednisone reduced by ≥25% to ≤7.5 mg/day during weeks 64–76	22/126 (17.5)	35/130 (26.9)	29/120 (24.2)
Severe flares according to the SLE Flare Index			
Patients with flare over 76 weeks§§	73 (26.5)	50 (18.5)‡	56 (20.5)
Patients with flare from weeks 24 to 76¶¶	52/239 (21.8)	31/245 (12.7)¶	37/236 (15.7)
Biologic markers			
Normalization of low C3 (<90 mg/dl)			
Week 52	16/77 (20.8)	24/74 (32.4)	37/85 (43.5)¶
Week 76	13/70 (18.6)	19/70 (27.1)	40/78 (51.3)††
Normalization of low C4 (<16 mg/dl)			
Week 52	17/99 (17.2)	35/105 (33.3)¶	52/112 (46.4)††
Week 76	17/93 (18.3)	36/98 (36.7)¶	52/102 (51.0)††
Anti-dsDNA positive to negative##			
Week 52	10 (8.3)	23 (17.0)‡	19 (14.5)
Week 76	11 (9.8)	31 (24.8)¶	23 (19.2)‡

* Values are the number (%) or the number/total number (%) of patients. SRI = SLE Responder Index (see Table 1 for other definitions).
† Percentage of patients with a ≥4-point reduction in SELENA–SLEDAI score, no new BILAG A organ domain flare and no more than 1 new BILAG B flare, and no worsening in physician's global assessment score versus baseline (<0.3-point increase).
‡ $P < 0.05$ versus placebo.
§ Major secondary end point.
¶ $P < 0.01$ versus placebo.
# No new BILAG 1A/2B flares.
** SRI modified based on 5–6-point reduction in SELENA–SLEDAI score included all patients for analysis.
†† $P < 0.001$ versus placebo.
‡‡ SRI modified based on 7–10-point score reduction in SELENA–SLEDAI included only patients who had ≥7–10-point score at baseline.
§§ Using the placebo group as the referent, the hazard ratio (HR) for the 1 mg/kg belimumab group was 0.66 (95% confidence interval [95% CI] 0.46–0.94), and the HR for the 10 mg/kg belimumab group was 0.77 (95% CI 0.54–1.09).
¶¶ Using the placebo group as the referent, the HR for the 1 mg/kg belimumab group was 0.55 (95% CI 0.35–0.86), and the HR for the 10 mg/kg belimumab group was 0.70 (95% CI 0.46–1.07).
In patients who were positive at baseline according to anti-dsDNA (IgG) assay with a detectable range of 30–3,600 IU/ml.

Figure 5. Select Clinical Outcomes

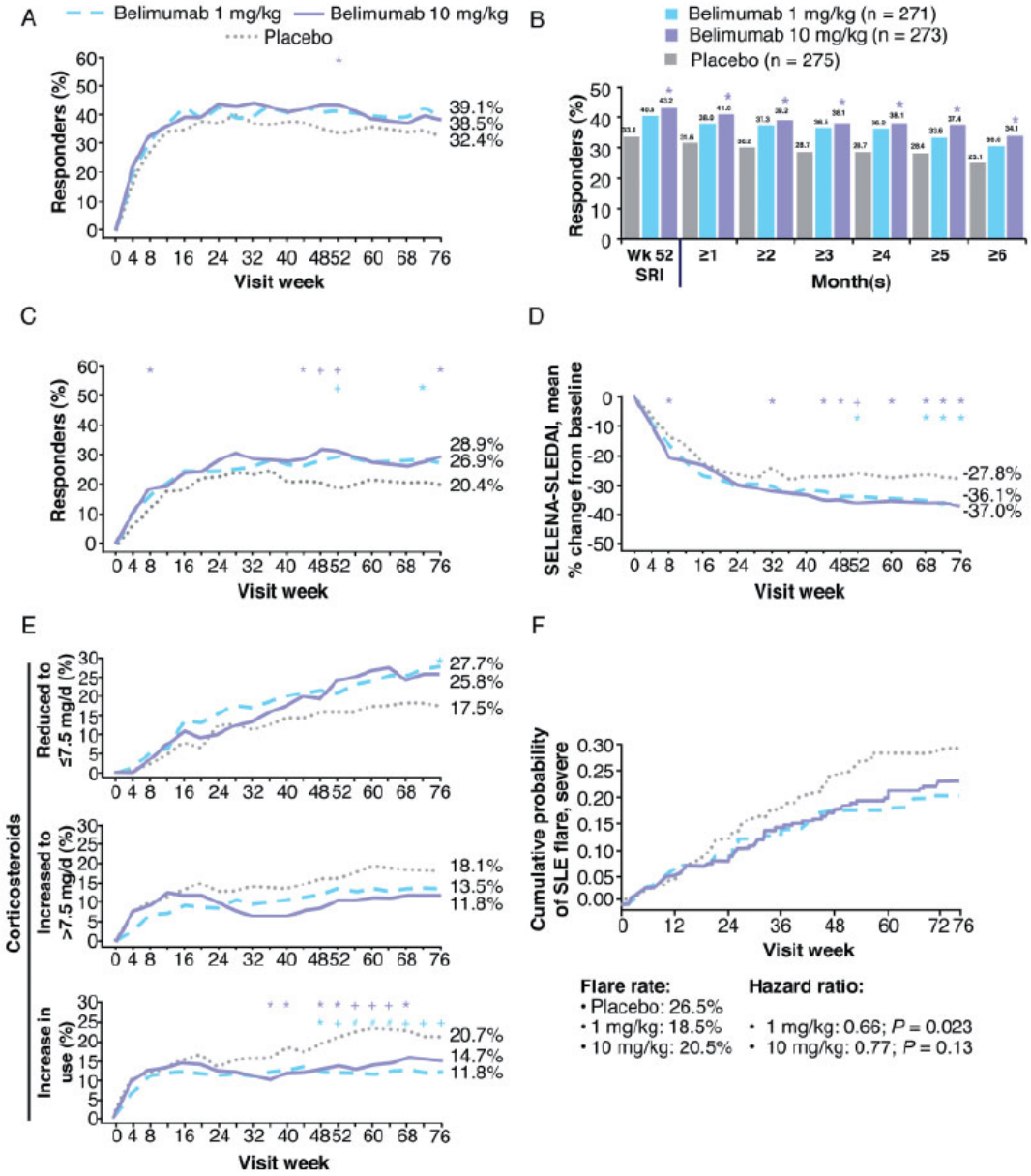


Figure 2. Select clinical outcomes. **A,** Systemic lupus erythematosus (SLE) Responder Index (SRI) response rate over 76 weeks. **B,** Durability of week 52 SRI response. Shown are SRI rates by number of consecutive months of response at any time between 1–6 months prior and 1–6 months after the week 52 response. **C,** Modified SRI response rate (based on ≥6-point reduction in the score on the Safety of Estrogens in Lupus Erythematosus National Assessment [SELENA] version of the SLE Disease Activity Index [SLEDAI]) over 76 weeks. **D,** Mean percent change from baseline in SELENA–SLEDAI score (last observation carried forward analysis). **E,** Percent of patients with corticosteroid dose reduced to ≤7.5 mg/day from >7.5 mg/day at baseline (n = 376) (top), with corticosteroid dose increased to >7.5 mg/day from ≤7.5 mg/day at baseline (n = 443) (middle), and with increased corticosteroid use over 76 weeks (bottom). **F,** Cumulative probability of severe SLE flare. * = $P < 0.05$; + = $P < 0.01$; # = $P < 0.001$ (blue indicates 1 mg/kg belimumab versus placebo; magenta indicates 10 mg/kg belimumab versus placebo).

Of note, the sponsor's expert stated, "Physicians routinely deal with uncertainty in time periods beyond clinical trial duration. In chronic disease, chronic treatment is generally required." The sponsor's expert also communicated that "the FDA 2010 guidance for SLE clinical trials advocates a year duration as sufficient to be predictive of longer term results, and these guidelines do not require trial durations of greater than one year in order to support treatments being used for longer periods".

Furthermore the sponsor's expert said, "There is no question that rheumatologists will gain additional information about Belimumab as they start using it longer term, with a larger number of patients. This information will help specialists refine its use and better target patients. But unless it is approved in Australia, this refinement and medical progress will never happen."

17-26% dropout rate at 52 weeks

In addition to meeting the criteria of the SRI endpoint, in order to be a responder, a patient could not have taken rescue SLE medications beyond protocol specified limits. Patients who required a rescue SLE medication had to have study agent discontinued, were required to drop out of the study and were considered non-responders in the primary analysis. Finally, a conservative analysis was used in which drop-outs, for whatever reason, were considered non-responders.

Compared with patients receiving belimumab, more placebo patients failed to achieve an SRI due to the need for rescue medications, driven mainly by increases in the use of steroids and immunosuppressants (In C1056 17.1%, 8.9% and 9.9% in the placebo, 1 mg/kg and 10 mg/kg groups respectively; In C1057 10.5%, 7.3% and 6.2% in the placebo, 1 mg/kg and 10 mg/kg groups respectively). The fact that belimumab patients required these rescue medications less frequently is clinically relevant since these therapies are associated with significant toxicities and are not prescribed unless there is a clear clinical need. The proportion of patients who failed to achieve an SRI due to dropout of other kinds was similar across treatment groups (In C1056 15.6%, 14.8% and 16.5% in the placebo, 1 mg/kg and 10 mg/kg groups respectively; In C1057 13.2%, 11.8% and 10.7% in the placebo, 1 mg/kg and 10 mg/kg groups respectively).

The complexity of concomitant therapy, the patient population and the disease itself renders a withdrawal rate of 20-25% over the course of a year unavoidable. Other published randomised placebo controlled trials in similar SLE populations have reported similar or greater dropout rates of 27-39%.[29, 30] In the belimumab Phase III program a greater proportion of patients who dropped out in the belimumab groups were responders at their last visit compared to those in the placebo group, indicating that dropout in the belimumab groups were less likely due to lack of efficacy compared to the placebo group. This is supported by the LOCF (last observation carried forward) sensitivity analysis for the primary endpoint (Table 57). In this analysis, the last response status of a patient before dropout is used to determine response rates. The LOCF analysis shows a greater treatment difference than the primary analysis in which all dropouts are considered non responders.

In summary, the dropout rate in the belimumab Phase III studies is consistent or less than with other studies in similar SLE populations. The conservative approach of analysis that has been undertaken, with any dropout counted as a treatment failure, may have, if anything caused an underestimate of the true treatment effect of belimumab.

[29] Merrill J. T. et al. (2010). The Efficacy and Safety of Abatacept in Patients With Non–Life-Threatening Manifestations of Systemic Lupus Erythematosus. Results of a Twelve-Month, Multicenter, Exploratory, Phase IIb, Randomized, Double-Blind, Placebo-Controlled Trial. Arthritis & Rheumatism 62:3077–3087

[30] Merrill J.T. et al (2010). Efficacy and Safety of Rituximab in Moderately-to-Severely Active Systemic Lupus Erythematosus. The Randomized, Double-Blind, Phase II/III Systemic Lupus Erythematosus Evaluation of Rituximab Trial. Arthritis & Rheumatism 62:222–233

Table 57. Response at Week 52 (sensitivity analyses).

	C1056			C1057		
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290
Primary Analysis	93 (33.8%)	110 (40.6%)	118 (43.2%)	125 (43.6%)	148 (51.4%)	167 (57.6%)
Observed difference vs placebo	-	6.77%	9.41%	-	7.83	14.03
OR (95% CI)[1] vs placebo	-	1.34 (0.94, 1.91)	1.52 (1.07, 2.15)	-	1.55 (1.10, 2.19)	1.83 (1.30, 2.59)
P-value[1]	-	0.1041	0.0207	-	0.0060	<0.0001
LOCF Response (adjusted)	101 (36.7%)	118 (43.5%)	132 (48.4%)	137 (47.7%)	155 (53.8%)	182 (62.8%)
Observed difference vs placebo	-	6.82%	11.62%	-	6.08	15.02
OR (95% CI)[2] vs placebo	-	1.33 (0.94, 1.89)	1.67 (1.17, 2.36)	-	1.44 (1.02, 2.03)	1.94 (1.37, 2.76)
P-value[2]	-	0.1096	0.0043	-	0.0402	0.0002

Lack of adequate dose finding data, with no dose response

GSK acknowledge that there was no clear dose response found in the Phase II trial (LBSL-02). However in this study, SOC medications could be adjusted as clinically indicated to manage disease activity and this may have blunted the ability to detect a treatment effect with belimumab as well as the ability to differentiate the effect across the dose levels. There was some evidence in this trial favouring 10 mg/kg (such as the trends for less steroid use and more rapid reduction of disease activity), which is why both 1 and 10 mg/kg were taken into Phase III trials in order to determine the appropriate dose. In both Phase III studies, the 10 mg/kg dose of belimumab met the primary endpoint of SRI response at Week 52 (including sensitivity analyses). Moreover, several clinical measures of improvement including, severe flare risk reduction, and complement normalization generally favoured the 10 mg/kg dose. Finally, fewer patients receiving the 10 mg/kg dose required increases in steroids over time.

The Delegate agreed with the lack of demonstration of a dose response, however also concluded that there was a clinically meaningful result achieved with the 10 mg/kg dose.

Non-validated SRI index

The individual components of the SRI (SELENA SLEDAI, BILAG, and PGA) have been assessed for specificity[31]. The validation is based on the concordance of scores with expert opinion, acceptable inter-observer variability among trained evaluators, correlation between individual patients' scores on different indices and correlation between increases in scores and clinical decisions to increase therapy. Although each Disease Activity Index has its unique strengths and weaknesses, all have demonstrated sensitivity to changes in disease activity in cohort studies, and therefore are suitable for use in clinical trials.

Numerous sensitivity analyses were performed for the primary endpoint of the Phase III trials. In all sensitivity analyses and in both studies the 10 mg/kg showed statistically

[31] Ward M. et al. (2000) Comparison of the validity and sensitivity to change of 5 activity indices in systemic lupus erythematosus. The Journal of Rheumatology 27:664-670.

significant differences from placebo. These analyses are included in the sponsor's Clinical Overview and in the individual study reports. Also post hoc analyses requiring improvements of SELENA SLEDAI of 5-10 points were performed and analyses excluding serologies (anti-dsDNA and Complement) are also included in the clinical evaluation report response; benefit continued to be demonstrated across these various analyses. The actual derivation of the SRI is described in Furie et.al[32]. The sensitivity analyses which were performed are described in it and include 5, 6 and 7 point improvement in SLEDAI. This improvement was not solely attributable to serological markers of improvement. Recent presentations at the 76th Annual Scientific Meeting of the American College of Rheumatology described Quality of Life outcomes in SRI responders versus non-responders[33] and other clinical and biomarker correlates in SRI responders versus non-responders. These results clearly demonstrate that an SRI response is clinically meaningful at several different levels.

The Delegate acknowledged the SRI Index and referenced the number of sensitivity analyses.

The clinical evaluator noted; "*Although novel in nature, the endpoint appears to be soundly based on evidence and clinical practice experience*". The sponsor's expert strongly agrees with this view.

Exclusion of lupus nephritis and cerebral lupus patients; SLE patients of unmet clinical need

The potential benefits of Benlysta for patients with active lupus nephritis requiring acute treatment will be investigated in a Phase III study. The reason for their exclusion in the current studies was that the nature of this disease and treatment paradigms requires a trial design and primary endpoint that is different from those needed in general lupus (and therefore employed in Studies C1056 and C1057). Of note, patients with chronic stable renal disease were included (15-20%) in the pivotal trials, as were patients who suffered from lupus headache. In addition, the extent of baseline concomitant medications (>85% and nearly 50% of subjects were receiving corticosteroids and other immunosuppressants, respectively, with ~43% of subjects receiving both) and average baseline SELENA SLEDAI score of 9.7, indicate moderately severe disease and a patient group with high unmet need for specific therapy. GSK agree that the product label should highlight the exclusion of patients with severe active lupus nephritis and severe active CNS lupus.

Change in SELENA SLEDAI score of ≥ 4

A SELENA SLEDAI of 6 or more has been shown to be consistent with active disease requiring therapy. A reduction of >3 points in SELENA SLEDAI score has been defined as clinically relevant improvement.34 Furthermore, clinically meaningful increased disease activity using the SELENA SLEDAI score has been described as an increase of 3 points or more35,36. Consequently, a reduction ≥ 4 is 6 considered to be a meaningful degree of improvement in disease activity. Moreover, on the SELENA SLEDAI a reduction of 4 points equates to resolution (rather than mere improvement) of a one or more disease manifestations and, as such, is a clear demonstration of clinical benefit, as highlighted by the sponsor's expert and Petri, both engaged with patients on Benlysta. Furthermore, even

[32] Furie R.A. et al (2009). Novel Evidence-Based Systemic LupusErythematosus Responder Index. Arthritis & Rheumatism (Arthritis Care & Research) 61:1143–1151
[33] Strand V. et al (2011). Abstract: Responders in the Phase 3 Belimumab Clinical Trials in Patients With Systemic Lupus ErythematosusPresented at ACR/ARHP Annual Scientific Meeting; November 4–9, 2011; Chicago, IL
[34] Gladman D.D.et al. (2000). Accurately describing changes ub disease activity in systemic lupus erythematosus. The Journal of Rheumatology 27: 377-379
[35] Petri M. et al (1991). Definition, incidence, and clinical description of flare in systemic lupus erythematosus A Prospective Cohort Study. Arthritis and Rheumatism 34:937-944
[36] Petri M et al (1999).Classification and definition of major flares in SLE clinical trials. Lupus 8:685.

if one sets the threshold for response higher, as is done with SRI 5-10, statistically significant benefit with belimumab 10 mg/kg remains and even improves.

The 4 point or greater reduction as the threshold for SELENA SLEDAI reduction as part of the SRI was agreed with the FDA and EMA at scientific advice meetings prior to the commencement of the Phase III studies, as well as via a Special Protocol Assessment (SPA) agreement with FDA. The other 2 measures used ensured that the improvement in disease activity was not offset by a worsening of the subject's condition overall (that is, no worsening [defined as a < 0.3 increase] in the Physician's Global Assessment [PGA]), or a worsening in any specific organ system (that is, no new BILAG A or 2 new B flares).

While 100% of responders at Week 52 from both C1056 and C1057 studies were classified as having a change in SELENA SLEDAI score of ≥4 points, it should be noted that 40% of responders showed a change of SELENA SLEDAI score of ≥7 points.

Geographical based differences in results

The results from the subgroup analyses refer to a minority population in Australia (Black race and North America subgroups). The CHMP assessment report (Ad Hoc Expert Meeting) stated that differences in response across racial groups are known for other drugs used in SLE and that all races are affected by SLE. The issue of a possible difference in effect between ethnicities was deemed to be considered manageable in clinical practice. It is appropriate to address this in the Product Information.

Post hoc analyses

GSK are seeking approval based on the primary efficacy outcomes reaching significance for the 2 Phase III pivotal trials. The post hoc analysis were included in the Clinical Trial section of the Product Information (Australian proposed PI, Canadian Monograph) as they had been identified as clinically useful information for the treating physician by two sponsor experts. They also formed the basis of the label approved by the EMA. The clinical evaluator concluded this subgroup analysis was noteworthy but contestable in terms of scientific rigour (that is, post hoc).

Safety

The safety dataset was inadequate with limited long term efficacy and safety to support the application

Data from 2,133 patients participating in 3 randomised, placebo controlled trials demonstrated a favourable safety profile over 12-18 months (exceeds ICH E1A guideline for the assessment of clinical safety for drugs intended for long term treatment of chronic disease) long-term safety/efficacy data exist for 296 patients who continued on treatment for up to six years after participating in the Phase III trial RMP commits to a large, 1 year, randomised, placebo controlled safety study in 5000 patients and additional separate ~2000 patient, 5 year registry.

The supervision of the administration of Benlysta by a healthcare professional and the proposed product information reinforces appropriate use and includes potential risks of Benlysta treatment. The incidence of adverse events, serious adverse events and malignancies has remained stable or declined over time. The on-going long term trials and proposed post marketing studies will further characterise the safety of Benlysta, focusing on events and populations of special interests.

Conclusion

GSK submits to the ACPM, that the evidence clearly supports approval for Benlysta. It is the first specific SLE therapy in 50 years to have demonstrated efficacy in Phase III clinical studies with an acceptable safety profile. Benlysta provides an advance in the current treatment options for patients with moderate to severe disease.

Advisory Committee considerations December 2011 meeting

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised that this submission to register belimumab (Benlysta) has not satisfactorily demonstrated adequate, safety and efficacy in the proposed indication for the following reasons:

Efficacy

Overall, the treated patients in the 2 Phase III clinical trials had a modest and variable improvement in disease parameters compared to the placebo groups. Typically there was a 7% greater response rate in the actively treated groups in the first 12 months; however, long term efficacy was not demonstrated at 72 weeks. The subjects had high baseline scores and there was a 17-26% dropout rate at 52 weeks. There was a lack of adequate dose finding data, with no obvious dose response. The committee noted the use of the non-validated SRI index, a change in SLEDAI score of ≥4, the exclusion of lupus nephritis and cerebral lupus patients, the geographically-based differences in results and the clear issues with post hoc analyses as indicators of uncertain and modest clinical benefit.

Safety

Belimumab was well tolerated at the doses studied and AEs and SAEs were generally of similar frequency in placebo and active drug groups. There was a slight increase in the frequency of infections in the actively treated population in the studies which was not significant. Similarly the assessment of rate of malignancies and mortality is currently based on a small dataset. The occurrence of neuropsychiatric adverse events was the unexpected safety finding.

Overall, the ACPM was of the view that the risk-benefit was not favourable due to insufficient evidence of efficacy at 52 weeks and beyond, along with minimal long term safety data for a medication likely to be taken for a considerable period.

On 2 November 2011 the sponsor sent a letter to the TGA requesting reconsideration by ACPM at the February 2012 ACPM meeting.

Advisory Committee considerations February 2012 meeting

The ACPM considered the previous and additional information, studies, evaluations and expert opinions, submitted by the delegate and sponsor and reaffirmed the committee's view that the evidence provided a negative benefit risk profile as recorded in the ACPM recommendation 9570.

In making this recommendation, the ACPM advised that the evidence does not support a clinically significant benefit or durability of response to treatment beyond 52 weeks sufficient to outweigh the adverse effect profile for this product together with concerns about possible neuropsychiatric effects.

The ACPM noted that while evidence for efficacy was stronger at the higher dose studied, the data were stronger for a steroid sparing effect at the lower dose, making selection of a suitable dose quite problematic.

The ACPM was not persuaded by the sponsor's argument that the benefit of this product is masked by other medications.

The clinical trials presented in the submission did not include patients with the more serious forms of the disease, those with active renal or neurological disease. The ACPM would welcome reviewing data in these population groups when it becomes available.

The ACPM also expressed a view that the sponsor had not adequately examined the mechanism for suicide and suicidal ideation reported in the trials.

Initial outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of Benlysta (belimumab) lyophilized powder for IV infusion for the indication:

> *For reducing disease activity in adult patients with active autoantibody positive systemic lupus erythematosus (SLE) who are receiving standard therapy.*

The reasons in relation to the decision pursuant to section 25 of the Therapeutic Goods Act 1989 not to approve Benlysta (belimumab) 120 mg and 400 mg powder for injection for inclusion in the Australian Register of Therapeutic Goods (ARTG).

The following material findings were instrumental in arriving at the decision for this submission:

1) The composite endpoint SLE Responder Index (SRI) at Week 52 was the designated primary efficacy variable in both trials. The placebo-corrected response rate (on background of standard SLE therapies in active and control groups) with respect to SRI at Week 52 was statistically significant for the 10 mg/kg treatment group in both trials but the effect was modest (9.4% & 14.0% respectively). The response rate with the 1 mg/kg dose was not statistically significant in Study C1056 (6.8%) but significant in Study C1057 (7.8%) as shown in Table 58 below.

Table 58. The response rate with the 1 mg/kg dose

	C1056			C1057		
	Placebo N = 275	1 mg/kg N = 271	10 mg/kg N = 273	Placebo N= 287	1 mg/kg N = 288	10 mg/kg N = 290
No.(%) Response	93 (33.8%)	110 (40.6%)	118 (43.2%)	125 (43.6%)	148 (51.4%)	167 (57.6%)
Observed absolute difference vs. Placebo	-	6.77%	9.41%	-	7.83%	14.03%
OR (95% CI)[1] vs. placebo	-	1.34 (0.94, 1.91)	1.52 (1.07, 2.15)	-	1.55 (1.10, 2.19)	1.83 (1.30, 2.59)
P-value[1]	-	0.1041	0.0207	-	0.0129	0.0006

[1] Odds Ratio (95% confidence interval) and p-values were from logistic regression for the comparison between each belimumab dose and placebo with covariates. Covariates include baseline SELENA SLEDAI score (<= 9 vs. >= 10), baseline proteinuria level (< 2 g/24 hour vs. >= 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs. other).

In general, higher response rates were seen in trial C1057 compared to C1056, especially for the 10 mg/kg dose. The response rates for placebo, 1 mg/kg and 10 mg/kg were 33.8%, 40.6% and 43.2% in Study C1056 respectively. In Study C1057, the reported responses were 43.6%, 51.4% and 57.6% respectively.

The differences between 1 mg and 10 mg were not large (approximately 3-6%) and were not formally examined for statistical significance.

The 10 mg/kg dose did not show consistent effect on all three components of the SRI across both studies as shown in Table 59 below.

Table 59. Results for 10 mg/kg dose on the three components of SRI

	C1056			C1057		
	Placebo N=275	1 mg/kg N=271	10 mg/kg N=273	Placebo N = 287	1 mg/kg N = 288	10 mg/kg N = 290
4-point reduction in SELENA SLEDAI	98 (35.6%)	116 (42.8%)	128 (46.9%)	132 (46.0%)	153 (53.1%)	169 (58.3%)
OR (95% CI)[1] vs. placebo	-	1.36 (0.96, 1.93)	1.63 (1.15, 2.32)	-	1.51 (1.07, 2.14)	1.71 (1.21, 2.41)
P-value[1]	-	0.0869	0.0062	-	0.0189	0.0024
No worsening in PGA	173 (62.9%)	197 (72.7%)	189 (69.2%)	199 (69.3%)	227 (78.8%)	231 (79.7%)
OR (95% CI)[2] vs. placebo	-	1.60 (1.11, 2.30)	1.32 (0.92, 1.90)	-	1.68 (1.15, 2.47)	1.74 (1.18, 2.55)
P-value[2]	-	0.0120	0.1258	-	0.0078	0.0048
No New 1A/2B BILAG domain scores	179 (65.1%)	203 (74.9%)	189 (69.2%)	210 (73.2%)	226 (78.5%)	236 (81.4%)
OR (95% CI)[3] vs. placebo	-	1.63 (1.12, 2.37)	1.20 (0.84, 1.73)	-	1.38 (0.93, 2.04)	1.62 (1.09, 2.42)
P-value[3]	-	0.0108	0.3193	-	0.1064	0.0181

[1] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates, including baseline SELENA SLEDAI (≤ 9 vs ≥ 10), baseline proteinuria level (< 2 g/24 hour vs ≥ 2 g/24 hour equivalent) and race (African descent or indigenous-American descent vs other).

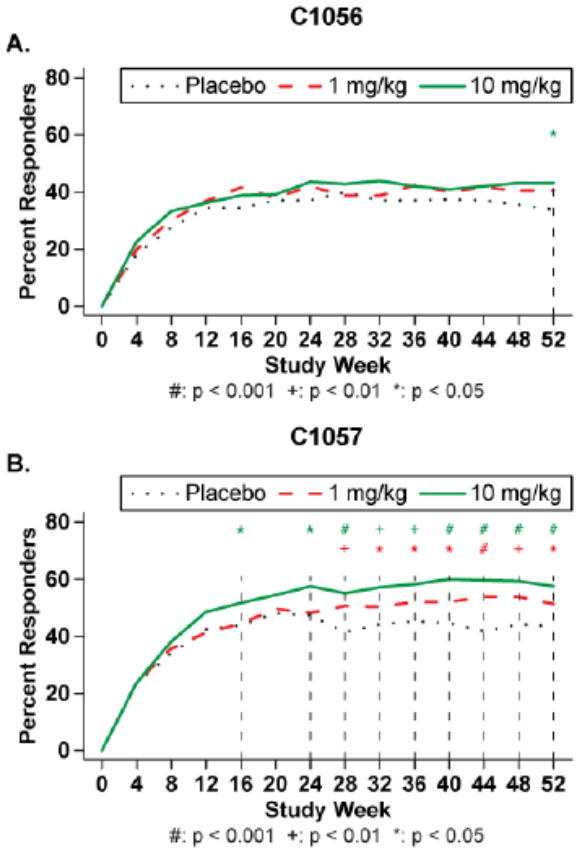
[2] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline PGA.

[3] Odds Ratio (95% confidence interval) and p-value were from logistic regression for the comparison between each belimumab dose and placebo with covariates as in footnote 1 and baseline BILAG domain involvement (at least 1A/2B vs at most 1B).

The results for SELENA SLEDAI (at least 4 point reduction) component were consistent with the SRI but the PGA and BILAG domain scores were variable and were statistically non significant with the 10mg/kg dose in Study C1056 compared to placebo.

The progression of SRI responders over 52 weeks of observation indicated significant separation of effect only at Week 52 for the 10 mg/kg dose in Study C1056. In Study C1057 the graphs begin to separate at about 8-10 weeks for the 10 mg/kg dose and were statistically significant from Week 16 to Week 52 compared to placebo. For the 1 mg/kg the graphs did not begin to separate until Week 24 and were significant thereafter (Figures 2A and B combined in Figure 6 below).

Figure 6. Progression of SRI responders over 52 weeks.



In Study C1056 the controlled treatment was carried out to Week 76. Only minimal details were included in the sponsor's submission. The results based on the reported frequencies (placebo corrected SRI response rate at Week 76) were as shown in Table 60 below.

Table 60. Placebo corrected SRI response rate at Week 76

C1056	r	n	%	OR	95%CI		Treatment Difference	95%CI		p value
					LL	UL		LL	UL	
10mg/kg										
Active	105	273	38.5	1.33	0.93	1.89	6.5%	-1.5%	14.4%	0.11
Control	88	275	32.5							
1mg/kg										
Active	106	271	39.10	1.37	0.96	1.94	7.1%	-0.9%	15.1%	0.08
Control	88	275	32.00							

As can be seen, the clinical effect was not maintained to an extent that was statistically significant with the continuing treatment. This finding is considered important. SLE is a chronic autoimmune disorder clinically characteristed by remissions and relapses of varying intensity affecting multiple organ systems, most notably skin, kidneys and the central nervous system with cumulative residual serious organ damage and dysfunction overtime. As the sponosor has also argued in Pre-ACPM responses and the Delegate agreed, that the therapy needs to be administered indefinitely. However, continuing

treatment is not supported by Week 76 results. The Delegate also formed the view that withdrawal of therapy at 52 weeks is not supported unless the the SRI or SELENA SLEDAI were validated outomes for *sustained* response which they are not. The Week 76 result is also considered reliable having been obtained in a randomised, placebo-controlled, double blind study with near complete follow up.

Taken together, the variable and at best a modest effect at Week 52 which could not be maintained by Week 76 despite continuing treatment does not support the intended long term use of this drug.

The uncertain nature of the expected clinical benefit needs also to be considered in reference to the expected toxicity/risks such as (1) serious infections especially opportunistic infections, and (2) development of malignancies. The overall survival benefit (all-cause mortality) must also be demonstrated.

The dataset based on all SLE studies is still too small in patient numbers and short term with respect to the length of exposure to belimumab to allow definitive assessment of these risks. However, as the Tables 53-55 show, the reported incidence rates were numerically higher compared to the concurrent placebo control arm (0.43 versus 0.55 death rate/100 patient-years (PY); zero versus 0.23 opportunistic infections/100 PY; and 0.28 versus 0.45 malignancies/100 PY for placebo versus belimumab, respectively).

An unexpected safety signal was the occurrence of neuropsychiatric adverse effects with the belimumab treatment including depression and suicide. The mechanism for this effect is unclear. It should be noted that CNS lupus patients were excluded from the trial.

Although a Risk Management Plan for collection of more safety data in the post market phase was submitted with the dossier, the findings of inconsistent, modest and unsustained clinical effect relative to the reported adverse outcomes in the premarket clinical trials does not indicate favourable benefit risk ratio.

The information about clinical effect in predefined subgroups was also assessed and did not indicate a differential effect in any specific subgroup. The Delegate also holds the view that the overall result is the best guide to the clinical effect in the subgroups due to loss of statistical power in the smaller strata. The results are shown in Table 49. The interaction tests were not reported but the overlapping confidence intervals do not indicate heterogeneous effect within these subgroups.

The sponsor also provided post hoc subgroup analyses, in particular arguing for efficacy in subpopulation of patients who were anti-dsDNA positive and had low C3/C4 levels at baseline.

Again such analyses suffer from limitations of subgroup analyses noted above and in addition represent bias due to selective interpretation of data. There is loss of benefits of randomisation and findings can only be considered observational in nature. These results are shown in Table 51 above. Please note that results are based on pooled data from both studies.

The clinical effect observed in this subpopulation (anti-dsDNA positive and Low C3/4), if this patient population can be clinically justified, may be appropriate for further prospective testing.

Lastly, the Delegate considered whether restricting the intended population, as has been done in some overseas approvals, may be employed. Such approvals have excluded the use of belimumab in SLE patient groups who were not studied such as severe lupus nephritis and lupus with active CNS involvement, as well as use in combination with other biological agents and in patients receiving IV cyclophosphamide.

The Delegate formed the view that while these restrictions appropriately exclude the patient groups for which clinical trials experience is not available, this approach does not

address the issue of equivocal clinical effect and unfavourable benefit relative to risk in the intended patient population representative of the belimumab clinical studies.

Final outcome

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act. The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

The following is an excerpt from the Delegate of the Minister's report.

Based on the section 60 Appeal's Delegate's review of the evidence listed above, the Delegate made the following findings of fact:

The initial decision maker provided the following reasons for rejecting approval of belimumab:

- "The efficacy of the product for the proposed indication could not be reliably established. This refers to the inconsistent and variable clinical effect that was shown in the two pivotal Phase 1/1 clinical trials (CIO56 & CIO57).
- The risk-benefit balance of the drug in the proposed indication could not be established clearly in favour of benefit. This refers to the magnitude of clinical effect relative to the adverse effects reported in the two pivotal Phase 111 clinical trials (CIO56 & CIO57)."

With respect to efficacy the initial decision maker noted:

- "The composite endpoint SLE Responder Index (SRI) at Week 52 was the designated primary efficacy variable in both trials. The placebo-corrected response rate (on background of standard SLE therapies in active and control groups) with respect to SRI at Week 52 was statistically significant for the 10 mg/kg treatment group in both trials but the effect was modest (9.49'0 and 14.0% respectively).
- In the Study CIO56 the controlled treatment was carried out to Week 76. Only minimal details were included in the submission. The results based on the reported frequencies (placebo corrected SRI response rate at Week 76) were as shown in Table 58.
- As can be seen, the clinical effect was not maintained, to an extent that was statistically significant, with the continuing treatment. This finding is considered important. SLE is a chronic autoimmune disorder which has a clinical course characterised by remissions and relapses of varying intensity affecting multiple organ systems, most notably skin, kidneys and the central nervous system with cumulative residual serious organ damage and dysfunction overtime. As the sponsor has also argued in Pre-ACPM responses and the Delegate agreed, that the therapy needs to be administered indefinitely. However, continuing treatment is not supported by Week 76 results. The Delegate also form the view that withdrawal of therapy at 52 weeks is not supported unless the SRI or SELENA SLEDAl were validated outcomes for sustained response which they are not. The Week 76 result is also considered reliable having been obtained in a randomised, placebo-controlled, double blind study with near complete follow up.
- Taken together, the variable and at best a modest effect at Week 52 which could not be maintained by Week 76 despite continuing treatment does not support the intended long-term use of this drug. "

With respect to safety the initial decision maker noted:

- "The uncertain nature of the expected clinical benefit needs also to be considered in reference to the expected toxicity/risks such as (1) serious infections especially opportunistic infections, and (2) development of malignancies. The overall survival benefit (all-cause mortality) must also be demonstrated.
- The dataset based on all SLE studies is still too small in patient numbers and short term with respect to the length of exposure to belimumab to allow definitive assessment of these risks. However, as the three tables below show (not replicated here), the reported incidence rates were numerically higher compared to the concurrent placebo control arm (0.43 versus 0.55 death rate/100 patient-years (PY); zero versus 0.23 opportunistic infections/100 PY; 0.28 versus 0.45 malignancies/100 PY for placebo versus belimumab respectively).
- An unexpected safety signal was the occurrence of neuropsychiatric adverse effects with the belimumab treatment including depression and suicide. The mechanism for this effect is unclear. It should be noted that CNS lupus patients were excluded from the trial.
- Although a Risk Management Plan for collection of more safety data in the post market phase was submitted, the findings of inconsistent, modest and unsustained clinical effect relative to the reported adverse outcomes in the premarket clinical trials does not indicate favourable benefit risk ratio. "

Overall the initial decision maker noted:

- "Lastly, the Delegate considered whether restricting the intended population, as has been done in some overseas approvals, may be employed. Such approvals have excluded the use of belimumab in SLE patient groups who were not studied such as severe lupus nephritis and lupus with active CNS involvement, as well as use in combination with other biological agents and in patients receiving intravenous cyclophosphamide.
- The Delegate formed the view that while these restrictions exclude, appropriateIy, the patient groups for which clinical trials experience is not available, this approach does not address the issue of equivocal clinical effect and unfavourable benefit relative to risk in the intended patient population representative of the belimumab clinical studies. "

Consideration of the appeal and the available evidence

The Delegate noted the following grounds of Appeal were set out in the sponsor's appeal statement and were summarised as follows:

- "The evaluation of the clinical data regarding Benlysta for the treatment of SLE is unequivocal that Benlysta displays a distinctly measurable degree of efficacy. The two Phase III pivotal clinical trials clearly met their primary efficacy endpoints for a 10 mg/kg dose, which by definition is clinicalIy relevant and therefore the statutory test has been met.
- The clinical evaluator has not given the appropriate weight to the subgroup analysis which clearly provides supporting evidence to the benefits of Benlysta for the higher disease SLE patient subgroup.
- The ACPM has not given the appropriate weight to the clinical context that the efficacy is being evaluated. The expert clinical opinions based on clinical experience with Benlysta and/or assessment of the related clinical data, are extremely important in providing information on standard of care, limitations of the current therapies, safety profiling and assessing a role for Benlysta in treating SLE.

- The SLE responder index (SRI) primary endpoint is a composite endpoint and interpretation of results isolating each component is not appropriate.
- In the absence of a clear dose response effect, the overwhelming conclusion based on all of the efficacy and safety data is that the 10 mg/kg dose is the most consistent dose for registration for Benlysta.
- In contrary to the conclusions of the ACPM, the clinical evidence shows that a steroid sparing effect is demonstrable for Benlysta, and that the overall sparing effects (3 out of 4 measures) were most favourable for the 10 mg/kg dose.
- Exclusion of patients with severe active lupus nephritis and severe active central nervous lupus from the BLISS studies should not impact on the register ability of Benlysta for the appropriate patient population which was included in the clinical trials and is reflected in the indication. This SLE population in the Australian context has been confirmed by epidemiology assessment and the Australian expert clinical opinion.
- Lack of data on the early identification of non-responders is not the cause for rejecting Benlysta as a treatment. Discontinuation of Benlysta treatment is appropriate if there is no clinical benefit by 6 months and information in the proposed Australian Product Information in the Dosage and Administration section provides this recommendation. This approach has been endorsed by expert clinical opinion and is in fact, clinical practice.
- Lack of absolute statistical evidence for the benefit at Week 76 is not conclusive evidence that there is a lessening of benefit and that Benlysta treatment should not be continued past Week 52. Individual patient assessment is necessary and GSK has proposed appropriate text to address efficacy past 52 weeks in the Australian Product Information in the Clinical Trial section, and in the Dosage and Administration section.
- The subgroup analysis has provided important information as to the benefits of Benlysta in the higher disease group and as such is further supporting evidence as to the benefits of Benlysta. As such, inclusion of this data in the Clinical Trial section of the Australian Product Information is appropriate.
- The overall safety profile of Benlysta is acceptable. The adverse events of special interest have been addressed in the Risk Management Plan (RMP) with many ongoing commitments in place. In addition, the Precautions section of the proposed Australian Product Information includes information on hypersensitivity reactions, infections, malignancies and depression. All of the clinical experts value the safety profile of Benlysta given the toxicities of the current standard of care for SLE. "

The section 60 Appeal's Delegate here relate their own findings of material fact to the decision:

1. These findings are based on the amended indication agreed to by the sponsor on 25 June 2012 which is more restrictive than the original application.
2. The pivotal Phase III clinical trials did meet their primary efficacy endpoints at 52 weeks with the 10 mg/kg dose, although efficacy was modest.
3. The pivotal Phase III clinical trial did not make a statistically significant primary efficacy endpoint at 76 weeks although there was still a favourable outcome. The section 60 Appeal's Delegate noted further post hoc data analysis may have identified a subgroup where evidence is supportive, however further studies are required to demonstrate that long term use post 52 weeks is supported in a readily identifiable patient group.

4. The non inclusion of patients with severe active lupus nephritis and severe active central nervous lupus from the BLISS studies excludes these patients from the approved indication, and hence the safety and efficacy in these populations has not been evaluated.
5. The lack of data on the ability to identify non-responders early requires information to be provided to prescribers that formal review of patients commenced on belimumab has to occur at the six month stage to decide on whether or not the patients should continue on it. Prescribers need to be aware that patients who have not responded at this stage should have their belimumab ceased.
6. The safety profile of belimumab is becoming more apparent and the identified significant adverse events are documented and warnings are included in the PI and RMP. The issue of hypersensitivity and infusion reactions has been identified and the section 60 Appeal's Delegate noted was the subject of a specific Health Canada endorsed update.
7. The latest PSUR has not noted any changes in adverse event profile and does include the post registration use in a greater number of patients to the trials. The neuropsychiatric adverse events are still present and active warning of their risk is required for patients and their health care professionals.

Reasons for decision

Efficacy

The section 60 Appeal's Delegate was of the view that efficacy has been demonstrated for belimumab for the amended indication of add-on therapy for reducing disease activity in adult patients with active, antibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (such as ANA titer ≥I:80 and/or anti-dsDNA titer ≥30 IU/inL) despite standard therapy. This efficacy is for those who respond after 6 months and has been statisticalIy proven at 52 weeks. As described above the efficacy post 52 weeks is less clear. This amended indication does restrict the population that belimumab will be administered to and takes into account issues raised in the original decision. As well your company has provided further post hoc data analysis that may have identified a readily identifiable patient subgroup where evidence is supportive in group.

Safety

The section 60 Appeal's Delegate was of the view that it there are some safety issues with the use of belimumab, however the Delegate believed that these can be managed with an appropriate RMP and advice to patients and prescribers. It is important that the adverse effects should be adequately documented in the Product Information and Consumer Medicine Information.

Summary

Notwithstanding that the evidence of efficacy of belimumab is modest and that there are incidences of adverse effects that will require appropriate management the section 60 Appeal's Delegate was of the view that, considering the amendment to the indication agreed to by the sponsor during the course of the Appeal Delegate's consideration of the sponsor's appeal, the requirements of efficacy and safety in the Act have been met.

Decision

The section 60 Appeal's Delegate replaced the "the initial decision" for belimumab (Benlysta) 100 mg and 400 mg powder for injection under Section 60 (2) of the *Therapeutic Goods Act 1989* ("the Act"). The reasons for the Delegate's decision and results of the reconsiderations of the initial decision are set above. Accordingly, pursuant to Section 60 of the Act, the Delegate notified the sponsor of the decision to approve the registration of:

Benlysta belimumab 120 mg powder for injection
Benlysta belimumab 400 mg powder for injection for the following indication:

> *Benlysta is indicated as add-on therapy for reducing disease activity in adult systemic lupus erythematosis (SLE) patients who have active disease and are autoantibody positive (ANA titre ≥ 1:80 and/or anti-dsDNA titre ≥ 30 IU/mL) at baseline, who are receiving standard therapy. The efficacy of Benlysta has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.*

This approval was based on the evaluation of the information and data provided with the original letter of application and with any subsequent correspondence and submissions relating to the application and with information submitted with the sponsor's appeal of 8 May 2012.

Notwithstanding that the evidence of efficacy of belimumab is modest and that there are incidences of adverse effects that will require appropriate management. The Delegate was of the view that, considering the amendment to the indication agreed to by the sponsor during the course of the consideration of the sponsor's appeal, the requirements of efficacy and safety in the *Act* have been met to include the Benlysta belimumab 120 mg and 400 mg powder for injections in the *Australian Register of Therapeutic Goods* [ARTG].

Specific conditions of registration applying to these therapeutic goods

- The implementation in Australia of the belimumab Risk Management Plan (RMP) version 9, dated 26 June 2012 and any subsequent revisions, as agreed with the TGA and its Office of Product Review.
- Drug Product batches from different Drug Substance batches

  It is a condition of registration that the first five batches of Benlysta (belimumab) imported into Australia are not released for sale until: (1) samples of each batch have been tested and approved by the TGA Office of Laboratories and Scientific Services (OLSS), and/or (2) the manufacturer's release data have been evaluated and approved by OLSS. These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency. If the any of these batches are derived from common drug substance batches then material should be provided from the first five batches derived from unique drug substance batches. The sponsor may also be required to provide evidence of satisfactory shipping conditions to Australia for every batch imported.

  These conditions remain in place until the sponsor is notified officially in writing of any change. Once notified of the end of these batch release conditions the sponsor will be required to provide to OLSS annual post marketing reports which shall include certificates of analysis and shipping details for each batch imported during that time.

  Five vials of each batch should be provided for testing by the Therapeutic Goods Administration OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (together with their Certificates of Analysis) for method development and validation.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

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Reference/Publication #