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Belimumab

In Systemic Lupus Erythematosus

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Contents

Abstract

Belimumab is a fully human recombinant IgG1λ monoclonal antibody that inhibits the binding of soluble B lymphocyte stimulator to B cells and hence prevents the survival and differentiation of selected B-cell subsets. It is available in the US, the EU and Canada for the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite receiving standard therapy.

At 52 weeks, a significantly greater proportion of belimumab 10 mg/kg than placebo recipients experienced a response as assessed by the SLE Responder Index (primary endpoint) in the randomized, double-blind, multinational, phase III BLISS-52 and BLISS-76 trials in patients with active seropositive SLE receiving standard therapy.

A significantly greater proportion of belimumab than placebo recipients achieved a ≥4 point reduction in the SELENA-SLEDAI score at week 52 in both BLISS trials. However, the SLE Responder Index response rate was not significantly different between belimumab and placebo at 76 weeks in BLISS-76.

Belimumab was generally well tolerated in the BLISS trials. During the double-blind periods of these trials and the phase II trial, twice as many deaths were reported with belimumab than placebo (six vs three). There were no meaningful differences between the incidence of serious infections and malignancies with belimumab or placebo.

Features and properties of belimumab (Benlysta®)	
Indication	
Systemic lupus erythematosus (SLE)	
Mechanism of action	
Binds to the soluble form of B lymphocyte stimulator (BLyS), thereby inhibiting BLyS-induced B lymphocyte survival	
Dosage and administration	
Dose	10 mg/kg
Route of administration	Intravenous infusion over 1 h
Frequency of administration	Once every 2 wk for first 3 doses then once every 4 wk
Predicted pharmacokinetic profile in patients with SLE receiving belimumab 10 mg/kg (based on a population pharmacokinetic analysis)	
Peak serum concentration	313 μg/mL
Area under the serum concentration-time curve from time zero to infinity	3083 μg • d/mL
Volume of distribution at steady-state	5.29 L
Terminal elimination half-life	19.4 d
Systemic clearance	215 mL/d
Most common treatment-emergent adverse events (incidence ≥5%)	
Nausea, diarrhoea, pyrexia, nasopharyngitis, bronchitis, insomnia, depression, pain in extremity, depression, migraine, pharyngitis	

Systemic lupus erythematosus (SLE) is a complex chronic autoimmune disease that involves multiple organ systems.[1] Prevalence estimates for various types of lupus, including SLE, vary greatly. It has been estimated that as many as 5 million people worldwide are affected by a form of lupus[2] and 161 000–322 000 adults have SLE in the US.[3] SLE primarily affects women and can occur at any age, but is most often diagnosed in patients aged 15–45 years.[2] Traditional SLE therapies include NSAIDs, antimalarials and oral corticosteroids for the treatment of patients with mild SLE, with the addition of immunosuppressive and cytotoxic agents (azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, methotrexate and nitrogen mustard) for patients with severe SLE.[4] However, these treatments have significant potential for toxicity and often result in incomplete disease control.[1,4]

Serologically, SLE is characterized by the presence of autoreactive B lymphocytes (B cells), which result in elevated levels of autoantibodies (against double-stranded DNA [dsDNA], the RNA molecule/protein complex Sm, the ribonucleoprotein [RNP] complex Ro, the RNA-binding protein La, RNPs, the C1 complement component subunit C1q and phospholipids).[5] These autoantibodies directly damage the body's cells and tissues, or form immune complexes that cause inflammation and tissue damage.[1]

B lymphocyte stimulator (BLyS, also known as the B-cell-activating factor) is a cytokine with a central physiological role in B-cell homeostasis and survival.[5] BLyS can bind to three receptors (BLyS receptor 3 [BR3], transmembrane activator-1 and calcium modulator and cyclophilin ligand-interactor [TACI] and B-cell maturation antigen [BCMA]) on the surface of B cells. BLyS is the only ligand for BR3, while BLyS and its closely related homologue APRIL (A proliferation inducing ligand) are ligands for TACI and BCMA.[5] Inhibiting the binding of BLyS to the BR3 receptor promotes apoptosis and prevents the differentiation and maturation of B cells. Elevated levels of BLyS have been observed in patients with autoimmune diseases, including SLE. Therefore, the BLyS cytokine represents an attractive target for biological therapy of SLE.[5]

Belimumab (Benlysta®), a monoclonal antibody directed against BLyS, binds to BLyS and blocks the interaction between BLyS and its cellular receptors. Belimumab is the first new drug approved for the treatment of adult SLE in more than 50 years.[6] It is also the first biological agent to be approved in the US and the EU for the treatment of patients with autoantibody-positive SLE who have active disease despite receiving standard therapy, including corticosteroids, antimalarials, immunosuppressives and NSAIDs.[7] This article provides an overview of the pharmacological properties of belimumab and reviews the clinical trial data available on the efficacy and tolerability of belimumab in patients with active SLE.

Medical literature (including published and unpublished data) on the use of belimumab in SLE was identified by searching databases for studies published since 1996 (including MEDLINE, EMBASE), bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug. Searches were last updated 11 November 2011.

1. Pharmacodynamic Profile

Data in this section are predominantly derived from a preclinical study,[8] and phase II[9] and III[10,11] studies in patients with SLE (see section 3 for phase III trial details). These data are supplemented with information from the US manufacturer's prescribing information.[7] Discussion in this section focuses on the recommended belimumab dosage of 10 mg/kg.

- Belimumab is a human IgG1λ monoclonal antibody against BLyS.[7] Belimumab binds to the soluble form of BLyS with high affinity (concentration producing 50% inhibition [IC_{50}] of binding *in vitro* = 8.5 nM) and selectively neutralizes BLyS without recognizing other tumour necrosis factor family members, including APRIL.[8] Once bound, belimumab inhibits the binding of BLyS to its three receptors (BR3, TACI and BCMA) on the B cell with equivalent potency (IC_{50} = 0.10–0.11 nM in an electrochemiluminescence detection assay).[8]

• In a randomized, double-blind, placebo-controlled, phase I trial in 70 patients with SLE, belimumab 1, 4, 10 or 20 mg/kg significantly ($p < 0.01$) reduced levels of circulating B (CD20+) cells.[12] Following a single dose, median reductions in CD20+ cells ranged from 11% to 47% at day 84 in belimumab recipients compared with a 23% increase in placebo recipients.

• Belimumab was associated with significant ($p < 0.001$) reductions in selected B-cell counts by week 24 of treatment compared with placebo in phase II and III trials.[9,11] In the combined belimumab (1, 4 and 10 mg/kg) groups in the phase II trial, median reductions in the levels of circulating CD20+ B cells, CD20+/CD138+ plasmacytoids, CD20+/CD27− naive B cells and CD20+/CD69+ activated B cells were 54.1%, 62.5%, 70.8% and 70.4%, respectively.[9] Reductions in circulating B cells were also observed in the phase III BLISS-76 trial.[11] The number of naive and transitional B cells continued to decline until day 532, after which they remained stable, during belimumab treatment in a long-term, open-label, treatment extension study in 17 patients from the phase II trial.[13]

• Transient increases in CD20+/CD27+ memory cells and T cells were observed in belimumab recipients.[9,14] In BLISS-76, memory B cells were initially increased almost 2-fold by week 8 then gradually declined back towards baseline levels by week 76.[14] Modest, but statistically significant ($p < 0.05$–0.001), increases in CD3+/4+, CD3+/8+ and total CD3+ subsets at 52 weeks were observed with belimumab 10 mg/kg compared with placebo in BLISS-76; this was considered a secondary effect of reductions in B cells.[14]

• Belimumab treatment significantly ($p < 0.05$) reduced autoimmune antibody titres at 52 weeks.[14] Pooled data from the phase III BLISS-52 and BLISS-76 trials showed that median reductions in titres of anti-dsDNA antibodies were 40.8% with belimumab 10 mg/kg compared with 10.2% for placebo in patients who were positive for the antibodies at baseline. Corresponding median reductions in anti-Sm titres were 53.6% and 29.6%, respectively. Significant ($p < 0.05$–0.0001) reductions in anti-ribosomal P and aCL IgG titres were also observed.[14]

• Belimumab significantly ($p < 0.001$) reduced serum levels of immunoglobulins.[10,11] IgG titres went from high to normal or low in 49–50% of belimumab 10 mg/kg recipients versus 19–21% with placebo in both BLISS trials.[10,11] Additionally, mean reductions in IgM titres were 30.0–35.0% with belimumab 10 mg/kg versus 3.2–3.8% with placebo and mean reductions in IgA titres were 16.0–20.4% versus 2.1–2.7% with placebo.[10,11]

• Low complement levels are associated with active SLE;[1] however, belimumab was associated with significant ($p < 0.05$) increases in C3 and C4 levels in patients with SLE.[14] Pooled data from the BLISS trials at 52 weeks showed that significantly more patients receiving belimumab 10 mg/kg shifted from low C3 levels (<900 mg/L) to normal/high levels (≥900 mg/L) than those receiving placebo (38% vs 17%; $p < 0.05$). The corresponding proportions of patients who shifted from low C4 levels (<16 mg/L) to normal/high levels (≥16 mg/L) were 44% and 18%, respectively ($p < 0.05$).[14]

• The clinical relevance of normalization of immunoglobulins or complement levels has not been definitively established.

2. Pharmacokinetic Profile

This section reviews pharmacokinetic data on belimumab that are available from the manufacturer's prescribing information,[7,15] with supplemental data from the manufacturer's briefing document for the US FDA Arthritis Advisory Committee hearing.[16]

• A maximum belimumab serum concentration of 313 μg/mL was attained shortly after the completion of a 1-hour infusion of belimumab 10 mg/kg based on a population pharmacokinetic analysis reported in the manufacturer's briefing document for the FDA Arthritis Advisory Committee hearing.[16] The estimated area under the serum concentration-time curve from time zero to infinity was 3083 μg • d/mL with belimumab 10 mg/kg.

• Based on the population estimates, the volume of distribution of belimumab at steady state was 5.29 L with belimumab 10 mg/kg.[7,16]

• The estimated distribution half-life of belimumab 10 mg/day was 1.75 days and the terminal elimination half-life was 19.4 days in the population

pharmacokinetic analysis.[7,15] The systemic clearance was 215 mL/day.

- Age, race and gender had no clinically relevant effect on the pharmacokinetics of belimumab, as determined by a population analysis.[7] Bodyweight was identified as a covariate; in general, an increased bodyweight was associated with an increase in central clearance and volume of distribution.[16]
- No formal studies have been conducted investigating the effects of renal or hepatic impairment on the pharmacokinetic profile of belimumab.[16] However, population pharmacokinetic analysis of 1603 patients (of whom 275 [17%] had renal impairment [95% moderate and 5% severe]) demonstrated that there was a clinically insignificant reduction in belimumab clearance in patients with renal impairment. The proteolytic degradation of belimumab is not dependent on the liver, therefore it is unlikely that hepatic impairment would affect the pharmacokinetics of belimumab.[16]
- No formal drug-drug interaction studies have been conducted with belimumab.[7] A wide range of co-medications were observed in the population pharmacokinetic analysis. Concurrent use of ACE inhibitors and steroids resulted in a clinically insignificant increase of the systemic clearance of belimumab. Antimalarials, immunosuppressants, aspirin, statins and NSAIDs did not significantly change belimumab pharmacokinetics.[7]

3. Therapeutic Efficacy

The efficacy of belimumab in the treatment of SLE has been evaluated in two fully published, randomized, double-blind, placebo-controlled, multicentre clinical trials: the phase III BLISS-52[10] and BLISS-76[11] trials. Additional data were obtained from the manufacturer's briefing document for the FDA Arthritis Advisory Committee hearing[16] and the FDA's briefing document for the same hearing.[17] While the two pivotal trials each included a 1 mg/kg treatment arm, discussion in this section focuses on the recommended belimumab dosage of 10 mg/kg.

The BLISS-52 trial[10] was conducted in Eastern Europe, Asia-Pacific and South America, while the BLISS-76 trial[11] was conducted predominantly in North America and Europe. These trials included adult patients (aged ≥18 years) with SLE diagnosed according to American College of Rheumatology (ACR) criteria, and active disease (defined as a Safety of Estrogens in Lupus Erythematosus: National Assessment [SELENA] version of the Systemic Lupus Erythematosus Disease Activity Index [SLEDAI] score ≥6; see table I for details of the SELENA-SLEDAI assessment tool) despite receiving standard therapy.[10,11] Additionally, patients needed to be on a stable (≥30 days prior to first dose) SLE treatment regimen, which could consist of prednisone (5–40 mg/day), NSAIDs, antimalarials or immunosuppressive agents.[10,11]

A *post hoc* subgroup analysis of the earlier phase II LBSL02 trial identified that serologically active patients responded better and were a more appropriate patient population for belimumab B-cell-targeted therapy than seronegative patients.[9] Therefore, for the BLISS trials, patients were also required to be autoantibody-positive (defined as antinuclear antibody [ANA] ≥1 : 80 and/or anti-dsDNA antibody ≥30 IU/mL) at two time points prior to randomization, with ≥1 positive test at screening.[10,11]

Exclusion criteria included severe active lupus nephritis (defined as proteinuria >6 g/24 hours or equivalent using spot urine protein to creatinine ratio, serum creatinine >2.5 mg/dL, haemodialysis within 90 days of study entry and prednisone >100 mg/day within 90 days of study entry), severe active CNS lupus (defined as treatment of any of the following within 60 days of study entry: seizures, cerebrovascular accident, psychosis, cerebritis, organic brain syndrome or CNS vasculitis) and previous treatment with cyclophosphamide within 3 months or any B-lymphocyte-targeted drug (including rituximab) at any time and intravenous immunoglobulin or prednisone (>100 mg/day) within 6 months.[10,11]

Patients were stratified according to the SELENA-SLEDAI score (6–9 vs ≥10), proteinuria concentration (<2 vs ≥2g/24 h) and ethnic origin (African descent or indigenous American descent vs other), and were randomly assigned to belimumab 1 mg/kg (n = 288[10] and 271[11]), or 10 mg/kg (n = 290[10] and 273[11]) or placebo

(n = 287[10] and 275[11]). Treatment was administered as an intravenous infusion over 1 hour on days 0, 14 and 28, then every 4 weeks until 48[10] or 72[11] weeks, along with continuation of standard therapy. Standard therapy could have consisted of NSAID, antimalarials, corticosteroids and immunosuppressives alone or in combination. Modifications to standard therapy (drug or dosage changes) were restricted and patients failing to meet the restrictions were considered non-responders.[17] The mean age of patients was 35 years in BLISS-52[10] and 40 years in BLISS-76.[11] Across both trials, most patients were female (94%) and the mean duration of SLE was 6.4 years.[16] Baseline SELENA-SLEDAI scores were ≥10 in 52% of patients, and more than 80% had a Physician Global Assessment (PGA) score of <2.[16] Patient disease characteristics were generally similar across both trials, with a couple of exceptions. The BLISS-52 trial included a higher proportion of patients with proteinuria and more patients had at least one BILAG A organ domain score, while patients had longer disease duration and more organ damage in the BLISS-76 trial.[16] In the BLISS-52 trial,[10] discontinuation rates were 17% in the belimumab 10 mg/kg arm and 21% in the placebo arm at 52 weeks; the corresponding rates were 20% and 23%, respectively, in the BLISS-76 trial.[11] Discontinuation rates were 27% in the belimumab 10 mg/kg arm and 30% in the placebo arm at week 76 in the BLISS-76 trial.[11]

Table I. Details of SLE disease activity assessment tools

Assessment tool	Description
BILAG classic index	The BILAG classic index is a measure of clinical disease activity in individual organ systems. There are 86 disease manifestations grouped into 8 organ domains. Each organ domain is given a score: A (severe disease); B (moderate disease); C (mild, stable disease); D (no current disease activity in a previously affected organ system); E (the organ system has never been involved)[16]
SELENA-SLEDAI	SELENA-SLEDAI is a measure of disease activity. It is a cumulative index that contains 24 individual manifestations. Manifestations are assigned a weighted score of 1 (e.g. fever, thrombocytopenia), 2 (e.g. pleurisy, rash), 4 (e.g. arthritis, haematuria) or 8 (e.g. vasculitis, visual disturbance). Higher scores represent increased disease activity; scores >20 are uncommon[16]
PGA	The PGA is a measure of the patient's general health status from 0–3 on a visual analogue scale: 0 (no disease activity); 1 (mild); 2 (moderate); 3 (severe)[16]
SRI	The SRI is a composite measure consisting of a ≥4-point reduction in the SELENA-SLEDAI score, no new BILAG A organ domain score (severe flare of disease activity) and with no more than one new BILAG B organ domain score (moderate flare of disease activity) and no >0.3-point worsening on the PGA[18]

BILAG = British Isles Lupus Assessment Group; **PGA** = Physician Global Assessment; **SELENA-SLEDAI** = Safety of Estrogen in Lupus National Assessment-Systemic Lupus Erythematosus Disease Activity Index; **SRI** = SLE Responder Index.

At baseline, 96% of patients in the BLISS-52 trial[10] and 76% of patients in the BLISS-76 trial[11] were receiving corticosteroids, and 69% of patients in the BLISS-52 trial and 46% of patients in the BLISS-76 trial were receiving higher doses of corticosteroids (prednisone equivalent >7.5 mg/day). Immunosuppressant agents were used by 56% of patients in BLISS-76 and 42% of patients in BLISS-52. There were no meaningful differences in azathioprine use across both trials, while methotrexate and mycophenolate mofetil use was numerically higher in the BLISS-76 trial (19% and 17%, respectively) than in the in BLISS-52 trial (9% and 6%, respectively).[10,11]

The primary efficacy endpoint in both trials was the SLE Responder Index (SRI) response rate at week 52 in the modified intent-to-treat (mITT) population.[10,11] The SRI is a novel responder index that more appropriately assessed response to treatment, which was defined from exploratory analyses of the phase II LBSL02 trial (see table I for details).[18] The major secondary endpoints included the percentage of patients with a ≥4-point reduction from baseline in SELENA-SLEDAI score, SRI response rate at week 76 (BLISS-76 only), mean change in PGA and Short Form 36 health survey questionnaire (SF-36) physical component summary (PCS) scores at week 24 and reduction in corticosteroid use.[10,11]

- In seropositive patients with active SLE receiving standard therapy, SRI response rates at 52 weeks (primary endpoint; figure 1) were significantly higher in patients receiving belimumab 10 mg/kg than in those receiving placebo in both

the BLISS-52 trial[10] (58% vs 44%; p < 0.001) and the BLISS-76 trial[11] (43.2% vs 33.5%; p < 0.05).

- The durability of the treatment effect of belimumab was not demonstrated at week 76 in the BLISS-76 trial.[11] The SRI response rate was not significantly different in belimumab 10 mg/kg recipients compared with placebo recipients at 76 weeks (39% vs 32%).
- In BLISS-52, significantly greater SRI rates were observed with belimumab 10 mg/kg versus placebo at most visits starting at week 16 (p < 0.05 at week 16, p < 0.001 at weeks 24 and 28, p < 0.01 at weeks 23 and 36, and p < 0.001 at weeks 40–52), although no significant difference was observed at week 20.[10] In contrast, in BLISS-76, the difference between the belimumab 10 mg/kg and placebo groups for the SRI response rate did not reach statistical significance until week 52.[16]
- Belimumab 10 mg/kg was associated with significantly greater improvements in disease activity, measured by a ≥4-point reduction in the SELENA-SLEDAI score at week 52 than placebo in BLISS-52[10] (58% vs 46%; p = 0.0024) and BLISS-76[11] (47% vs 35%; p = 0.006).
- Among patients receiving >7.5 mg/day of prednisone at baseline, the proportion of patients who decreased their prednisone dosage by ≥25% to ≤7.5 mg/day during weeks 40–52 was numerically higher in the belimumab 10 mg/kg group than in the placebo group in BLISS-52 (19% vs 12%) and BLISS-76 (17.5% vs 12.7%).[10,11]
- The mean change from baseline in PGA score at week 24 was significantly greater in belimumab 10 mg/kg than placebo recipients in BLISS-52 (–0.50 vs –0.35; p = 0.0003).[10] In contrast, no significant between-group differences for the same endpoint at week 24 were observed in BLISS-76 (–0.44 vs –0.49).[11]
- Mean improvements in health-related quality of life, as assessed by mean increases in SF-36 PCS scores, were not statistically significant at week 24 with belimumab 10 mg/kg compared with placebo in BLISS-52 (3.34 vs 3.26) or BLISS-76 (5.36 vs 5.63).[10,17] However, improvements were significant at week 52 in BLISS-52 (4.19 vs 2.84; p < 0.05).[10]
- In BLISS-52, the median time to the first SLE flare, assessed by the modified SLE Flare Index, was significantly (p < 0.01) increased from 84 days with placebo to 119 days with belimumab 10 mg/kg.[10] Moreover, belimumab 10 mg/kg was associated with a reduction in the risk of a serious flare compared with placebo over 52 weeks (hazard ratio [HR] 0.57; 95% CI 0.39, 0.85; p < 0.01).[10] In contrast, in the BLISS-76 trial, the median time to the first SLE flare was 84 days with belimumab 10 mg/kg and 82 days with placebo,[17] and the risk of serious flare was not significantly reduced at 52 weeks (HR 0.72; 95% CI 0.50, 1.05; p = 0.08)[17] or 76 weeks (HR 0.77; 95% CI 0.54, 1.09; p = 0.13).[11] Of note, ≈90% of patients who achieved an SRI response at week 52 did not experience a severe flare during their last 6 months of treatment.[19]
- A *post hoc* subgroup analysis of SRI response rate in patients who were of African American or African heritage revealed a lack of belimumab efficacy.[16] Pooled SRI response rates from BLISS-52 and BLISS-76 (n = 148) were numerically lower in the belimumab 10 mg/kg arm than in the placebo

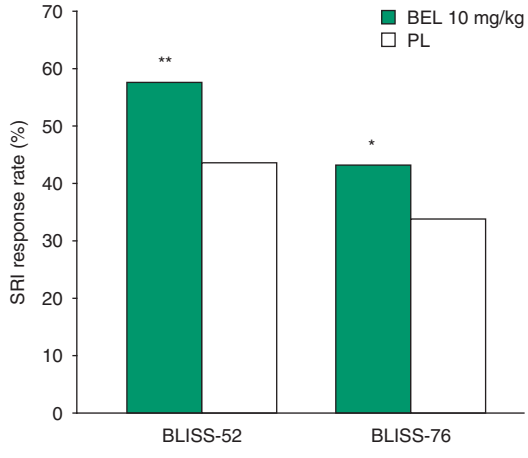

Fig. 1. Efficacy of belimumab (BEL) 10 mg/kg in the treatment of patients (pts) with systemic lupus erythematosus (SLE) in the BLISS-52[10] and BLISS-76[11] trials. The primary efficacy endpoint in both trials was the SLE Responder Index (SRI) response rate (see table I for details) at wk 52 in the modified intent-to-treat population. Patients were randomized to receive BEL 1 mg/kg (n = 288[10] and 271[11]), BEL 10 mg/kg (n = 290[10] and 273[11]) or placebo (PL) [n = 287[10] and 275[11]]. Treatment was administered as an intravenous infusion over 1 h on days 0, 14 and 28, and then every 4 wk. Data for the recommended dosage of 10 mg/kg are presented here. * p < 0.05, ** p < 0.001 vs PL.

arm (36% vs 44%). However, in the phase II trial, Black patients (n = 106) did not appear to have a different response rate from the rest of the study population.[9]

4. Tolerability

The primary focus of this section is pooled tolerability data from patients in the two pivotal trials discussed in section 3[10,11] and the phase II LBSL02 trial.[9] Although dosages of 1 and 4 mg/kg were included in the clinical development programme for belimumab, the discussion in this section is limited to the tolerability for the recommended belimumab dose of 10 mg/kg (n = 674). Additional data were obtained from the manufacturer's prescribing information[7] and the manufacturer's briefing document for the FDA Arthritis Advisory Committee hearing.[16]

- Intravenous belimumab 10 mg/kg as a treatment for SLE was generally well tolerated.[9-11] Most patients (approximately 93% in the belimumab 10 mg/kg and 92% in the placebo groups) experienced an adverse event during treatment. Across the clinical trials, serious or severe adverse events occurred in 22.6% of patients in the belimumab 10 mg/kg group and 21.5% of patients in the placebo group.[20]
- The most frequently reported adverse events (≥7% of patients) occurring during treatment with belimumab 10 mg/kg or placebo are shown in figure 2.[16] Of these, nausea, diarrhoea, fever, nasopharyngitis, bronchitis and insomnia were reported at least 1% more frequently in patients receiving belimumab 10 mg/kg than in those receiving placebo.[7]
- Infections were reported in 69.9% of belimumab 10 mg/kg recipients and 66.7% of placebo recipients.[20] The most frequently reported infections (≥5%) were upper respiratory tract infections, urinary tract infections, nasopharyngitis, sinusitis, bronchitis, influenza and gastroenteritis.[16] Serious infections occurred in 5.2% of patients in both the belimumab 10 mg/kg and the placebo groups.[16]
- Infusion reactions (including hypersensitivity reactions) were reported in 16.8% of belimumab 10 mg/kg recipients compared with 14.7% of placebo recipients.[20] Most infusion reactions were mild or moderate in severity and occurred during the first or second infusion. Serious hypersensitivity reactions were reported in two belimumab 10 mg/kg recipients (0.3%) during the first infusion.[16] Of note, 13% of all patients received premedication, such as paracetamol and diphenhydramine, to prevent infusion reactions.[7] This use of premedication may have masked or mitigated infusion reactions so the true incidence of these reactions may be different. However, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions.[7]
- Psychiatric events were reported in 14.8% of belimumab 10 mg/kg recipients compared with 12.1% of placebo recipients.[16] Depression was reported in 5.2% of belimumab recipients versus 3.7% of placebo recipients. Corresponding rates for insomnia were 6.5% versus 5.3%.[16]
- During the double-blind periods of the clinical trials, twice as many deaths were reported in the belimumab 10 mg/kg group than in the placebo group (six vs three deaths).[16] Of the six deaths in belimumab patients, three were related to infections. The death rate was 1.8-fold higher (95% CI 0.49, 10.08) in belimumab-treated patients (any dosage) compared with placebo-treated patients (0.79 vs 0.43 per 100 patient-years).[16]
- Malignancies were reported in 0.4% of patients treated with belimumab 10 mg/kg compared with 0.3% of patients treated with placebo.[20] The malignancy rate, excluding non-melanoma skin cancer, was reported to be 0.48 per 100 patient-years following exposure to any dosage of belimumab during any clinical trial of belimumab.[20]
- As belimumab is a therapeutic protein, there is potential for an immune response.[16] Anti-belimumab antibodies were detected in 0.7% of patients receiving belimumab 10 mg/kg in the two BLISS trials.[16] Of these patients, one patient experienced mild dyspnoea and moderate exanthema, pruritus and eyelid oedema during the first infusion.
- Belimumab 10 mg/kg was generally well tolerated over the long term.[21] The incidence rate of overall adverse events, serious adverse events, infections and serious infections remained stable over 6 years.[21]

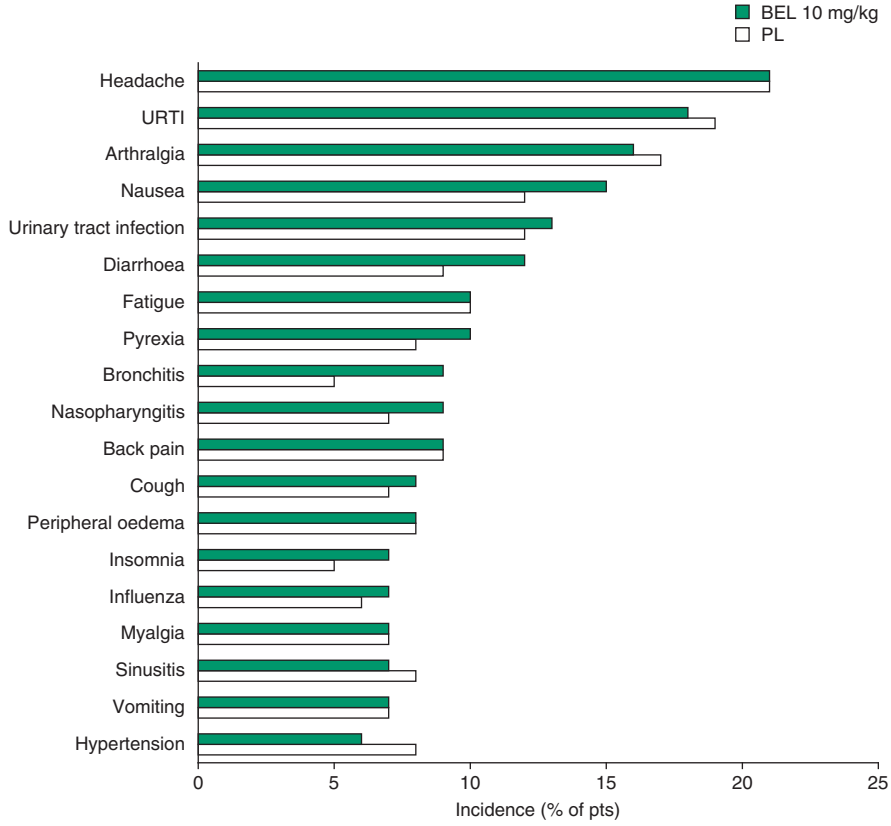

Fig. 2. Tolerability of belimumab (BEL) 10 mg/kg in patients (pts) with systemic lupus erythematosus. Incidence of clinical adverse events (≥7% of pts) occurring in a pooled analysis of results from the pivotal randomized, double-blind, multicentre phase III BLISS-52 and BLISS-76 trials and the phase II LBSL02 trial in which 674 pts received BEL and 675 pts received placebo (PL) for 52 or 76 wk.[7] **URTI** = upper respiratory tract infection.

5. Dosage and Administration

Belimumab is approved in Europe,[15] the US[7] and Canada[22] for the treatment of adult patients with active SLE who are also autoantibody-positive and have a high degree of disease activity despite receiving standard therapy. The recommended dosage is a 10 mg/kg intravenous infusion administered on days 0, 14 and 28, and then once every 4 weeks thereafter. The infusion should be administered over 1 hour and appropriate premedication for prophylaxis against infusion reactions and hypersensitivity reactions may be considered. The safety of belimumab in pregnancy and lactation has not been tested. Thus, belimumab is not recommended for use in pregnancy or in breast-feeding mothers. No dosage modifications are recommended for special patient populations (elderly patients or patients with renal or hepatic impairment).[7,15]

Local prescribing information should be consulted for warnings and precautions, contraindications and drug interactions.

6. Belimumab: Current Status

In the US, the EU and Canada, belimumab is approved as add-on therapy in adult patients with active, autoantibody-positive SLE with a high degree of disease activity despite receiving standard therapy.[7,15,22] Two large, well designed,

phase III trials, BLISS-52 and BLISS-76, have shown that intravenous infusions of belimumab 10 mg/kg once every 2 weeks for the first three doses and then once every month thereafter significantly increased the SRI response rate at 52 weeks compared with placebo, each in combination with standard therapy, in patients with active, autoantibody positive, SLE.[10,11] However, belimumab no longer demonstrated a significant advantage over placebo in the SRI response rate at 76 weeks in the BLISS-76 study. Belimumab was generally well tolerated in BLISS-52 and BLISS-76 and was not associated with a meaningfully higher rate of adverse events compared with placebo. Two open-label extension studies of BLISS-52 and BLISS-76 to investigate the long-term tolerability and efficacy of belimumab in patients with autoantibody-positive SLE are ongoing.[23,24]

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