



**Belimumab: a technological advance for SLE patients?
Report of a systematic review and meta-analysis**

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3 **Belimumab: a technological advance for SLE patients? Report of a systematic review**
4 **and meta-analysis**
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Short Title:

Systematic review on belimumab for SLE

ARTICLE FOCUS

- SLE is a complex multi-organ auto-immune disease subject to relapse and remission.
- Patients almost always have fatigue, skin rashes and arthritis and there is a wide variety of other problems which the disease can cause.
- Belimumab is a new treatment specifically targeted against SLE.

KEY MESSAGES

1. Combining the results from two RCTs suggests that belimumab is clinically effective for SLE patients.
2. However, all outcomes were systematically superior in one trial compared with the other.
3. Different trial conduct and populations mean that it is too early to draw generalisable conclusions.

STRENGTHS AND LIMITATIONS

- At first sight combined meta analytic evidence suggests that belimumab is clinically effective for patients with severe SLE
- We suggest that it is too early to draw strong conclusions because the 2 relevant trials cover different populations in different countries and there may be differences in trial conduct and outcome assessment.

Abstract

Objectives: To undertake a systematic review and meta-analysis to investigate clinical effectiveness of belimumab for patients with SLE and anti-nuclear and/or anti-dsDNA autoantibodies.

Methods: We searched eight electronic databases and reference lists for randomised controlled trials (RCTs) of belimumab against placebo or best supportive care. Quality assessment and random effects meta-analysis were undertaken.

Design: A meta-Analysis of RCTs.

Setting: NA

Participants: 2133 SLE patients

Interventions: NA

Primary and secondary outcome measures: Responder Index (SRI) at week 52.

Results: Three double-blind placebo-controlled RCTs (L02, BLISS-52 BLISS-76) investigated 2133 SLE patients. BLISS-52 and BLISS-76 trials recruited patients with anti-nuclear and/or anti-dsDNA autoantibodies and demonstrated belimumab effectiveness for the SLE Responder Index (SRI) at week 52. Ethnicity and geographical location of participants varied considerably between BLISS trials. Although tests for statistical heterogeneity were negative, BLISS-52 results were systematically more favourable for all measured outcomes. Meta-analysis of pooled 52-week SRI BLISS results showed benefit for belimumab (OR 1.63, 95% CI 1.27-2.09). By week 76, the primary SRI outcome in BLISS-76 was not statistically significant (OR 1.31, 95% CI 0.919-1.855).

Conclusions: Meta-analysis shows a statistically significant benefit of belimumab for patients with SLE and anti-nuclear and/or anti-dsDNA autoantibodies at 52 weeks only. In view of the different populations studied at different locations and the consistently superior results from one trial compared to the other, the generalizability of pooled results should be viewed with caution. Population heterogeneity, geography and/or variation in trial conduct may be hidden confounders. These findings require further replication or explanation before uncritical acceptance of the positive pooled meta-analytic result is accepted.

INTRODUCTION

SLE is an auto-immune disease subject to relapse and remission. Incidence is estimated at between 1.0 and 10.0 per hundred thousand person years using different measures, and prevalence at between 20-70 per 100,000.[1, 2] SLE is a complex multi-organ disease with a number of different manifestations.[3] Patients almost always have fatigue, often have skin rashes and arthritis and there is a wide variety of other problems which the disease can cause.

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3 The American College of Rheumatology has defined 11 classification criteria, including:
4 rash; photosensitivity; oral ulcers; arthritis; serositis; renal or neurological disorder.[4, 5]
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6 Assessment of the patient can be difficult, as flares of the disease have to be distinguished
7 from its complications, from comorbidity especially infection, and from adverse effects of
8 medications.[6] SLE is more common in women (in most studies 90% or more of cases are
9 women)[2] and in those from black and ethnic minorities. Recently age-adjusted incidence
10 rates have been produced showing that rates are highest in women aged 40 years and
11 over.[7] Mortality rates show that 5 year survival is high, at over 90%[8, 9] and the overall
12 SMR has been calculated as 2.4.[10]
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18 Antinuclear antibodies are present in virtually all patients with SLE.[11] Anti-ds DNA
19 antibodies are present in 50-60% patients at some point in their disease but often transiently
20 with active disease.[11] The aim of treatment is to maintain normal function whilst
21 suppressing disease activity and preventing organ damage.[6] Achieving these conflicting
22 aims can be difficult. Corticosteroids are the mainstay of treatment. Other drugs used
23 include antimalarials such as hydroxychloroquine, and immunosuppressive drugs such as
24 azathioprine and mycophenolate mofetil. More recently rituximab (a monoclonal antibody
25 which reacts with the CD20 antigen, which is expressed on B cells) has also been used,
26 although the largest trial undertaken to date failed to reach its end point.[12]
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33 Belimumab (Benlysta®) is an IgG1 monoclonal antibody which inhibits the activity of the
34 soluble cytokine BLyS (B lymphocyte stimulator; also known as BAFF). In contrast to earlier
35 SLE treatments, belimumab is targeted at the fundamental pathology of SLE and has been
36 widely interpreted as representing a step change in treatment options.
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41 Belimumab was recently licensed in the USA and in Europe for treatment of autoantibody-
42 positive SLE and is the first drug to be so licensed for several decades. The European
43 indication is for severely affected SLE patients with active, autoantibody-positive disease
44 and a high degree of disease activity exemplified by positive anti-dsDNA and low
45 complement despite standard therapy.[13] Belimumab is administered by IV infusion
46 recommended at 10mg belimumab /kg on days 0, 14 and 28, and at 28 day intervals
47 thereafter. A course of belimumab treatment for a 64kg patient using the US list price of
48 \$1,477 (£926.37) for a 400 mg vial[14] would be \$56,527 (£35,454) per year, and according
49 to the US average whole sale price of \$4.432 (£2780)/400mg vial)[15] would be \$42,545
50 (£26,684) per year.
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3 A number of clinical measures have been developed for tracking the progression of SLE[16]
4 and for estimating the effects of treatment.[17] They include the Physician's Global
5 Assessment (PGA); SELENA-SLEDAI (Safety of Estrogen in Lupus National Assessment-
6 Systemic Lupus Erythematosus Disease Activity Index); and the BILAG Index (British Isles
7 Lupus Assessment Group) and the SRI (SLE Response Index). Their major features are
8 summarised in Figure 1. Their complexity means that outside specialised centres they may
9 not be widely used in routine clinical practice.
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18 Our objective was to synthesise findings from randomised controlled trials of belimumab for
19 patients with SLE and anti-nuclear and /or anti-dsDNA autoantibodies, to make an overall
20 assessment of the performance of this drug in relation to comparator treatments using the
21 SRI and other outcomes (as listed in Figure 1) and to assess the findings of trials in the light
22 of population samples or geographical factors.[18]
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27 **METHODS**

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30 The study was undertaken as part of work for the National Institute for Health Research,
31 Health technology Assessment programme (Grant funding reference 10/73/01. Further
32 information is available from: www.hta.ac.uk/).
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36 **Search scope**

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38 We searched for randomised controlled trials investigating belimumab administered i.v. for
39 patients with SLE and anti-nuclear and /or anti-dsDNA autoantibodies. Comparators
40 considered were Belimumab versus placebo and Belimumab versus best supportive care.
41 Outcomes included all disease-related or health-status-related measures. There was no
42 publication year restriction, but the search was restricted to English language references
43 only.
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47 **Search strategy**

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49 The following eight databases were searched: Cochrane Database of Systematic Reviews;
50 the Cochrane Central Register of Controlled Trials (CENTRAL); DARE; EMBASE; HTA
51 Database; Medline; Pre-Medline; Science Citation Index. Search strategies for these
52 databases used a combination of terms related to the population and interventions listed
53 above; the specific search strategies are provided in Appendix 1. In Medline and EMBASE
54 the subject strategies were combined with search strategies designed to identify randomised
55 controlled trials (See Appendix 1).
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4 Unpublished studies were identified using: Clinical Trials, Current Controlled Trials, EU
5 Clinical Trials Register, UK Clinical Research Network Study Portfolio, National Research
6 Register, WHO Clinical Trials Search Portal, NHS Evidence, Conference Proceedings
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8 Citation Index -Science and Google.
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12 In addition, specific websites were searched: Medicines and Healthcare products Regulatory
13 Agency (MHRA); European Medicines Agency (EMA); US Food and Drug Administration
14 (FDA) and the following specific conference proceedings: American College of
15 Rheumatology; British Society of Rheumatology; European League Against Rheumatism
16 (EULAR).
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21 *Inclusion criteria:* Two reviewers assessed retrieved publications for inclusion. Publications
22 were included if they described results from RCTs of Belimumab for SLE patients with
23 positive autoantibodies. Any disagreements were resolved with reference to third reviewer.
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27 *Date extraction:* Potentially relevant publications were obtained in full text and assessed by
28 the same two reviewers. One reviewer extracted data for all specified primary and secondary
29 outcome measures, for adverse events and deaths. A second reviewer checked extracted
30 data.
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35 *Quality evaluation:* Quality assessment and risk of bias was guided by the CRD checklist[19]
36 based on all information in the included publications which specifies reporting of
37 randomisation, concealment of allocation, group balance, blinding, drop-outs, outcome
38 reporting bias, and whether ITT analysis was used.
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43 *Statistical analysis:* Unadjusted odds ratios and mean differences for binary and continuous
44 outcomes were calculated respectively. Statistical heterogeneity was calculated using the I^2
45 statistic.[20] Adjusted outcome measures were tabulated where these were reported. A
46 random effects meta-analysis[21] was undertaken using STATA version 10 software.[22]
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50 RESULTS

51 Characteristics of included studies

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53 We identified three placebo controlled RCTs of belimumab versus standard care: the phase
54 III trials termed BLISS-52[23] and BLISS-76[24] and a phase II trial (study L02).[25] The
55 PRISMA flow chart shows the process of identification of publications (see Figure 2). We
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3 identified that there is an on-going trial in Asia.[26] All three completed trials appeared to be
4 of good quality; however details of allocation concealment were meagre (Table 1).
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14 BLISS-52,[23] BLISS-76[24] and study L02[25] have been published in peer reviewed
15 journals, however the fullest accounts in the public domain are in the FDA licensing approval
16 documents[27, 28] and the manufacturer's 2011 submission to NICE.[29] Each of these
17 placebo-controlled randomised trials was designed with multiple randomised groups. In the
18 L02 trial, patients received 1 or 4 or 10 mg/kg of belimumab or placebo, while in the BLISS
19 trials the belimumab dose regimens were 1mg/kg or 10 mg/kg. Both US and European
20 licensing is for the 10mg/kg dose regimen. In this article we focus on efficacy results for the
21 10mg/kg licensed regimen relative to placebo. We also consider the off licence 1 mg/kg and
22 4 mg/kg dose regimens for investigation of adverse events.
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29 Centralised, stratified randomisation was reported as used in all three trials and arms were
30 generally well balanced. All three trials recruited predominantly female patients (~90%) and
31 were described as double blind. The two BLISS studies were conducted according to similar
32 protocols.
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37 There were differences in geographical distribution of the study centres and in the resulting
38 ethnic racial make-up of the study populations (Table 2 and Figure 3). Thus in BLISS-76,
39 70% were Caucasian, 13% native American and 3% Asian respectively, whereas in BLISS-
40 52, 27% were Caucasian, 32% native American and 38% were Asian. Table 3 lists the major
41 outcomes pre-specified in the BLISS trials.
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46 There were additional population differences between BLISS and L02 trials at recruitment.
47 Reporting of results for patients with anti-nuclear and /or anti-dsDNA autoantibodies in L02
48 was only included for a post-hoc subgroup. Primary outcomes measured in L02 were not
49 comparable with those of the BLISS studies. For these reasons, L02 study results were not
50 included in the meta-analysis of clinical effectiveness. For the BLISS trials a composite
51 primary outcome measure was developed and termed the SLE Response Index (SRI) (see
52 Figure 1 and Table 3). This pre-specified primary end point is the primary outcome
53 investigated in this meta-analysis.
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18 Efficacy results for the BLISS trials for major binary outcomes and for the time to first SLE
19 flare are summarised in Figure 4. The pre-specified primary efficacy end point was the
20 proportion of responders at week 52 according to the novel SRI composite outcome. Both
21 trials satisfied this primary end point with a better result for BLISS-52. The difference in
22 percentage responders in the belimumab group relative to placebo group was 14% in
23 BLISS-52, 9.4% in BLISS-76 and 11.8% when pooled across trials using logistic
24 regression[27] and the corresponding adjusted odds ratios for a response in BLISS-52 and
25 in BLISS-76 were respectively 1.83 (95% CI: 1.30, 2.59; $p = 0.0006$) and 1.52 (95% CI: 1.07,
26 2.15; $p = 0.0207$). By week 76, the proportion of SRI responders in the BLISS-76 trial
27 ceased to reach statistical significance; this also held for the odds ratio adjusted by logistic
28 regression (OR1.31, 95% CI: 0.92 – 1.87, $p = 0.1323$).[28]
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36 For all other binary effectiveness outcomes, and for time to first flare or to first severe flare,
37 the BLISS-52 trial delivered results which were more favourable to Belimumab than did
38 BLISS-76, with the latter results failing to reach a conventional level of statistical significance
39 except for the ≥ 4 point improvement in SLEDAI score at week 52. Results for continuous
40 outcomes are summarised in Figure 5. These revealed a similar pattern of BLISS-52
41 superiority for all reported outcomes. Mean changes from baseline for FACIT-fatigue scores
42 and for EQ-5D utility scores (belimumab versus placebo) (not pictured) did not reach
43 statistical significance although again, improvement observed in BLISS-52 for these
44 outcomes was superior to that seen in BLISS-76. BLISS-52 showed a systematic superiority
45 over BLISS-76 across the full range of effectiveness outcomes (binary, time to event and
46 continuous).In BLISS-76 the primary outcome response rates were 32% (46 out of 145), and
47 35% (47 out of 136) for placebo and belimumab respectively for patients from the US and
48 Canada. In comparison, the corresponding rates for patients from Latin America in BLISS-52
49 were 49% (71 out of 145), and 61% (85 out of 140).
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3 Figure 4 shows the results for major safety outcomes across the three trials (L02 BLISS-52
4 and BLISS-76). Although there were more serious adverse events, more serious infections
5 and more deaths associated with belimumab than with placebo, none of the odds ratios for
6 these outcomes reached statistical significance. There were 14 deaths during the controlled
7 phase of the three trials; 3 in the placebo group (n=675), and 11 in the belimumab groups
8 (n=1458) with 6 in the 10mg/kg and 5 in the 1mg/kg groups, respectively (odds ratio 11.7;
9 95% CI 0.474 to 6.124). The causes of death were various.
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19 Meta-analysis of study level results showed a statistically significant benefit of belimumab for
20 all main outcomes SRI, SELENA SLEDAI, worsening in PGA, BILAG score or steroid use
21 (Figure 6). Tests for statistical heterogeneity were not significant. However in the BLISS-52
22 study, Physicians' global assessments (PGA) (which also constitute a component of SRI and
23 SELENA SLEDAI) were more positive for change by week 24 by almost 10% than they were
24 for the BLISS-76 study (BLISS-52: placebo 22.44%; belimumab 36.75% and BLISS-76:
25 placebo 26.18%; belimumab 27.57%).
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35 DISCUSSION

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37 We undertook a systematic review of the clinical effectiveness of Belimumab, a new
38 treatment targeted at systemic lupus erythematosus (SLE) patients with anti-nuclear and /or
39 anti-dsDNA autoantibodies. We performed an extensive search and systematic review of
40 both completed and on-going trials using a number of databases and by checking reference
41 lists. Data were extracted independently and studies were quality assessed. Random effects
42 meta-analysis was undertaken.
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47 We identified three RCTs (L02, BLISS-52 BLISS-76) reporting data on over 2000 patients. In
48 contrast to the BLISS trials, L02 recruited patients were not necessarily current carriers of
49 anti-nuclear or anti dsDNA antibodies at study commencement. L02 failed to demonstrate
50 clinical effectiveness for the primary end points. Meta-analysis of the BLISS studies showed
51 a benefit of belimumab with the main primary outcome (SRI), showing improvement at 52
52 weeks, (OR 1.63; 95% CI: 1.27-2.09) although by week 76, the proportion of SRI responders
53 in the BLISS-76 trial ceased to reach statistical significance (OR 1.31 (95% CI: 0.92–1.87
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3 p=0.1323). There were no significant differences between placebo and intervention groups
4 in quality of life or adverse events.
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8 We found that the benefits of belimumab were systematically greater across the board
9 (although not significantly so) in the BLISS-52 trial for all outcomes and although tests for
10 statistical heterogeneity were negative, the racial background and ethnicity of participants
11 varied considerably. If the two BLISS trials were drawn from the same underlying
12 populations, whilst one might expect outcomes to differ, they should differ randomly – some
13 better some worse than the other.
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18 A few studies have directly assessed the existence of and importance of geographical
19 differences in trial outcomes.[30-32] Key factors contributing to such differences are
20 variation in underlying patient population characteristics and variation in study execution.
21 Vickers et al[31], found that Eastern Asian and Eastern European studies had a higher
22 proportion of positive trial results when compared to other countries. O’Shea and De Mets
23 also report that within the Beta-Blocker Heart Attack Trial (BHAT), not only was there a
24 difference in the direction, but also in the size of treatment effect between Canada and the
25 US, although it should be noted that the original aim of that trial was not investigation of
26 international differences in treatment effect.[33] One study found that 96-99% of the total
27 variance in the Global utilisation of strategies to open occluded coronary arteries IV acute
28 coronary syndromes (GUSTO IV ACS) trial could be accounted for by patient-level
29 factors.[34]
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38 International trials need to harmonise training of investigators, patient selection, treatment
39 management, thresholds to centre admission, access to facilities, ascertainment of
40 endpoints and, by implication, results of interest.[35-42] and it is possible that in each
41 country’s centres these factors may differ systematically.[35]
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45 Equally, underlying differences in populations and countries (ethnicity, genetics, socio-
46 economic status and health-care systems) and the nature and epidemiology of SLE
47 according to ethnic background may result in differences in reporting of outcomes and
48 pooled results.
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53 The outcomes used in the BLISS trials would be unfamiliar to most of the investigators and it
54 is possible that criteria may have differed between countries. In particular the Physician
55 Global Assessment (PGA) is an important element of the outcomes measured (see Figure
56 1). PGA was measured as an outcome in itself, and it is also incorporated in SRI.
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PGA is of particular concern because as a global physician assessment of a patient's SLE status, it is subjective. The investigators reported a nearly 10% difference between the BLISS-52 and BLISS-76 studies in estimates of percentage change in PGA score in intervention groups at week 24 compared to baseline and this single result in one of the two trials is likely to have had an important influence on our findings of the effectiveness of belimumab in SLE patients.

The latest results of belimumab in patients with SLE(phase 2 study design) of 449 patients with active SLE (USA/Canada) show that 177 (39.4%) patients remained on treatment after 7 years of therapy (i.e. approximately 1746 cumulative patients-years) with durable sustained improvement in SLE disease activity (SRI and PAG) [43].

CONCLUSIONS

In conclusion, systematic review and random effects meta-analysis of two RCTs of belimumab for patients with autoantibody positive SLE demonstrated positive results in the main outcome at week 52. However in view of the different populations studied at different locations in the BLISS trials and the consistently superior results from one trial compared to the other, we consider that population heterogeneity; geography and/or variation in trial conduct and outcome assessment should be considered as potential hidden confounders. The generalizability of meta-analytically pooled results should be viewed with caution and we suggest that it is too early to draw strong conclusions in this case.

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Competing interest statement

No conflicts of interest.

Contributions:

N-BK : Conception and design. Data analysis and interpretation. Drafting the article. Critical revisions for important intellectual content. Approval of final article for submission.

MC: Conception and design. Data analysis and interpretation. Literature review. Interpretation of results. Drafting the article. Critical revisions for important intellectual content. Approval of final article for submission.

AG: Interpretation of results. Critical revisions for important intellectual content.

PS: Literature review. Interpretation of results. Critical revisions for important intellectual content.

SM: Data analysis and interpretation. Interpretation of results. Critical revisions for important intellectual content.

LH: Literature review. Interpretation of results. Critical revisions for important intellectual content.

RC: Literature review. Critical revisions for important intellectual content.

EC: Interpretation of results. Critical revisions for important intellectual content.

CG: Interpretation of results. Critical revisions for important intellectual content.

AC: Interpretation of results. Critical revisions for important intellectual content.

All authors read and approved the final manuscript.

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Appendix 1

Search Strategies

Cochrane Central Register of Controlled Trials (CENTRAL)

CENTRAL searched via Cochrane Library Interface on 18/05/11

1	MeSH descriptor Lupus Erythematosus, Systemic explode all trees	418
2	(lupus NEAR/3 erythematosus) or (systemic* NEAR/3 lupus) or (SLE)	630
3	(#1 OR #2)	703
4	belimumab OR benlysta	6
5	(#3 AND #4)	4

Medline

Medline searched via Ovid Interface on 19/05/11

1	exp Lupus Erythematosus, Systemic/	42025
2	(lupus adj3 erythematosus).tw.	35497
3	(systemic* adj3 lupus).tw.	31639
4	1 or 2 or 3	50358
5	belimumab.mp.	68
6	benlysta.mp.	3
7	5 or 6	68
8	4 and 7	48
9	randomized controlled trial.pt.	305892
10	controlled clinical trial.pt.	82328
11	randomized.ab.	212836
12	placebo.ab.	124063
13	clinical trials as topic.sh.	153987
14	randomly.ab.	154440
15	trial.ti.	91188
16	9 or 10 or 11 or 12 or 13 or 14 or 15	711420
17	exp animals/ not humans.sh.	3582822
18	16 not 17	656689
19	8 and 18	24

RCT search filter used: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format. Box 6.4.b in the Cochrane handbook. Reference: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Medline In-process

Medline In-Process searched via Ovid Interface on 19/05/11

1	exp Lupus Erythematosus, Systemic/	0
2	(lupus adj3 erythematosus).tw.	1213
3	(systemic* adj3 lupus).tw.	873
4	1 or 2 or 3	1236
5	belimumab.mp.	8
6	benlysta.mp.	4
7	5 or 6	10
8	4 and 7	6

Embase

1	belimumab.mp.orexpbelumumab/	427
2	benlysta.mp.	24
3	1 or 2	428
4	exp systemic lupus erythematosus/	50906
5	(lupus adj3 erythematosus).tw.	40637
6	(systemic: adj3 lupus).tw.	36554
7	4 or 5 or 6	59739
8	3 and 7	302
9	random:.tw.	632763
10	placebo:.mp.	250140
11	double-blind:.tw.	116148
12	9 or 10 or 11	796900
13	8 and 12	144

RCT search filter used: Wong, et al. (2006) Best optimization of sensitivity and specificity.
 Reference: Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for
 detecting clinically sound treatment studies in EMBASE. J Med Libr Assoc. 2006
 Jan;94(1):41-7. PubMed PMID: 16404468; PubMed Central PMCID: PMC1324770.



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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis. http://bmjopen.bmj.com/site/about/guidelines.xhtml)	5



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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2 and Figure 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 1 and Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	See Figure 6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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SELENA-SLEDAI: encompasses 24 weighted items scored dichotomously as present or absent in the previous 10 days, thus improvement or worsening of a manifestation is not captured. Overall disease activity is scored over a range of 0 to 105 points. A minimum clinically meaningful score change = a decrease of 6 points (overall improvement) or an increase of 8 points (overall worsening). A designated change in score (≥ 4 points) between baseline and follow up can be used to dichotomise patients into responders or non-responders for overall disease.

BILAG¹⁶: Includes 86 items grouped in 8 organ systems to assesses organ system involvement over the last 4 weeks compared to preceding 4 weeks based on physicians intention to treat using classifications ranging from A to E as follows: A = worsening usually requiring intensification of steroids or immunosuppressant treatments; B = worsening usually requiring antimalarials, nonsteroidal anti-inflammatory drugs (NSAIDs), or low dose steroids; C = stable disease (symptomatic therapy); D = improvement; E = system never involved. Unlike SELENA-SLEDAI it can detect worsening or improvement in individual organ system involvement.

PGA: employed to monitor change in patient overall disease activity; typically a visual analogue scale is used ranging between no disease = 0, mild disease = 1, moderate disease = 2, and severe disease = 3.

SRI: A composite instrument (combining elements of SELENA-SLEDAI, BILAG and PGA) developed by belimumab-trialists in conjunction with the US FDA. It allows patients to be dichotomised into responders or non-responders according to predefined assessment criteria in each of the component elements, such as: a SELEN-SLEDAI improvement of ≥ 4 points, plus no worsening in PGA score by > 0.3 points, plus no new BILAG organ system involvement scoring category A in one system or category B in two or more systems. An advantage of SRI, over any one of its components used alone, may be that it can detect SLE improvement in some initial manifestation(s) while guarding against the possibility that worsening in organ systems or overall disease activity might be masked.



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Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5-6
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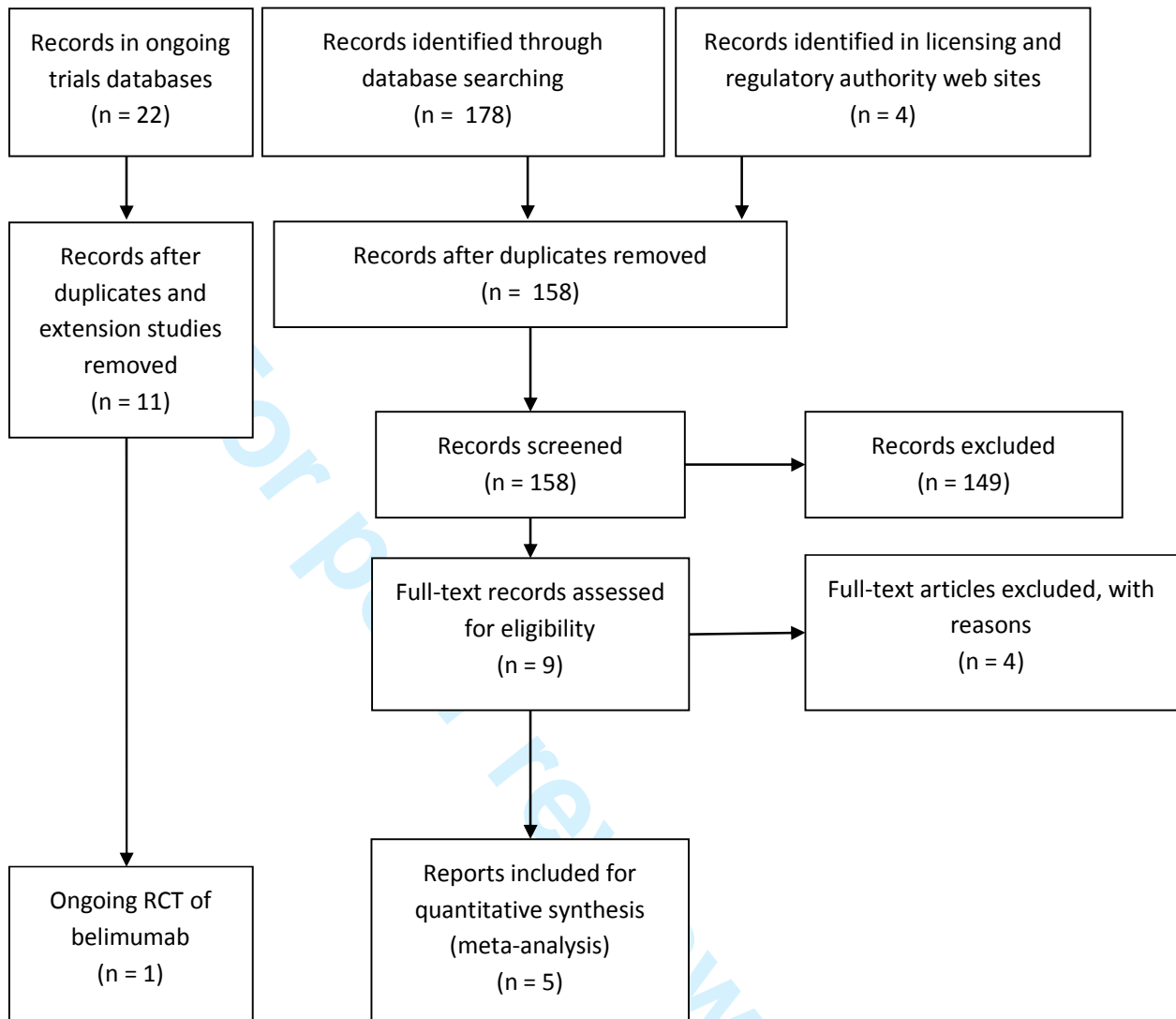
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RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8-12
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FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	End of paper

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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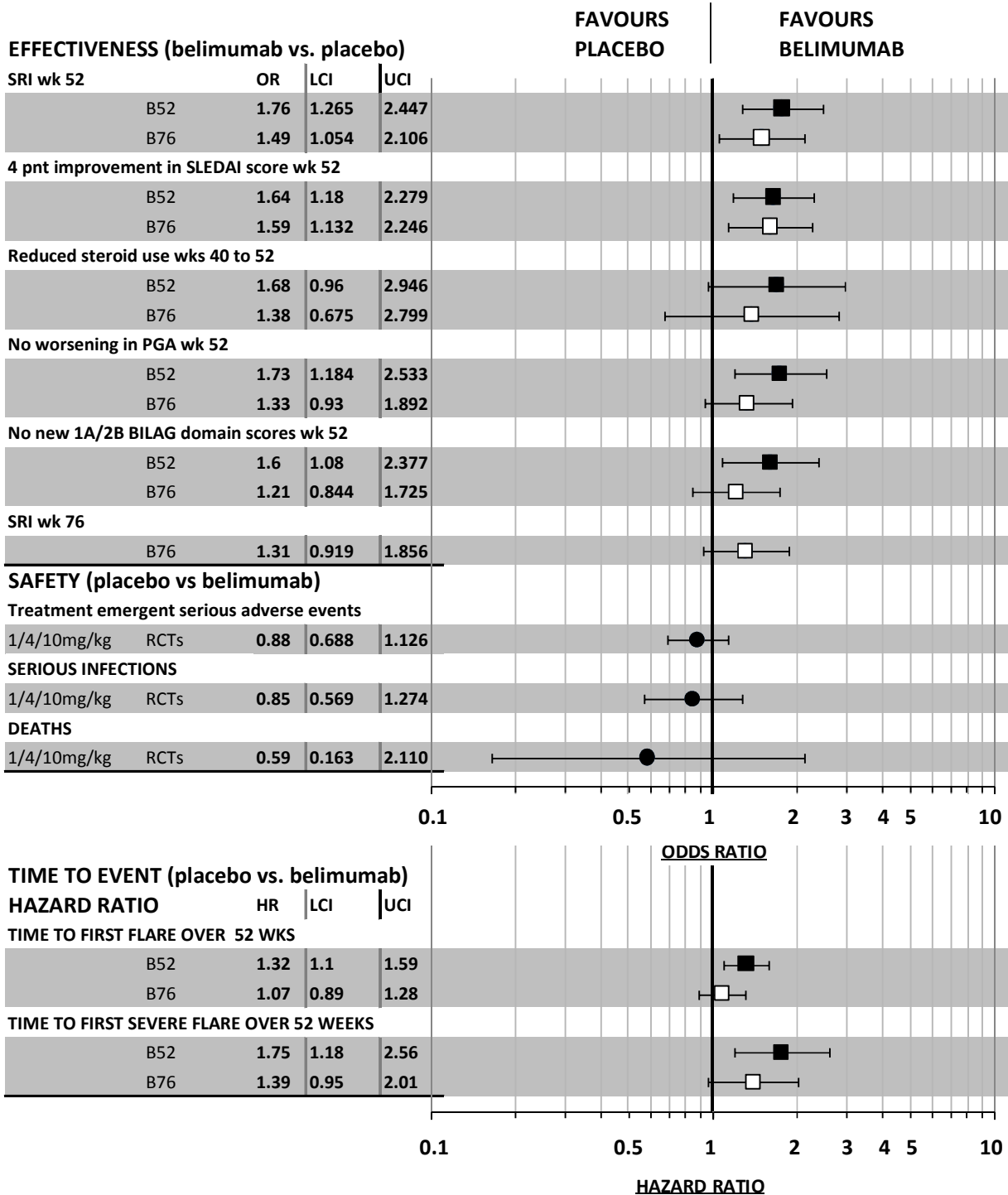


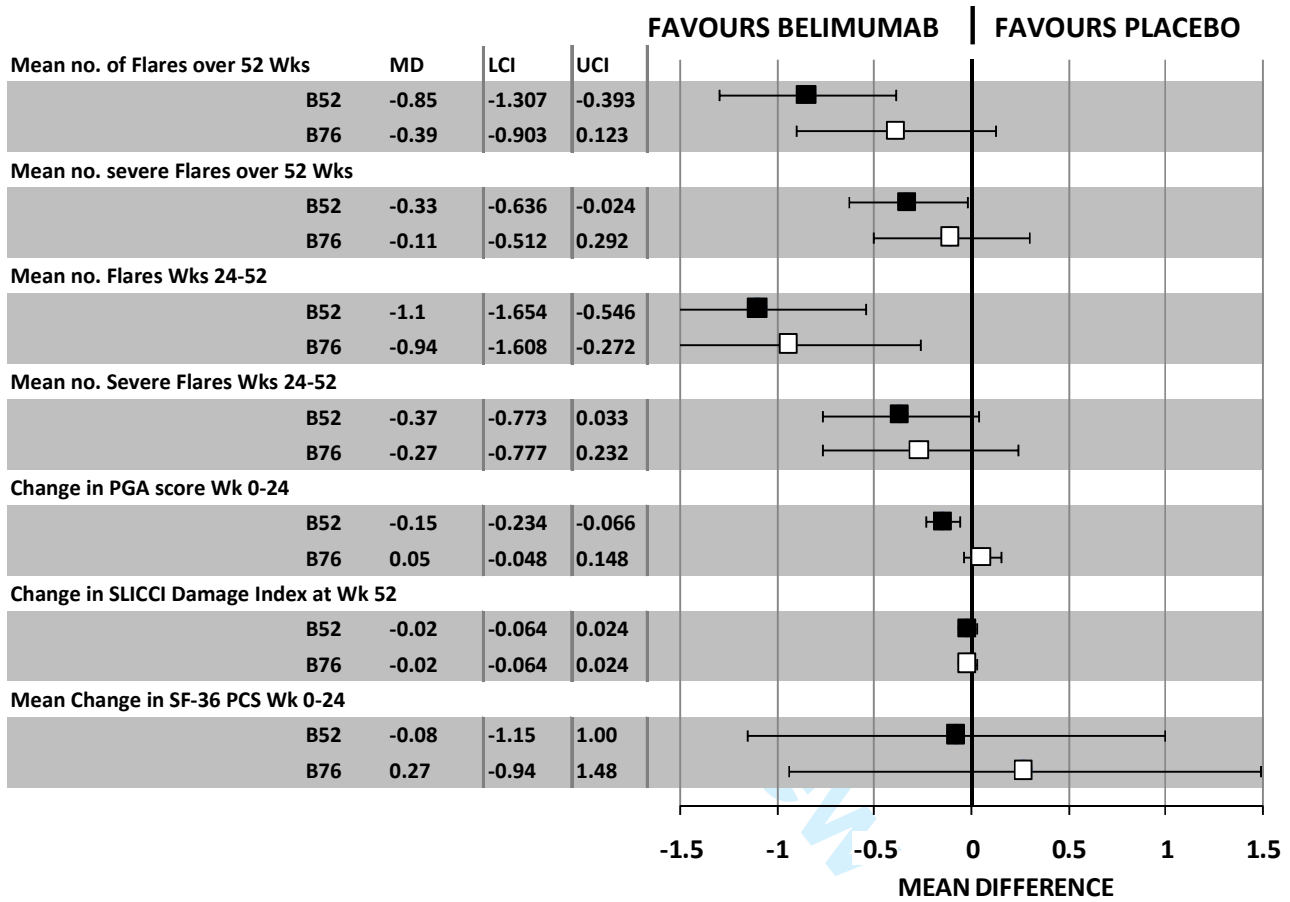


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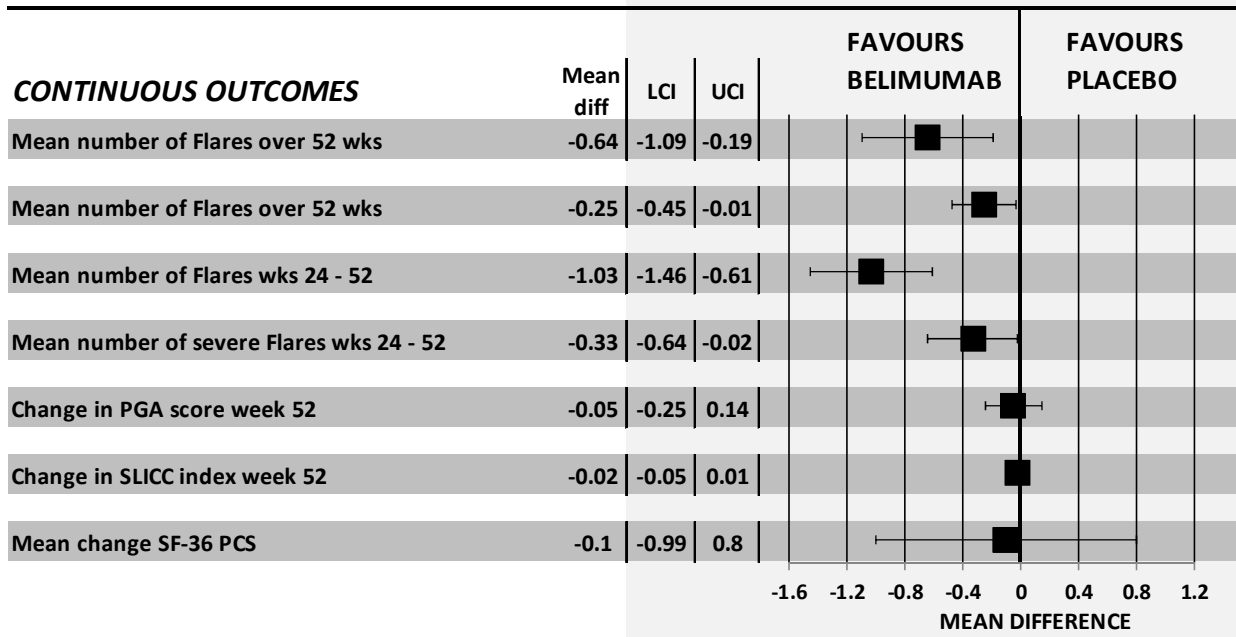
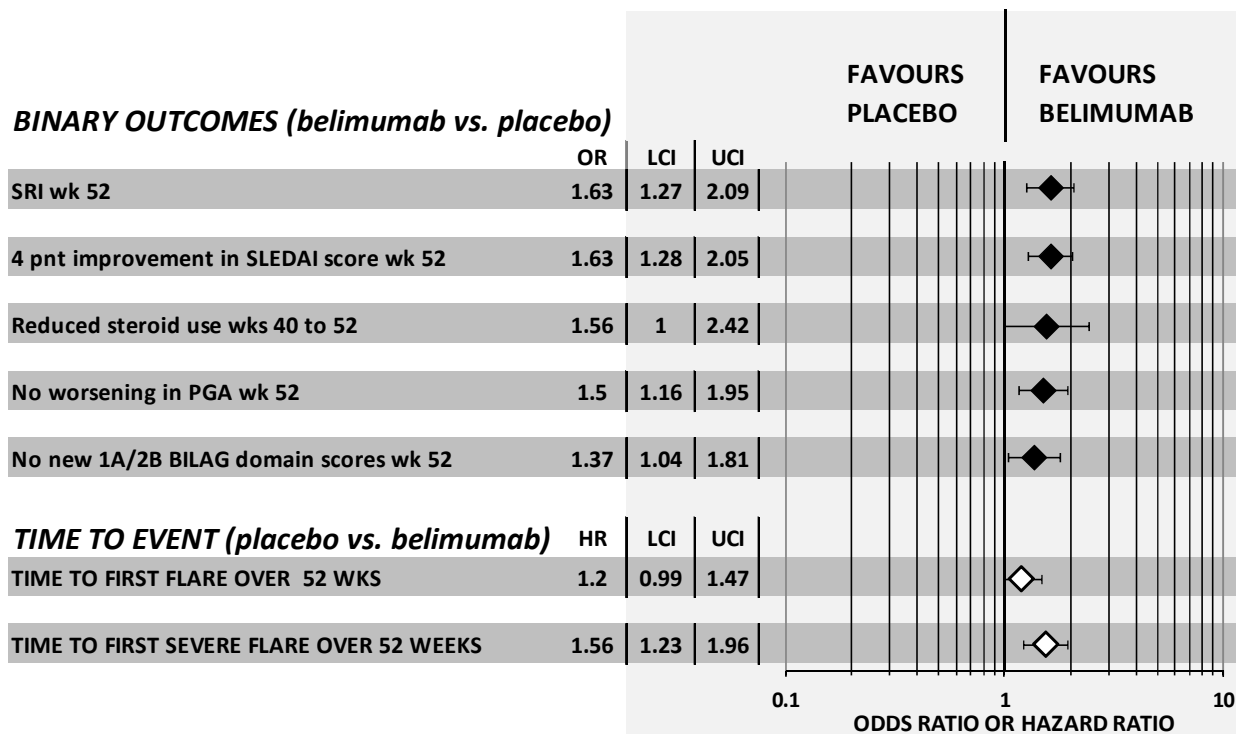


Table 1 Quality assessment of the included trials

	L02	BLISS-52	BLISS-76
Does reporting suggest that randomisation was carried out appropriately?	Yes	Yes	Yes
Does reporting suggest that the concealment of treatment allocation adequate?	Unclear	Unclear	Unclear
Were the groups reported as similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors reported as blind to treatment allocation?	Yes	Yes	Yes
Were any unexpected imbalances in drop-outs reported between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

Based on the Centre for Reviews and Dissemination (2008) Systematic reviews. CRD guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination[19]

Table 2: Major characteristics of included studies

Study	Treatment (IV)	N	Mean Age (SD) yrs	SELENA-SLEDAI at entry	Geographical distribution of patients	Ethnic make-up of trial participants			Number and location of study centres
L02 2006 Phase II 52 week	Bel 1 mg/kg Bel 4 mg/kg Bel 10 mg/kg Placebo	114 111 111 113	42 (11)	> 4 points	US (98%), Canada (2%)	Caucasian	NR*	69.9%	59 North America
						African American	NR*	24.7%	
						Latino	NR*	18.5%	
BLISS-52 Phase III 52 week	Bel 1 mg/kg Bel 10 mg/kg Placebo	288 290 287	36 (11)	> 6 points	Latin America (50%), Asia (38%), Eastern Europe & Australia (13%)	Caucasian	229	27%	90 in Pacific Asia. 11 in South America & Eastern Europe
						Asian	327	38%	
						Black/African Am	30	4%	
						Alaskan Native / American Indian	279	32%	
						Native Hawaiian / Pacific Islands	0	0%	
Multiracial	5	1%							
BLISS-76 Phase III 76 week	Bel 1 mg/kg Bel 10 mg/kg Placebo	271 273 275	40 (12)	> 6 points	US & Canada (53%), Western Europe (25%), Eastern Europe (11%), Latin America (11%)	Caucasian	569	70%	136 in North America & Europe

NR*=numbers not reported

Table 3: Outcomes reported for the BLISS-52 and 76 trials

Outcome	Measure	Outcome specification
SLE Responder Index (SRI*)	% responders at week 52	Primary outcome
Reduction in SLEDAI score by ≥ 4 points	% responders at week 52	Major secondary outcome
<i>Change in PGA score from baseline</i>	<i>Mean change at week 24</i>	<i>Major secondary outcome</i>
Steroid reduction weeks 40 to 52	% responders	Major secondary outcome
<i>SF-36 Physical component summary score</i>	<i>Mean change at week 24</i>	<i>Major secondary outcome</i>
SLE Responder Index	% responders at week 76	Major secondary outcome
<i>SLICC/ACR damage index</i>	<i>Mean change at week 52</i>	<i>Secondary outcome</i>
<i>FACIT-fatigue scale mean change from baseline</i>	<i>Mean change at clinic visits</i>	<i>Secondary outcome</i>
<i>EQ-5D score</i>	<i>Mean change at clinic visits</i>	<i>Secondary outcome</i>
<i>Change in PGA score from baseline</i>	<i>Mean change at week 52</i>	<i>Secondary outcome</i>
<i>SF-36 Physical component summary score</i>	<i>Mean change at week 52</i>	<i>Secondary outcome</i>
SLEDAI SLE flare index over 52 weeks	Time to first flare	Secondary outcome
SLE Responder Index (SRI)	% responders at timed clinic visits	Other outcome reported
Modified SLE responder index	% responders at week 52	Other outcome reported
No worsening in PGA score by ≥ 0.3	% responders at week 52	Other outcome reported
No new BILAG 1A/2B domain scores	% responders at week 52	Other outcome reported
<i>Change in SLEDAI score from baseline</i>	<i>Mean change at week 52</i>	<i>Other outcome reported</i>
Death	Number during exposure	Safety outcome
Treatment emergent adverse events	Number during exposure	Safety outcome
Serious infections	Number during exposure	Safety outcome
*Composite outcome measure consisting of ≥ 4 points improvement in SLEDAI score, no worsening in PGA by ≥ 0.3 points and no new BILAG 1A or 2B domain scores; FACIT = Functional Assessment of Chronic Illness Therapy; EQ-5D = EuroQoL 5 dimensions; BILAG = British Isles Lupus Assessment Group; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SF-36 = Short Form 36-Item Health Survey; SLICC = Systemic Lupus International Collaborating Clinics; ACR = American College of Rheumatology. Continuous outcomes are in <i>italics</i> .		



**Belimumab: a technological advance for SLE patients?
Report of a systematic review and meta-analysis**

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3 1 **Belimumab: a technological advance for Systemic Lupus Erythematosus patients?**
4 **Report of a systematic review and meta-analysis**
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53 34 **Short Title:**

54 35 Systematic review on belimumab for SLE
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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an auto-immune disease subject to relapse and remission. Incidence is estimated at between 1.0 and 10.0 per hundred thousand person years using different measures, and prevalence at between 20-70 per 100,000.^{1,2} SLE is a complex multi-organ disease with a number of different manifestations.³ Patients almost always have fatigue, often have skin rashes and arthritis and there is a wide variety of other problems which the disease can cause.

The American College of Rheumatology has defined 11 classification criteria, including: rash; photosensitivity; oral ulcers; arthritis; serositis; renal and neurological disorder.^{4,5} Assessment of the patient can be difficult, as flares of the disease have to be distinguished from its complications, from comorbidity especially infection, and from adverse effects of medications.⁶ SLE is more common in women (in most studies 90% or more of cases are women²) and in those from black and other ethnic groups. Recently age-adjusted incidence rates have been produced showing that rates are highest in women aged 40 years and over.⁷ Mortality rates show that five year survival is high, at over 90%^{8,9} and an overall SMR has been calculated as 2.4.¹⁰

Antinuclear antibodies are present in virtually all patients with SLE.¹¹ Anti-ds DNA antibodies are present in 50-60% patients at some point in their disease but often transiently with active disease.¹¹ Corticosteroids are the mainstay of treatment, they suppress disease but may themselves cause organ damage. The aim of treatment is to maintain normal function whilst suppressing disease activity and preventing organ damage,⁶ achieving these conflicting aims can be difficult. Other drugs used include antimalarials such as hydroxychloroquine, and immunosuppressive drugs such as azathioprine and mycophenolatemofetil. More recently rituximab (a monoclonal antibody which reacts with the CD20 antigen expressed on B cells) has also been used, although the largest trial undertaken to date failed to reach its end point.¹²

Belimumab (Benlysta®) is an IgG1 monoclonal antibody which inhibits the activity of the soluble cytokine BLyS (B lymphocyte stimulator; also known as BAFF).¹³ In contrast to earlier SLE treatments, belimumab is targeted at the fundamental pathology of SLE and has been widely interpreted as representing a step change in treatment options.¹³

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3 72 Belimumab was recently licensed in the USA and in Europe for treatment of autoantibody-
4 73 positive SLE and is the first drug to be so licensed for several decades. The European
5 74 indication is for severely affected SLE patients with active, autoantibody-positive disease
6 75 and a high degree of disease activity exemplified by positive anti-ds DNA and low
7 76 complement despite standard therapy.¹³ Belimumab is administered by IV infusion
8 77 recommended at 10 mg belimumab / kg on days 0, 14 and 28, and at 28 day intervals
9 78 thereafter. A course of belimumab treatment for a 64 kg patient using the US list price of
10 79 \$1,477 (£926.37) for a 400 mg vial¹⁴ would be \$56,527 (£35,454) per year, and according to
11 80 the US average whole sale price of \$4.432 (£2780) / 400 mg vial¹⁵ would be \$42,545
12 81 (£26,684) per year.
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20 83 A number of clinical measures have been developed for tracking the progression of SLE¹⁶
21 84 and for estimating the effects of treatment.¹⁷ They include the Physician's Global
22 85 Assessment (PGA), the SELENA-SLEDAI (Safety of Estrogen in Lupus National
23 86 Assessment-Systemic Lupus Erythematosus Disease Activity Index), the BILAG Index
24 87 (British Isles Lupus Assessment Group Index), and the SRI index (SLE Response Index).
25 88 Their major features are summarised in Figure 1. Their complexity means that outside
26 89 specialised centres they may not be widely used in routine clinical practice. The multiplicity
27 90 of SLE manifestations and of the systems developed to measure them has resulted in a
28 91 proliferation of outcome measures that can be reported in trials of interventions for SLE. This
29 92 in turn means that by chance at least some outcome measures will generate favourable
30 93 results for an intervention; hence the US Federal Drug agency (FDA) in conjunction with
31 94 belimumab-trialists developed the SRI aimed at guarding against the possibility that
32 95 worsening in overall disease might be masked by apparent improvement in a more narrowly
33 96 defined manifestation.
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46 100 Our objective was to synthesise findings from randomised controlled trials (RCTs) of
47 101 belimumab for patients with SLE and anti-nuclear and /or anti-ds DNA autoantibodies, to
48 102 make an overall assessment of the performance of this drug in relation to comparator
49 103 treatments using the SRI and other outcomes (as listed in Figure 1) and to assess the
50 104 findings of trials in the light of population samples and geographical factors.¹⁸
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55 106 **METHODS**

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3 108 The study was undertaken as part of work for the National Institute for Health Research,
4 109 Health Technology Assessment programme (Grant funding reference 10/73/01. Further
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6 110 information is available from:www.hta.ac.uk/).
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9 112 **Search scope**

10 113 We searched for RCTs investigating belimumab administered i.v. for patients with SLE and
11 114 anti-nuclear and /or anti-ds DNA autoantibodies. Comparators considered were belimumab
12 115 versus placebo and belimumab versus best supportive care. Outcomes included all disease-
13 116 related or health-status-related measures. There was no publication year restriction, but the
14 117 search was restricted to English language references only.
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17 119 **Search strategy**

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20 120 The following eight databases were searched: Cochrane Database of Systematic Reviews;
21 121 the Cochrane Central Register of Controlled Trials (CENTRAL); DARE; EMBASE; HTA
22 122 Database; Medline; Pre-Medline and Science Citation Index. Search strategies for these
23 123 databases used a combination of terms related to the population and interventions listed
24 124 above; the specific search strategies are provided in Appendix 1. In Medline and EMBASE
25 125 the subject strategies were combined with search strategies designed to identify RCTs.
26 126 (Appendix 1).
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28 127

29 128 Unpublished studies were identified using: Clinical Trials, Current Controlled Trials, EU
30 129 Clinical Trials Register, UK Clinical Research Network Study Portfolio, National Research
31 130 Register, WHO Clinical Trials Search Portal, NHS Evidence, Conference Proceedings
32 131 Citation Index -Science and Google.
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35 133 In addition, specific websites were searched: Medicines and Healthcare products Regulatory
36 134 Agency (MHRA), European Medicines Agency (EMA), US Food and Drug Administration
37 135 (FDA) and the following specific conference proceedings: American College of
38 136 Rheumatology, British Society of Rheumatology and the European League Against
39 137 Rheumatism (EULAR).
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42 139 *Inclusion criteria:* Publications were included if they described results from RCTs of
43 140 belimumab for SLE patients with positive autoantibodies. Two reviewers independently
44 141 assessed retrieved publications for inclusion. There were no disagreements between
45 142 reviewers.
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3 144 *Date extraction:* Potentially relevant publications were obtained in full text and assessed by
4 145 the same two reviewers. One reviewer extracted data for all specified primary and secondary
5 146 outcome measures, for adverse events and deaths. A second reviewer checked extracted
6 147 data.
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11 149 *Quality evaluation:* Quality assessment and risk of bias was guided by the Centre for
12 150 Reviews and Dissemination (CRD) checklist¹⁹ based on all information in the included
13 151 publications which specifies reporting of randomisation, concealment of allocation, group
14 152 balance, blinding, drop-outs, outcome reporting bias, and whether intention to treat analysis
15 153 was used.
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20 155 *Statistical analysis:* Unadjusted odds ratios (ORs) and mean differences were calculated for
21 156 binary and continuous outcomes respectively. Statistical heterogeneity was calculated using
22 157 the I² statistic.^{20;21} There were too few studies for an analysis of publication bias.²¹
23 158 Adjusted outcome measures were tabulated where these were reported. A random effects
24 159 meta-analysis²² was undertaken using the DerSimonian Laird method in STATA version
25 160 11..²³ All graphs were prepared in Microsoft Excel 2010.
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32 163 **RESULTS**

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34 165 **Characteristics of included studies**

35 166 We identified three placebo controlled RCTs of belimumab versus standard care: the phase
36 167 III trials termed BLISS-52²⁴ and BLISS-76²⁵ and a phase II trial (study L02).²⁶ The PRISMA
37 168 flow chart shows the process of identification of publications (see Figure 2). We identified an
38 169 on-going trial in Asia.²⁷ All three completed trials appeared to be of good quality; however
39 170 details of allocation concealment were meagre (Table 1).
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52 176 BLISS-52,²⁴ BLISS-76²⁵ and study L02²⁶ have been published in peer reviewed journals,
53 177 however the fullest accounts in the public domain are in the FDA licensing approval
54 178 documents^{28;29} and the manufacturer's 2011 submission to the UK National Institute of
55 179 Health and Clinical Excellence (NICE).³⁰ Each of these placebo-controlled randomised trials
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3 180 was designed with multiple randomised groups. In the L02 trial, patients received 1 or 4 or
4 181 10 mg/kg of belimumab or placebo, while in the BLISS trials the belimumab dose regimens
5 182 were 1mg/kg or 10 mg/kg. Both US and European licensing is for the 10mg/kg dose
6 183 regimen. In this article we focus on efficacy results for the 10mg/kg licensed regimen relative
7 184 to placebo. We also consider the off licence 1 mg/kg and 4 mg/kg dose regimens for
8 185 investigation of adverse events.
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12 187 Centralised, stratified randomisation was used in all three trials and arms were generally well
13 188 balanced. For the phase III trials, stratification was undertaken according to race, baseline
14 189 proteinuria and disease activity score (SELENA SLEDAI); for the phase I study, disease
15 190 activity only was used as a stratification factor. All three trials recruited predominantly
16 191 female patients (~90%) and were described as double blind. The two BLISS studies were
17 192 conducted according to similar protocols.
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21 194 There were differences in geographical distribution of the study centres and in the resulting
22 195 ethnic racial make-up of the study populations (Table 2 and Figure 3). Thus in BLISS-76,
23 196 70% were Caucasian, 13% native American and 3% Asian, respectively, whereas in BLISS-
24 197 52, 27% were Caucasian, 32% native American and 38% were Asian. Table 3 lists the major
25 198 protocol pre-specified outcomes in the BLISS trials.
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29 200 There were additional population differences between BLISS and L02 trials at recruitment.
30 201 Reporting of results for patients with anti-nuclear and /or anti-ds DNA autoantibodies in L02
31 202 was only included for a post-hoc subgroup and primary outcomes measured in L02 were not
32 203 comparable with those of the BLISS studies. For these reasons, L02 study results are
33 204 included here only with regard to safety outcomes. For the BLISS trials a composite novel
34 205 primary outcome measure was developed *a priori* from discussions between the FDA and
35 206 the manufacturer and termed the SLE Response Index (SRI) (see Figure 1 and Table 3).
36 207 The protocol pre-specified primary end point was the proportion of SRI responders at week
37 208 52. This is taken as the primary outcome in this systematic review.
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3 216 **[Insert Figure 4 here]**

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6 218 Efficacy results in the two BLISS trials for major binary effectiveness outcomes including the
7 219 time to first SLE flare and to first severe flare are summarised in Figure 4. ORs have been
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9 220 calculated using the proportions of patients with and without events reported in the journal
10 221 articles for these trials.^{24;25} Safety outcomes shown in Figure 4 were calculated after pooling
11 222 the number of events across the three trials (L02, BLISS-52 and BLISS-76) and are taken
12 223 from the FDA documents. The hazard ratios (HRs) for time to flares were poorly reported in
13 224 journal articles and the data presented are taken from the manufacturer's submission to the
14 225 FDA.^{28;29} As shown in Figure 4 both trials satisfied this primary end point with a better result
15 226 for BLISS-52. The difference in percentage responders in the belimumab group relative to
16 227 placebo group was larger in BLISS-52 (14%), than in in BLISS-76 (9.4%).
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229 For the other binary effectiveness outcomes, the BLISS-52 trial delivered results which were
230 more favourable to belimumab than did BLISS-76, with the latter results failing to reach a
231 conventional level of statistical significance except for the ≥ 4 point improvement in SLEDAI
232 score at week 52. The journal articles and manufacturer's submissions to the FDA and to
233 NICE used a logistic regression model and reported ORs adjusted according to the
234 stratification factors employed at randomisation. Adjusted ORs for a response in BLISS-52
235 and in BLISS-76 were respectively 1.83 (95% CI: 1.30-2.59; $p = 0.0006$) and 1.52 (95% CI:
236 1.07-2.15; $p = 0.0207$). Again a superior response was found for the BLISS-52 trial. By
237 week 76, the unadjusted OR for the SRI response in the BLISS-76 trial ceased to reach
238 statistical significance (Figure 4); this also held for the reported OR adjusted by logistic
239 regression (OR 1.31, 95% CI: 0.92 – 1.87, $p = 0.1323$).²⁹
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242 With regard to time to first flare or to first severe flare (each estimated over 52 weeks follow
243 up) the responses reported in the FDA submission are again superior for BLISS-52. Each
244 outcome failed to reach conventional statistical significance for BLISS-76. The FDA
245 submission additionally reported more mature results estimated over 76 weeks of follow up
246 for BLISS-76, and again these indicate lack of statistical significance for both outcomes (HR
247 for first flare: 1.05, 95% CI: 0.88 – 1.27; HR for first severe flare 1.30, 95% CI: 0.92 – 1.85).

248

249 Figure 4 shows the results for major safety outcomes. Although there were more serious
250 adverse events, more serious infections and more deaths associated with belimumab than
251 with placebo, none of the ORs for these outcomes reached statistical significance. There
252 were 14 deaths during the controlled phase of the three trials; three in the placebo group
($n=675$), and 11 in the belimumab groups ($n=1458$) with six in the 10mg/kg and five in the

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3 253 1mg/kg groups, respectively (odds ratio 11.7; 95% CI 0.474 to 6.124). The causes of death
4 254 were various: five were infection-related, three were strokes, three cardiovascular events,
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6 255 two suicides, one cancer, one from SLE-related complications, and two were of unknown
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8 256 cause.
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11 258 Results for continuous outcomes are summarised in Figure 5. Mean changes from baseline
12 259 reported in the BLISS journal articles and in the manufacturer's submissions to the FDA and
13 260 NICE have been used to generate a mean difference statistic (sometimes termed "weighted
14 261 mean difference"³¹). These revealed superiority of response in BLISS-52 relative to BLISS-
15 262 76 for all reported outcomes, a pattern similar to that for binary outcomes. Mean changes
16 263 from baseline for FACIT-fatigue scores and for EQ-5D utility scores (not pictured) did not
17 264 reach statistical significance and again improvement seen in BLISS-52 for these was
18 265 superior to that seen in BLISS-76.
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21 267 In summary, BLISS-52 showed a systematic superiority over BLISS-76 in apparent benefit of
22 268 belimumab across the full range of effectiveness outcomes (binary, time to event and
23 269 continuous), which may reflect geographical differences between the trials (Table 2 and
24 270 Figure 3). The primary outcome in BLISS-76 was achieved (adjusted OR 1.52, 95% CI 1.07
25 271 to 2.15) but large geographical differences within BLISS-76 were striking: rates of 32% (46
26 272 out of 145), and 35% (47 out of 136), for placebo and belimumab respectively, were reported
27 273 for patients from North America and Canada (a < 3% greater response for belimumab),
28 274 whereas for BLISS-76 patients outside these regions a > 15% greater response for
29 275 belimumab over placebo was reported, 71 of 137 (51.8%) for belimumab and 47 of 130
30 276 (36.1%) for placebo. In comparison, the corresponding rates for patients from Latin America
31 277 in BLISS-52 were 49% placebo (71 out of 145), and 61% belimumab (85 out of 140).
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43 279 **[Insert Figure 5 here]**

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45 281 The manufacturer's submissions to the FDA and to NICE combined results from the two
46 282 BLISS trials by pooling the patients and applying the logistic regression model described
47 283 above; for the primary outcome (proportion of SRI responders at week 52), the difference
48 284 between the belimumab and placebo groups was 11.8%.²⁸
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53 286 An alternate method of combining trials by meta-analysis of study level results from the two
54 287 BLISS trials showed a statistically significant benefit of belimumab for most main outcomes
55 288 including SRI, SELENA-SLEDAI, worsening in PGA, steroid use, BILAG score or, time to
56 289 first severe flare, and mean number of flares and severe flares over 52 weeks and weeks 24
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3 290 to 52 (Figure 6). Tests for statistical heterogeneity of ORs and HR outcomes were not
4 291 significant. These results, and those from pooling individual patient data from the two trials
5 292 prior to logistic regression, mask the systematic difference between trials across all
6 293 outcomes.
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11 295 **[Insert Figure 6 here]**
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13 14 297 **DISCUSSION**

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16 298 We undertook a systematic review of the clinical effectiveness of belimumab, a new
17 299 treatment targeted at systemic lupus erythematosus (SLE) patients with anti-nuclear and /or
18 300 anti-ds DNA autoantibodies. We performed an extensive search and systematic review of
19 301 both completed and on-going trials using a number of databases and by checking reference
20 302 lists. Data were extracted independently and studies were quality assessed. Random effects
21 303 meta-analysis was undertaken.
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27 305 We identified three RCTs (L02, BLISS-52, BLISS-76) reporting data on over 2000 patients.
28 306 In contrast to the BLISS trials, L02 recruited patients who were not necessarily current
29 307 carriers of anti-nuclear or anti ds DNA antibodies at study commencement. L02 failed to
30 308 demonstrate clinical effectiveness for its primary end points.²⁶ Meta-analysis of the BLISS
31 309 studies showed a benefit of belimumab with the main primary outcome (SRI), showing
32 310 improvement at 52 weeks (OR 1.63; 95% CI: 1.27-2.09 p<0.001) although by week 76, the
33 311 proportion of SRI responders in the BLISS-76 trial ceased to reach statistical significance
34 312 (OR 1.31; 95% CI: 0.92–1.87 p=0.1323). There were no significant differences between
35 313 placebo and intervention groups in quality of life or adverse events.
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42 315 We found that the benefits of belimumab were systematically greater across the board
43 316 (although not significantly so) in the BLISS-52 trial and although tests for statistical
44 317 heterogeneity were negative, geographical location of study centres and the racial
45 318 background and ethnicity of participants varied considerably. If the two BLISS trials were
46 319 drawn from the same underlying populations, whilst one might expect outcomes to differ, we
47 320 would anticipate that this would occur randomly between trials– some better some worse
48 321 than the other.
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53 323 A few studies have directly assessed the existence of and importance of geographical
54 324 differences in trial outcomes.³²⁻³⁴ Key factors contributing to such differences are variation in
55 325 underlying patient population characteristics and variation in study execution. Vickers et al,³³
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3 326 found that Eastern Asian and Eastern European studies had a higher proportion of positive
4 327 trial results when compared to other countries. This is seen in the present case for the
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6 328 primary outcome where both the belimumab and placebo response rates in BLISS 52 study
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8 329 were greater than those in BLISS-76 and, remarkably, the placebo response rate in BLISS-
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10 330 52 (49%) was greater than that for the belimumab arm of BLISS-76 (43%). O'Shea and
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12 331 DeMets also report that within the Beta-Blocker Heart Attack Trial (BHAT), not only was
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14 332 there a difference in the direction, but also in the size of treatment effect between Canada
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16 333 and the US, although it should be noted that the original aim of that trial was not
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18 334 investigation of international differences in treatment effect.³⁵ One study found that 96-99%
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20 335 of the total variance in the "Global utilisation of strategies to open occluded coronary arteries
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22 336 IV acute coronary syndromes" (GUSTO IV ACS) trial could be accounted for by patient-level
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24 337 factors.³⁶

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28 339 International trials need to harmonise training of investigators, patient selection, treatment
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30 340 management, thresholds to centre admission, access to facilities, ascertainment of
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32 341 endpoints and, by implication, results of interest³⁷⁻⁴⁴ since it is possible that in centres in
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34 342 different countries these factors may differ systematically.³⁷ Equally, underlying differences
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36 343 in populations and countries (ethnicity, genetics, socio-economic status and health-care
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38 344 systems), and the nature and epidemiology of SLE according to ethnic background may
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40 345 result in differences in reporting of outcomes and pooled results.

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44 347 The outcomes used in the BLISS trials would be unfamiliar to most of the investigators and it
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46 348 is possible that criteria may have differed between countries. In particular the Physician
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48 349 Global Assessment (PGA) is an important element of the outcomes measured (see Figure
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50 350 1). PGA was measured as an outcome in itself, and it is also incorporated in SRI. PGA is of
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52 351 concern because as a global physician assessment of a patient's SLE status, it is subjective.
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54 352 The investigators reported a nearly 10% difference between the BLISS-52 and BLISS-76
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56 353 studies in estimates of percentage change in PGA score in intervention groups at week 24
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58 354 compared to baseline and this single result in one of the two trials is likely to have had an
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60 355 important influence on findings of the effectiveness of belimumab in SLE patients.

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64 357 The latest results of belimumab in patients with SLE (phase II study design, uncontrolled
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66 358 extension study) reported that of 449 patients with active SLE (USA/Canada) 177 (39.4%)
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68 359 patients remained on treatment after 7 years of therapy (i.e. approximately 1746 cumulative
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70 360 patients-years) and that this subgroup exhibited durable sustained improvement in SLE
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362 361 disease activity (SRI and PGA).³⁰

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3 363 **CONCLUSIONS**

4 364 In conclusion, systematic review and random effects meta-analysis of two RCTs of
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6 365 belimumab for patients with autoantibody positive SLE demonstrated positive results in the
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8 366 main outcome at week 52. However, in view of the different populations studied at different
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10 367 locations in the BLISS trials and the consistently superior results from one trial compared to
11
12 368 the other, we consider that population heterogeneity, geographical differences and variation
13
14 369 in trial conduct and outcome assessment, may have played a role in influencing outcomes.
15
16 370 However the generalisability of results pooled meta-analytically or by logistic regression
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18 371 should be viewed with caution and we suggest that it is too early to draw strong conclusions
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20 372 in this case.
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32 374 **ARTICLE FOCUS**

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- 375 • SLE is a complex multi-organ auto-immune disease subject to relapse and remission.
 - 376 • Patients almost always have fatigue, skin rashes and arthritis and there is a wide
377 variety of other problems which the disease can cause.
 - 378 • Belimumab is a new treatment specifically targeted against SLE.

379
380 **KEY MESSAGES**

- 381
382 1. Combining the results from two RCTs suggests that belimumab is clinically effective
383 for SLE patients.
- 384 2. However, all outcomes were systematically superior in one trial compared with the
385 other.
- 386 3. Different trial conduct and populations mean that it is too early to draw generalisable
387 conclusions.
388

389 **STRENGTHS AND LIMITATIONS**

- 390 • At first sight combined meta analytic evidence suggests that belimumab is clinically
391 effective for patients with severe SLE.
- 392 • We suggest that it is too early to draw strong conclusions because the two relevant
393 trials cover different populations in different countries and there may be differences in
394 trial conduct and outcome assessment.
395

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2
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5
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8
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11
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13 403

14
15 404 **Competing interest statement**

16 405 No conflicts of interest.

17
18 406

19 407 **Contributions:**

20
21 408 N-BK: Conception and design. Data analysis and interpretation. Drafting the article. Critical
22
23 409 revisions for important intellectual content. Approval of final article for submission.

24 410 MC: Conception and design. Data analysis and interpretation. Literature review.

25
26 411 Interpretation of results. Drafting the article. Critical revisions for important intellectual
27
28 412 content. Approval of final article for submission.

29 413 AG: Interpretation of results. Critical revisions for important intellectual content.

30 414 PS: Literature review. Interpretation of results. Critical revisions for important intellectual
31
32 415 content.

33 416 SM: Data analysis and interpretation. Interpretation of results. Critical revisions for important
34
35 417 intellectual content.

36 418 LH: Literature review. Interpretation of results. Critical revisions for important intellectual
37
38 419 content.

39 420 RC: Literature review. Critical revisions for important intellectual content.

40 421 EC: Interpretation of results. Critical revisions for important intellectual content.

41 422 CG: Interpretation of results. Critical revisions for important intellectual content.

42
43 423 AC: Conception and design. Interpretation of results. Drafting the article. Critical revisions
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45 424 for important intellectual content. Approval of final article for submission.

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47 425 All authors read and approved the final manuscript.

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1 **Belimumab: a technological advance for Systemic Lupus Erythematosus patients?**
2 **Report of a systematic review and meta-analysis**

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34 **Short Title:**

35 Systematic review on belimumab for SLE

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537 **INTRODUCTION**

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39 **Systemic Lupus Erythematosus** (SLE) is an auto-immune disease subject to relapse and
40 remission. Incidence is estimated at between 1.0 and 10.0 per hundred thousand person
41 years using different measures, and prevalence at between 20-70 per 100,000.^{1,2} SLE is a
42 complex multi-organ disease with a number of different manifestations.³ Patients almost
43 always have fatigue, often have skin rashes and arthritis and there is a wide variety of other
44 problems which the disease can cause.

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46 The American College of Rheumatology has defined 11 classification criteria, including:
47 rash; photosensitivity; oral ulcers; arthritis; serositis; renal and neurological disorder.^{4,5}

48 Assessment of the patient can be difficult, as flares of the disease have to be distinguished
49 from its complications, from comorbidity especially infection, and from adverse effects of
50 medications.⁶ SLE is more common in women (in most studies 90% or more of cases are
51 women²) and in those from black and **other ethnic groups**. Recently age-adjusted incidence
52 rates have been produced showing that rates are highest in women aged 40 years and
53 over.⁷ Mortality rates show that five year survival is high, at over 90%^{8,9} and **an** overall SMR
54 has been calculated as 2.4.¹⁰

32 55

56 Antinuclear antibodies are present in virtually all patients with SLE.¹¹ Anti-ds DNA antibodies
57 are present in 50-60% patients at some point in their disease but often transiently with active
58 disease.¹¹ Corticosteroids are the mainstay of treatment, **they suppress disease but may**
59 **themselves cause organ damage**. The aim of treatment is to maintain normal function whilst
60 suppressing disease activity and preventing organ damage,⁶ achieving these conflicting
61 aims can be difficult. Other drugs used include antimalarials such as hydroxychloroquine,
62 and immunosuppressive drugs such as azathioprine and mycophenolatemofetil. More
63 recently rituximab (a monoclonal antibody which reacts with the CD20 antigen expressed on
64 B cells) has also been used, although the largest trial undertaken to date failed to reach its
65 end point.¹²

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67 Belimumab (Benlysta®) is an IgG1 monoclonal antibody which inhibits the activity of the
68 soluble cytokine BLyS (B lymphocyte stimulator; also known as BAFF).¹³ In contrast to
69 earlier SLE treatments, belimumab is targeted at the fundamental pathology of SLE and has
70 been widely interpreted as representing a step change in treatment options.¹³

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3 72 Belimumab was recently licensed in the USA and in Europe for treatment of autoantibody-
4 73 positive SLE and is the first drug to be so licensed for several decades. The European
5 74 indication is for severely affected SLE patients with active, autoantibody-positive disease
6 75 and a high degree of disease activity exemplified by positive anti-ds DNA and low
7 76 complement despite standard therapy.¹³ Belimumab is administered by IV infusion
8 77 recommended at 10 mg belimumab / kg on days 0, 14 and 28, and at 28 day intervals
9 78 thereafter. A course of belimumab treatment for a 64 kg patient using the US list price of
10 79 \$1,477 (£926.37) for a 400 mg vial¹⁴ would be \$56,527 (£35,454) per year, and according to
11 80 the US average whole sale price of \$4.432 (£2780) / 400 mg vial¹⁵ would be \$42,545
12 81 (£26,684) per year.
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20 83 A number of clinical measures have been developed for tracking the progression of SLE¹⁶
21 84 and for estimating the effects of treatment.¹⁷ They include the Physician's Global
22 85 Assessment (PGA), the SELENA-SLEDAI (Safety of Estrogen in Lupus National
23 86 Assessment-Systemic Lupus Erythematosus Disease Activity Index), the BILAG Index
24 87 (British Isles Lupus Assessment Group Index), and the SRI index (SLE Response Index).
25 88 Their major features are summarised in Figure 1. Their complexity means that outside
26 89 specialised centres they may not be widely used in routine clinical practice. **The multiplicity
27 90 of SLE manifestations and of the systems developed to measure them has resulted in a
28 91 proliferation of outcome measures that can be reported in trials of interventions for SLE. This
29 92 in turn means that by chance at least some outcome measures will generate favourable
30 93 results for an intervention; hence the US Federal Drug agency (FDA) in conjunction with
31 94 belimumab-trialists developed the SRI aimed at guarding against the possibility that
32 95 worsening in overall disease might be masked by apparent improvement in a more narrowly
33 96 defined manifestation!**
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42 98 **[Insert Figure 1 here]**
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46 100 Our objective was to synthesise findings from randomised controlled trials (RCTs) of
47 101 belimumab for patients with SLE and anti-nuclear and /or anti-ds DNA autoantibodies, to
48 102 make an overall assessment of the performance of this drug in relation to comparator
49 103 treatments using the SRI and other outcomes (as listed in Figure 1) and to assess the
50 104 findings of trials in the light of population samples and geographical factors.¹⁸
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55 106 METHODS

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108 The study was undertaken as part of work for the National Institute for Health Research,
109 Health Technology Assessment programme (Grant funding reference 10/73/01. Further
110 information is available from:www.hta.ac.uk/).

111

112 **Search scope**

113 We searched for RCTs investigating belimumab administered i.v. for patients with SLE and
114 anti-nuclear and /or anti-ds DNA autoantibodies. Comparators considered were belimumab
115 versus placebo and belimumab versus best supportive care. Outcomes included all disease-
116 related or health-status-related measures. There was no publication year restriction, but the
117 search was restricted to English language references only.

118

119 **Search strategy**

120 The following eight databases were searched: Cochrane Database of Systematic Reviews;
121 the Cochrane Central Register of Controlled Trials (CENTRAL); DARE; EMBASE; HTA
122 Database; Medline; Pre-Medline and Science Citation Index. Search strategies for these
123 databases used a combination of terms related to the population and interventions listed
124 above; the specific search strategies are provided in Appendix 1. In Medline and EMBASE
125 the subject strategies were combined with search strategies designed to identify RCTs.
126 (Appendix 1).

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128 Unpublished studies were identified using: Clinical Trials, Current Controlled Trials, EU
129 Clinical Trials Register, UK Clinical Research Network Study Portfolio, National Research
130 Register, WHO Clinical Trials Search Portal, NHS Evidence, Conference Proceedings
131 Citation Index -Science and Google.

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133 In addition, specific websites were searched: Medicines and Healthcare products Regulatory
134 Agency (MHRA), European Medicines Agency (EMA), US Food and Drug Administration
135 (FDA) and the following specific conference proceedings: American College of
136 Rheumatology, British Society of Rheumatology and the European League Against
137 Rheumatism (EULAR).

138

139 *Inclusion criteria:* Publications were included if they described results from RCTs of
140 belimumab for SLE patients with positive autoantibodies. Two reviewers **independently**
141 assessed retrieved publications for inclusion. **There were no disagreements between**
142 **reviewers.**

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3 144 *Date extraction:* Potentially relevant publications were obtained in full text and assessed by
4 145 the same two reviewers. One reviewer extracted data for all specified primary and secondary
5 146 outcome measures, for adverse events and deaths. A second reviewer checked extracted
6 147 data.
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10 149 *Quality evaluation:* Quality assessment and risk of bias was guided by the **Centre for**
11 **Reviews and Dissemination** (CRD) checklist¹⁹ based on all information in the included
12 150 publications which specifies reporting of randomisation, concealment of allocation, group
13 151 balance, blinding, drop-outs, outcome reporting bias, and whether intention to treat analysis
14 152 was used.
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17 155 *Statistical analysis:* Unadjusted odds ratios (ORs) and mean differences were calculated for
18 156 binary and continuous outcomes respectively. Statistical heterogeneity was calculated using
19 157 the I² statistic.^{20;21} **There were too few studies for an analysis of publication bias.**²¹
20 158 Adjusted outcome measures were tabulated where these were reported. A random effects
21 159 meta-analysis²² was undertaken using the **DerSimonian Laird** method in STATA version
22 160 11..²³ **All graphs were prepared in Microsoft Excel 2010.**
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26 164 **RESULTS**

27 165 **Characteristics of included studies**

28 166 We identified three placebo controlled RCTs of belimumab versus standard care: the phase
29 167 III trials termed BLISS-52²⁴ and BLISS-76²⁵ and a phase II trial (study L02).²⁶ The PRISMA
30 168 flow chart shows the process of identification of publications (see Figure 2). We identified an
31 169 on-going trial in Asia.²⁷ All three completed trials appeared to be of good quality; however
32 170 details of allocation concealment were meagre (Table 1).
33 171

34 172 **[Insert Table 1 here]**

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36 174 **[Insert Figure 2 here]**
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38 176 BLISS-52,²⁴ BLISS-76²⁵ and study L02²⁶ have been published in peer reviewed journals,
39 177 however the fullest accounts in the public domain are in the FDA licensing approval
40 178 documents^{28;29} and the manufacturer's 2011 submission to the UK National Institute of
41 179 Health and Clinical Excellence (NICE).³⁰ Each of these placebo-controlled randomised trials
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3 180 was designed with multiple randomised groups. In the L02 trial, patients received 1 or 4 or
4 181 10 mg/kg of belimumab or placebo, while in the BLISS trials the belimumab dose regimens
5 182 were 1mg/kg or 10 mg/kg. Both US and European licensing is for the 10mg/kg dose
6 183 regimen. In this article we focus on efficacy results for the 10mg/kg licensed regimen relative
7 184 to placebo. We also consider the off licence 1 mg/kg and 4 mg/kg dose regimens for
8 185 investigation of adverse events.
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13 187 Centralised, stratified randomisation was used in all three trials and arms were generally well
14 188 balanced. For the phase III trials, stratification was undertaken according to race, baseline
15 189 proteinuria and disease activity score (SELENA SLEDAI); for the phase I study, disease
16 190 activity only was used as a stratification factor. All three trials recruited predominantly
17 191 female patients (~90%) and were described as double blind. The two BLISS studies were
18 192 conducted according to similar protocols.
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25 194 There were differences in geographical distribution of the study centres and in the resulting
26 195 ethnic racial make-up of the study populations (Table 2 and Figure 3). Thus in BLISS-76,
27 196 70% were Caucasian, 13% native American and 3% Asian, respectively, whereas in BLISS-
28 197 52, 27% were Caucasian, 32% native American and 38% were Asian. Table 3 lists the major
29 198 protocol pre-specified outcomes in the BLISS trials.
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34 200 There were additional population differences between BLISS and L02 trials at recruitment.
35 201 Reporting of results for patients with anti-nuclear and /or anti-ds DNA autoantibodies in L02
36 202 was only included for a post-hoc subgroup and primary outcomes measured in L02 were not
37 203 comparable with those of the BLISS studies. For these reasons, L02 study results are
38 204 included here only with regard to safety outcomes. For the BLISS trials a composite novel
39 205 primary outcome measure was developed *a priori* from discussions between the FDA and
40 206 the manufacturer and termed the SLE Response Index (SRI) (see Figure 1 and Table 3).
41 207 The protocol pre-specified primary end point was the proportion of SRI responders at week
42 208 52. This is taken as the primary outcome in this systematic review.
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50 **[Insert Table 2 here]**

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52 **[Insert Figure 3 here]**

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6 218 Efficacy results in the two BLISS trials for major binary effectiveness outcomes including the
7 219 time to first SLE flare and to first severe flare are summarised in Figure 4. ORs have been
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9 220 calculated using the proportions of patients with and without events reported in the journal
10 221 articles for these trials.^{24;25} Safety outcomes shown in Figure 4 were calculated after pooling
11 222 the number of events across the three trials (L02, BLISS-52 and BLISS-76) and are taken
12 223 from the FDA documents. The hazard ratios (HRs) for time to flares were poorly reported in
13 224 journal articles and the data presented are taken from the manufacturer's submission to the
14 225 FDA.^{28;29} As shown in Figure 4 both trials satisfied this primary end point with a better result
15 226 for BLISS-52. The difference in percentage responders in the belimumab group relative to
16 227 placebo group was larger in BLISS-52 (14%), than in in BLISS-76 (9.4%).
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23 229 For the other binary effectiveness outcomes, the BLISS-52 trial delivered results which were
24 230 more favourable to belimumab than did BLISS-76, with the latter results failing to reach a
25 231 conventional level of statistical significance except for the ≥ 4 point improvement in SLEDAI
26 232 score at week 52. The journal articles and manufacturer's submissions to the FDA and to
27 233 NICE used a logistic regression model and reported ORs adjusted according to the
28 234 stratification factors employed at randomisation. Adjusted ORs for a response in BLISS-52
29 235 and in BLISS-76 were respectively 1.83 (95% CI: 1.30-2.59; $p = 0.0006$) and 1.52 (95% CI:
30 236 1.07-2.15; $p = 0.0207$). Again a superior response was found for the BLISS-52 trial. By
31 237 week 76, the unadjusted OR for the SRI response in the BLISS-76 trial ceased to reach
32 238 statistical significance (Figure 4); this also held for the reported OR adjusted by logistic
33 239 regression (OR 1.31, 95% CI: 0.92 – 1.87, $p = 0.1323$).²⁹
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41 241 With regard to time to first flare or to first severe flare (each estimated over 52 weeks follow
42 242 up) the responses reported in the FDA submission are again superior for BLISS-52. Each
43 243 outcome failed to reach conventional statistical significance for BLISS-76. The FDA
44 244 submission additionally reported more mature results estimated over 76 weeks of follow up
45 245 for BLISS-76, and again these indicate lack of statistical significance for both outcomes (HR
46 246 for first flare: 1.05, 95% CI: 0.88 – 1.27; HR for first severe flare 1.30, 95% CI: 0.92 – 1.85).
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51 247
52 248 Figure 4 shows the results for major safety outcomes. Although there were more serious
53 249 adverse events, more serious infections and more deaths associated with belimumab than
54 250 with placebo, none of the ORs for these outcomes reached statistical significance. There
55 251 were 14 deaths during the controlled phase of the three trials; three in the placebo group
56 252 (n=675), and 11 in the belimumab groups (n=1458) with six in the 10mg/kg and five in the
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3 253 1mg/kg groups, respectively (odds ratio 11.7; 95% CI 0.474 to 6.124). The causes of death
4 254 were various: five were infection-related, three were strokes, three cardiovascular events,
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6 255 two suicides, one cancer, one from SLE-related complications, and two were of unknown
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8 256 cause.
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12 258 Results for continuous outcomes are summarised in Figure 5. Mean changes from baseline
13 259 reported in the BLISS journal articles and in the manufacturer's submissions to the FDA and
14 260 NICE have been used to generate a mean difference statistic (sometimes termed "weighted
15 261 mean difference"³¹). These revealed superiority of response in BLISS-52 relative to BLISS-
16 262 76 for all reported outcomes, a pattern similar to that for binary outcomes. Mean changes
17 263 from baseline for FACIT-fatigue scores and for EQ-5D utility scores (not pictured) did not
18 264 reach statistical significance and again improvement seen in BLISS-52 for these was
19 265 superior to that seen in BLISS-76.
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21 267 In summary, BLISS-52 showed a systematic superiority over BLISS-76 in apparent benefit of
22 268 belimumab across the full range of effectiveness outcomes (binary, time to event and
23 269 continuous), which may reflect geographical differences between the trials (Table 2 and
24 270 Figure 3). The primary outcome in BLISS-76 was achieved (adjusted OR 1.52, 95% CI 1.07
25 271 to 2.15) but large geographical differences within BLISS-76 were striking: rates of 32% (46
26 272 out of 145), and 35% (47 out of 136), for placebo and belimumab respectively, were reported
27 273 for patients from North America and Canada (a < 3% greater response for belimumab),
28 274 whereas for BLISS-76 patients outside these regions a > 15% greater response for
29 275 belimumab over placebo was reported, 71 of 137 (51.8%) for belimumab and 47 of 130
30 276 (36.1%) for placebo. In comparison, the corresponding rates for patients from Latin America
31 277 in BLISS-52 were 49% placebo (71 out of 145), and 61% belimumab (85 out of 140).
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45 281 The manufacturer's submissions to the FDA and to NICE combined results from the two
46 282 BLISS trials by pooling the patients and applying the logistic regression model described
47 283 above; for the primary outcome (proportion of SRI responders at week 52), the difference
48 284 between the belimumab and placebo groups was 11.8%.²⁸
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52 286 An alternate method of combining trials by meta-analysis of study level results from the two
53 287 BLISS trials showed a statistically significant benefit of belimumab for most main outcomes
54 288 including SRI, SELENA-SLEDAI, worsening in PGA, steroid use, BILAG score or, time to
55 289 first severe flare, and mean number of flares and severe flares over 52 weeks and weeks 24
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3 290 to 52 (Figure 6). Tests for statistical heterogeneity of ORs and HR outcomes were not
4 291 significant. These results, and those from pooling individual patient data from the two trials
5 292 prior to logistic regression, mask the systematic difference between trials across all
6 293 outcomes.
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11 295 **[Insert Figure 6 here]**
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13 14 297 **DISCUSSION**

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16 298 We undertook a systematic review of the clinical effectiveness of belimumab, a new
17 299 treatment targeted at systemic lupus erythematosus (SLE) patients with anti-nuclear and /or
18 300 anti-ds DNA autoantibodies. We performed an extensive search and systematic review of
19 301 both completed and on-going trials using a number of databases and by checking reference
20 302 lists. Data were extracted independently and studies were quality assessed. Random effects
21 303 meta-analysis was undertaken.
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27 305 We identified three RCTs (L02, BLISS-52, BLISS-76) reporting data on over 2000 patients.
28 306 In contrast to the BLISS trials, L02 recruited patients who were not necessarily current
29 307 carriers of anti-nuclear or anti ds DNA antibodies at study commencement. L02 failed to
30 308 demonstrate clinical effectiveness for its primary end points.²⁶ Meta-analysis of the BLISS
31 309 studies showed a benefit of belimumab with the main primary outcome (SRI), showing
32 310 improvement at 52 weeks (OR 1.63; 95% CI: 1.27-2.09 p<0.001) although by week 76, the
33 311 proportion of SRI responders in the BLISS-76 trial ceased to reach statistical significance
34 312 (OR 1.31; 95% CI: 0.92–1.87 p=0.1323). There were no significant differences between
35 313 placebo and intervention groups in quality of life or adverse events.
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42 315 We found that the benefits of belimumab were systematically greater across the board
43 316 (although not significantly so) in the BLISS-52 trial and although tests for statistical
44 317 heterogeneity were negative, geographical location of study centres and the racial
45 318 background and ethnicity of participants varied considerably. If the two BLISS trials were
46 319 drawn from the same underlying populations, whilst one might expect outcomes to differ, we
47 320 would anticipate that this would occur randomly between trials— some better some worse
48 321 than the other.
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53 323 A few studies have directly assessed the existence of and importance of geographical
54 324 differences in trial outcomes.³²⁻³⁴ Key factors contributing to such differences are variation in
55 325 underlying patient population characteristics and variation in study execution. Vickers et al,³³
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3 326 found that Eastern Asian and Eastern European studies had a higher proportion of positive
4 327 trial results when compared to other countries. This is seen in the present case for the
5 328 primary outcome where both the belimumab and placebo response rates in BLISS 52 study
6 329 were greater than those in BLISS-76 and, remarkably, the placebo response rate in BLISS-
7 330 52 (49%) was greater than that for the belimumab arm of BLISS-76 (43%). O'Shea and
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9 331 DeMets also report that within the Beta-Blocker Heart Attack Trial (BHAT), not only was
10 332 there a difference in the direction, but also in the size of treatment effect between Canada
11 333 and the US, although it should be noted that the original aim of that trial was not
12 334 investigation of international differences in treatment effect.³⁵ One study found that 96-99%
13 335 of the total variance in the "Global utilisation of strategies to open occluded coronary arteries
14 336 IV acute coronary syndromes" (GUSTO IV ACS) trial could be accounted for by patient-level
15 337 factors.³⁶
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23 339 International trials need to harmonise training of investigators, patient selection, treatment
24 340 management, thresholds to centre admission, access to facilities, ascertainment of
25 341 endpoints and, by implication, results of interest³⁷⁻⁴⁴ since it is possible that in centres in
26 342 different countries these factors may differ systematically.³⁷ Equally, underlying differences
27 343 in populations and countries (ethnicity, genetics, socio-economic status and health-care
28 344 systems), and the nature and epidemiology of SLE according to ethnic background may
29 345 result in differences in reporting of outcomes and pooled results.
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35 347 The outcomes used in the BLISS trials would be unfamiliar to most of the investigators and it
36 348 is possible that criteria may have differed between countries. In particular the Physician
37 349 Global Assessment (PGA) is an important element of the outcomes measured (see Figure
38 350 1). PGA was measured as an outcome in itself, and it is also incorporated in SRI. PGA is of
39 351 concern because as a global physician assessment of a patient's SLE status, it is subjective.
40 352 The investigators reported a nearly 10% difference between the BLISS-52 and BLISS-76
41 353 studies in estimates of percentage change in PGA score in intervention groups at week 24
42 354 compared to baseline and this single result in one of the two trials is likely to have had an
43 355 important influence on findings of the effectiveness of belimumab in SLE patients.
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50 357 The latest results of belimumab in patients with SLE (phase II study design, uncontrolled
51 358 extension study) reported that of 449 patients with active SLE (USA/Canada) 177 (39.4%)
52 359 patients remained on treatment after 7 years of therapy (i.e. approximately 1746 cumulative
53 360 patients-years) and that this subgroup exhibited durable sustained improvement in SLE
54 361 disease activity (SRI and PGA).³⁰
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363 CONCLUSIONS

364 In conclusion, systematic review and random effects meta-analysis of two RCTs of
365 belimumab for patients with autoantibody positive SLE demonstrated positive results in the
366 main outcome at week 52. However, in view of the different populations studied at different
367 locations in the BLISS trials and the consistently superior results from one trial compared to
368 the other, we consider that population heterogeneity, geographical differences and variation
369 in trial conduct and outcome assessment, may have played a role in influencing outcomes.
370 However the generalisability of results pooled meta-analytically or by logistic regression
371 should be viewed with caution and we suggest that it is too early to draw strong conclusions
372 in this case.

374 ARTICLE FOCUS

- 375 • SLE is a complex multi-organ auto-immune disease subject to relapse and remission.
- 376 • Patients almost always have fatigue, skin rashes and arthritis and there is a wide
377 variety of other problems which the disease can cause.
- 378 • Belimumab is a new treatment specifically targeted against SLE.

380 KEY MESSAGES

- 382 1. Combining the results from two RCTs suggests that belimumab is clinically effective
383 for SLE patients.
- 384 2. However, all outcomes were systematically superior in one trial compared with the
385 other.
- 386 3. Different trial conduct and populations mean that it is too early to draw generalisable
387 conclusions.

389 STRENGTHS AND LIMITATIONS

- 390 • At first sight combined meta analytic evidence suggests that belimumab is clinically
391 effective for patients with severe SLE.
- 392 • We suggest that it is too early to draw strong conclusions because the two relevant
393 trials cover different populations in different countries and there may be differences in
394 trial conduct and outcome assessment.

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15 404 **Competing interest statement**

16 405 No conflicts of interest.

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19 407 **Contributions:**

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21 408 N-BK: Conception and design. Data analysis and interpretation. Drafting the article. Critical
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23 409 revisions for important intellectual content. Approval of final article for submission.

24 410 MC: Conception and design. Data analysis and interpretation. Literature review.
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26 411 Interpretation of results. Drafting the article. Critical revisions for important intellectual
27
28 412 content. Approval of final article for submission.

29 413 AG: Interpretation of results. Critical revisions for important intellectual content.

30 414 PS: Literature review. Interpretation of results. Critical revisions for important intellectual
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32 415 content.

33 416 SM: Data analysis and interpretation. Interpretation of results. Critical revisions for important
34
35 417 intellectual content.

36 418 LH: Literature review. Interpretation of results. Critical revisions for important intellectual
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38 419 content.

39 420 RC: Literature review. Critical revisions for important intellectual content.

40 421 EC: Interpretation of results. Critical revisions for important intellectual content.

41 422 CG: Interpretation of results. Critical revisions for important intellectual content.

42 423 AC: Conception and design. Interpretation of results. Drafting the article. Critical revisions
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44 424 for important intellectual content. Approval of final article for submission.

45 425 All authors read and approved the final manuscript.

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3 **June 4, 2013**
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6 Mr. Richard Sands
7 Managing Editor, BMJ Open
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10 **RE: Manuscript ID bmjopen-2013-002852**

11 **Title: Belimumab: a technological advance for SLE patients? Report of a systematic review**
12 **and meta-analysis**
13

14 Dear Mr Richard Sands,
15

16 Please find enclosed our revised manuscript, which addresses the reviewers' concerns and
17 suggestions. What follows is a point-by-point response to the comments provided as part of the
18 review process. Each group of responses has been numbered to correspond with those on the
19 comments. Moreover, in the revised manuscript we have highlighted in red colour the areas that
20 have been substantively modified compared to the original submission.
21

22 We would like to thank the reviewers and managing editor for thoughtful comments and
23 suggestions. We truly appreciate your interest in our work. We believe that as a result of the
24 review process our paper has greatly improved and hope that it is now acceptable for publication
25 in BMJ Open.
26
27

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30 **Editor:**

31 From the managing editor:

32 None of the references include dates. Please add where possible.
33
34

35 **Reply: Thank you for the comment. We have now included dates of references as suggested.**
36
37

38
39 **Reviewer 1:**

40 Reviewer: Peter Watson
41 Statistician
42

43 MRC Cognition and Brain Sciences Unit
44 15 Chaucer Road
45 Cambridge
46 UK
47 CB2 7EF
48

49 I have no conflicting interests with the research presented in this study.
50
51

52
53 1. There appear to be many analyses and response variables without any particular one being of
54 primary interest. I have a concern given the heterogeneity of the ethnicity (page 10 second
55 paragraph) and the small implied number of studies (page 3, results, first sentence) of
56 generalisability of the results and representativeness to other populations. The degree of between
57 study heterogeneity could be stated using I^2 and, if not already, accounted for in deriving pooled
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3 estimates. Other aspects of the results and figures could be described in greater depth (see
4 comments below) including labeling and captioning of all the figures and more clearly linking the
5 results in the text to those in the figures and stating which analyses are used to produce the
6 results plotted in the figures.
7

8
9 Reply: We would like to thank the reviewer for his comments on our manuscript. We have now
10 carefully checked the manuscript to account for these comments and suggestions.

11
12 The reviewer is right, although the main primary outcome to determine the effectiveness of
13 belimumab was the Responder Index (SRI) at week 52, we also examined other
14 outcomemeasures for the three RCTs that evaluated belimumab effectiveness e.g. examining the
15 SLE Responder Index (SRI) at week 76. We also included those outcomes identified by the
16 belimumab investigators in their protocol as “major secondary and other outcomes”. We have
17 now clearly identified the primary outcome designated in the RCTs (namely SRI at 52 weeks), we
18 have stated that this is also our primary outcome, and have included text to explain the origin of
19 this novel outcome measure as developed between the FDA and the belimumab trialists.
20

21 We have attempted to highlight more explicitly that our manuscript concerns the generalizability
22 of pooled results and that these should be viewed with caution. We noted that population
23 heterogeneity; geography and / or variation in trial conduct may be influence results; we have
24 removed reference to “*hidden confounders*”. Although formal tests for statistical heterogeneity
25 were negative, BLISS-52 results were systematically more favourable for all measured outcomes.
26

27 These elaborations on the interpretation of our results are found mainly in lines:

28 89-95; 197-201; 261-271.
29

30
31 2. A couple of references on meta-analysis that may be of use I put in the comments below which
32 may be worth adding to the bibliography.

33 Reply: We have added the Higgins reference as suggested; the reference for publication bias
34 has not been added because it was not possible to ascertain if there was publication bias with
35 only two RCTs; we have added text to this effect (line 154) the reference to the Cochrane
36 Handbook (number 21) was therefore considered sufficient. Ref 21 (page 317) recommends at
37 least 10 studies would be required for analysis of small study bias and we have been guided by
38 this.
39

40
41 3. It is not clear how the unnumbered and uncaptioned figures (pages 27-29) relate to the results
42 (pages 8-9) and if, and how adjusted, the pooled odds ratios quoted on page 8 (first paragraph
43 lines 8-9) relate to the binary responses in Table 3 (page 32). I think the lack of statistical
44 significance of both inter-study heterogeneity of effect sizes (page 10 first paragraph) and the
45 confidence intervals of the figures mostly containing values ('1' for odds ratios and '0' for mean
46 differences) suggesting no group differences could be down to limited power and possibly low
47 sample sizes. This weakness may be mitigated by the number of point estimates suggesting a
48 (hopefully clinically meaningful) benefit of the belimumab treatment but this need to be motivated
49 in the text.
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54 Reply: We have revised and numbered captions of figures and relate them clearly to the results
55 section as suggested. Lines 214-218 explain how the results depicted in figure were derived;
56 lines 227-230 explain how the adjusted odds ratios were derived / reported. As for the weakness
57 of the study as mentioned by the reviewer, the reviewer makes an important point. The reviewer
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3 indicates that confidence intervals “suggesting no group differences” might be attributable to lack
4 of power is of course probable, however the modest effect size (small benefit of belimumab) is a
5 major contributory factor. Due to the scarcity of RCTs evaluating the effectiveness of belimumab,
6 we restricted our study to the available evidence. The three RCTs combined investigated 2133
7 SLE patients, which may be a good sample size for this type of rare condition (e.g. the SLE
8 Rituximab trial, the only other major recent trial for SLE, recruited 184 patients into two arms).
9

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12 4. There are limitations (conclusions section on page 3) concerning 'hidden confounders' and
13 interpretability of pooled estimates. It is not clear to me (see later comments) if this is 'merely'
14 downplaying a pooled estimate and usefulness of a meta-analysis as the (limited number, three,
15 of) populations being pooled are so different from each other or, more seriously, if there could be
16 possible uncontrolled differences in clinically meaningful characteristics (confounders) between
17 the placebo and treatment groups in one or more studies which would render any differences
18 between the groups problematic to interpret as they could be simply due to factors other than the
19 belimumab treatment. There is some mention of stratified randomisation on page 7 (start of
20 second paragraph) but no details of what factors were used as stratifiers.
21

22
23 Reply: We have attempted to clarify these issues. We have removed the phrase “hidden
24 confounders” and have explicitly considered the influence of geographical / ethnic / trial conduct
25 differences between the BLISS trials by first pointing to the systematic difference in results
26 between B52 and B76 (lines: 236-242; 262-272) and by alluding to the ethnic / geographical data
27 presented in Table2 and Figure3; lines 262-272) . We now provide explicit information about the
28 stratification undertaken in the BLISS trials and the use of strata in adjusting results reported in
29 the published accounts (lines 182-184; 227-229). The limitation we mentioned is not only limited
30 to the general applicability of the nature of meta-analysis but also to real limitations due to
31 confounders such as the geographic location and the ethnicity where the studies were conducted.
32

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34
35 5. This study compares a group using a new treatment for multi-organ auto-immune disease,
36 Belimumab, with a placebo group by, on pages 8 and 9, obtaining confidence intervals for odds
37 ratios (for a series of binary responses) plotted in the figures on page 27 and mean differences
38 (for continuous ones) plotted in the figure on page 28 and reports a meta-analysis on page 9
39 for each of five (?) outcomes which look at the group effect which I suspect may be plotted in the
40 figures on page 29.
41

42
43 Reply: Please see the method section of the paper. We performed a meta-analysis of two
44 randomized controlled trials (RCTs) of belimumab against placebo or best supportive care. To
45 improve clarity we have edited the figure captions and Method sections. The Meta-analysis figure
46 (Figure 6) shows the results of random effects meta- analysis of the two BLISS trials for each of
47 14 outcomes designated by belimumab trialists as primary or major secondary or “other major”
48 outcomes. For convenience of viewing we combined the results for different types of outcome
49 into a single figure (binary, time to event and continuous) using Excel.
50

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53 6. I, unfortunately, found the description (on pages 8 and 9) and presentation of the results (in the
54 figures on pages 27-29) confusing and imprecise making it difficult to marry together the
55 description of the results in the text and the confidence intervals plotted in the figures. The
56 structure of the data being analysed needs to be fleshed out in the body of the text to help
57 understanding of the results e.g. I am not sure if the meta-analyses are pooling across different
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3 studies or different subgroups within a single study or precisely what the SLE in the title of this
4 paper stands for (it presumably is an abbreviation?)
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7 **Reply:** We have defined SLE in the title and text. We have clarified the results and figures
8 presented to explain that the pooling was across different studies (the two RCTs). We also
9 present within-study results for the primary outcome according to different geographical
10 subgroups (lines 262-272). With many outcomes and sub-groups analysis it became difficult for
11 the reader we consider that we have improved the paper in this regard.
12
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15 7. In particular the figures on pages 27-29 were not numbered or captioned which made it more
16 difficult to know which analyses and effect sizes (odds ratio or 'mean difference') they were
17 referring to and, in particular, which is the Figure 6 listed as corresponding to the meta-analyses
18 reported briefly in the second paragraph on page 9. There is also an effect size called the 'hazard
19 ratio' in a figure on page 27 which does not seem to be defined in the text. There are a lot of
20 responses (listed both within the figures and represented by these different figures on pages 27-
21 29 and also mentioned as a basis for various meta-analyses in the first sentence of the second
22 paragraph on page 9). It is not clear to me if the results of analyses of these separate responses
23 are being presented or discussed separately or together.
24

25 **Reply:** Thank you for these comments. We have now explained the derivation of the hazard ratio
26 results (lines 236-242). We have attempted to explain why so many outcome measures exist for
27 SLE (lines 88 to 95) and how this led to the development of the SRI measure. These results are
28 mainly, but not exclusively, discussed together since the most noticeable feature common to all is
29 the better performance of belimumab in B52 relative to B76 (lines 262 265; 307-313).
30
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33 8. Page 6. I think it makes more sense grammatically to say at the end of the first sentence of the
34 'Statistical analysis' paragraph on page 6 that odds ratios and mean differences 'were calculated
35 for binary and continuous outcomes respectively'. Two reviewers are mentioned on page 6 under
36 'inclusion criteria' as assessing inclusion of studies. Was this assessment done independently by
37 the two raters and, if so, could a kappa statistic, or alternative, be quoted to show inter-rater
38 agreement?
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41 **Reply:** We have added modified the sentence as suggested and clarified the independence and
42 tasks of the two reviewers (lines 138-145).
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44

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46 9. Pages 6 and 8. The statistical analysis on page 6 mentions 'unadjusted odds ratios'. Adjusted
47 odds ratios are then presented (fifth line from bottom of first paragraph on page 8) but it doesn't
48 mention in either sentence what these odds ratios are adjusted for or how or why both unadjusted
49 and adjusted odds ratios are used. If its ok to use unadjusted odds ratios why adjust them?
50

51 **Reply:** We have now clarified the use of adjusted and unadjusted odds ratio to make it clear to
52 the reader why both were presented (lines 214-218; 227-229)
53
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56 10. Pages 6 and 8. Is the 'mean difference' reported in the 'Statistical analysis' paragraph on
57 page 6 and in the second paragraph on page 8 a standardised group one such as Cohen's d if
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3 you are wishing to compare results for different responses which may have different scales?
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6 **Reply:** The mean difference' reported in the 'Statistical analysis' in paragraph 6 and 8 is mean
7 difference' reported in the BLISS RCTs. Each outcome used the same assessment tool in both
8 trials and "standardized mean difference" such as Cohen's d was not appropriate.
9

10
11 11. Pages 6 and 9. I would like to see in the meta-analysis (second paragraph on page 9) the
12 value of I^2 and any associated p-value, which was used (as stated on page 6 in the second last
13 paragraph labelled 'statistical analysis') to test for the heterogeneity of effect size as this is an
14 important test given that the degree of study heterogeneity is referred to throughout this paper.
15 There are rules of thumb for small, medium and large values of I^2 that could be used. A value of
16 0% indicates no observed heterogeneity, 25%-49% is low heterogeneity, 50%-74% is moderate
17 and 75% and above is large (Higgins et al, 2003). You could also mention in the statistical
18 analysis paragraph on page 6 if you used a Der Simonian pooled estimate for the effect sizes or a
19 fixed effect one such as the Mantel-Haenszel estimate for odds ratios in the meta-analysis as you
20 found (page 9) little or no between study variation.
21
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23
24 **Reply:** We now explain that we used the random effects method of DerSimonian Laird (line 156)
25 to pool effect sizes. We anticipated heterogeneity so a random effects model was more
26 appropriate in this case than the fixed effects model. We have now displayed (in Figure 6) the
27 value of I^2 and the associated p-value as suggested, and we have tightened the text so the lack
28 of statistical heterogeneity refers specifically to binary and time to event outcomes.
29
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31
32 12. Page 7. Second paragraph, line 1 mentions 'stratified randomisation' was used. What factors
33 were stratified for and for what factors were the arms 'well balanced'?

34
35 **Reply:** We have now clarified this (lines 227-229). Baseline balance included values for:
36 proteinuria, disease duration, gender, race, IgG, autoantibody, and complement levels, baseline
37 SLEDAI and PGA scores, BILAG organ domain involvement and SLICC Damage Index score;
38 we have now included this information in the caption to figure 5.
39
40

41
42 13. Page 8. I am not clear from the results on pages 8 and 9 how we should go about interpreting
43 the confidence intervals in the figures on pages 27 to 29. Confidence intervals for odds ratios
44 'pooled across trials' are presented in the first paragraph (line 6) on page 8 but these are not
45 graphed in the figures on pages 27 and 28 and I am not sure how these tie in with the confidence
46 intervals in the figures. Are the results on lines 8-9 of the first paragraph on page 8 pooling odds
47 ratios across all the binary variables mentioned in Table 3 (page 32) in BLISS-52 and BLISS-76
48 and is a pooled odds ratio interpretable when pooling over apparently different tests? The 'pooled
49 across trials' implies some meta-analysis may have been performed to yield these pooled odds
50 ratios.
51
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54 **Reply:** In the figures referred to (on pages 27 to 29) ORs are unadjusted (now explained more
55 clearly lines 214-218). Additionally we have explained that the BLISS trial journal articles and the
56 manufacturer's submissions to the FDA and to NICE used a logistic regression model
57 (individually for each trial in the journal articles, and after pooling populations in the case of the
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3 submissions to the approval authorities; lines -229; 227 and 276-279).
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7 14. Page 9. The first line of the second paragraph on page 9 implies that a meta-analysis is
8 performed on each of at least five different responses (as meta-analyses usually pool over trials
9 measuring effect sizes using the same response and groups) and there is a mention of figure 6
10 which is the last figure in the paper presumably the one on page 29 yet I can't see six separate
11 plots here. I would also have expected to see a confidence interval for a pooled effect size at the
12 base of each of the forest plots corresponding to the meta-analysis of each response.
13

14 Reply: The text referring to Figure 6 has been clarified (lines 282-285). The figure has been
15 redrawn and figure caption improved to correct for errors and improve clarity for the reader.
16
17

18
19 15. Page 9. The last sentence of the first paragraph on page 9 mentions there were various
20 causes of death but does not mention what these were which I would have thought would be of
21 interest in giving a background to the data. I am not sure if the 'study level' referred to in the first
22 sentence of the second paragraph on page 9 refers to separate subgroups within studies or, the
23 usual pooling unit of pooling in meta-analyses, separate studies.
24

25 Reply: We have now included the causes of death (lines 250-251). The term "study level" was
26 used to distinguish the results presented from those in the manufacturer's submission to the FDA
27 in which IPD from the two BLISS trials was pooled prior to logistic regression analysis; hopefully
28 this is now clear from the text (lines 281-287)
29
30

31 16. Pages 9 and 29. I don't see any mention of a funnel plot to test and adjust for any possible
32 publication bias. This analysis, at least, is usually performed and plotted routinely in meta-
33 analyses including those submitted to this journal. Other tests can also be used – see, for
34 example, Peters et al. (2010).
35

36 Reply: The reviewer makes a potentially important point here. We did not include a formal test of
37 small study bias because there are too few trials evaluating the effectiveness of Belimumab (see
38 line 154 with accompanying reference 21) . We believe, a test of publication bias in this context
39 may not be useful.
40
41

42
43 17. Pages 9, 27-29. Page 9 implies a meta-analysis has been performed and, in light of this, I
44 was surprised to see the size of the point estimates in the middle of all the confidence intervals
45 plotted in the figures on pages 27-29 looking the same size as these usually differ in size as they
46 are proportional to the weighting given to the studies in the meta-analysis to construct a pooled
47 estimate. I also think, therefore, for the forest plot(s) you could add in a column by the plot
48 showing the value of the weights used to confirm the studies had a similar weighting used in
49 constructing the pooled estimate.
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52 Reply: All points are the same size because each refers to the pooled estimate for a particular
53 outcome, not to a single study estimate given a specific weight in the analysis. We hope the text
54 and figure caption and redrawn figure now make this clearer.
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3 18. Page 10. The first paragraph mentions that there was no heterogeneity found (across the
4 studies or subgroups?) in the BLISS-52 trial but, counterintuitively, the racial background and
5 ethnicity of participants 'varied considerably' and concludes there should be heterogeneity which
6 confuses the conclusion and makes one start to doubt the tests of heterogeneity that have been
7 used in this analysis as basis for obtaining pooled estimates. I am not sure if the conclusion (page
8 10 first line of first paragraph) that the benefits of belimumab are 'greater across the board' is
9 warranted looking at the confidence interval plots on pages 27-29 since most of these intervals
10 contain either an odds ratio of one or a zero difference which both correspond to no difference.
11 One might possibly argue that, ignoring variances, the bulk of the point estimates, comprising
12 odds ratios and mean group differences, are benefitting the use of the treatment, belimumab, but
13 this needs to be carefully argued in the light that few of them are statistically significant and given
14 the acknowledged heterogeneity (on page 10) which the authors may wish to account for if they
15 have not done so already in obtaining pooled effect sizes despite the 'usual' tests of these not
16 flagging this which may be due to lack of power from heterogeneity across only three studies
17 being tested.
18
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22 **Reply:** We performed the I squared test for statistical heterogeneity between the two BLISS trials
23 used in the meta analyses and found low values for all outcomes. But we believe that there are
24 other sources of heterogeneity (geographical, trial conduct etc.) which have exerted a systematic
25 influence on the outcomes, the major indicator of this influence being the consistently superior
26 performance of one trial compared to the other across multiple outcomes. Hopefully the new text
27 (e.g. lines 262 -272) explains this more clearly. The fact that BLISS 76 outcomes almost always
28 fail to reach statistical significance is now brought out more clearly (e.g. lines 253-260); even
29 though the fact that the primary outcome in BLISS 76 was satisfied on extending observation to
30 76 weeks eliminates the statistical significance of the SRI. While the lack of statistical
31 significance may be attributable to some extent to lack of power it is also clear that effect sizes in
32 BLISS 76 are modest.
33
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36 19. Pages 27, 28 and 29. The figure(s) containing the forest plots need to be numbered and
37 captioned. Is it necessary to both plot and quote the confidence intervals for group differences in
38 these figures? Would simply plotting these confidence intervals be enough?
39
40

41 **Reply:** We have now numbered and captioned the plots.

42
43 Figures 3 and 4 present the comparison (intervention versus control) separately for the two
44 BLISS trials because this highlights the fact that BLISS 52 always gives a better result for
45 belimumab than does BLISS 76. We think the CIs are necessary because again they highlight
46 the difference between the trials.
47
48

49 20. The plot on page 28 plots hazard ratios (as opposed to rates?) in the 'time to event' figure
50 which are, generally, not the same as odds ratios. The hazard ratios should be defined in the text
51 but I can't see any mention of hazard ratios anywhere else in the paper (e.g. in the statistical
52 analysis paragraph on page 6 or in the results sections on pages 8 and 9).
53

54 **Reply:** Thank you for the comments. We have now explained the hazard ratios in lines 236-242.
55
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57 21. The study does not explicitly state on page 9 in the meta-analysis results section how many
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3 trials are being pooled to obtain pooled effect sizes in the meta-analyses although elsewhere (for
4 example on page 3, first line in first paragraph) three trials are mentioned and two 'relevant trials'
5 (page 2 second bullet point under 'strengths and limitations'). Usually one has sufficient numbers
6 of studies being pooled to make any results generalizable across different types of study to
7 different populations. I mention this, as three trials, if this is the number used, does not seem very
8 many for a meta-analysis particularly one where there is considerable between study
9 heterogeneity at least in ethnicity (as already noted in the first paragraph on page 10), and as
10 some of the plots in the figures on pages 27-29 only contain four rows (and then assuming one
11 would be pooling BLISS-52 and BLISS-76 whose pooling might be questionable given separate
12 confidence intervals are presented for these in the fifth last row from the end of the first paragraph
13 on page 8).

14
15
16 **Reply:** We performed the meta-analyses using outcomes from two randomized controlled trials
17 (the two BLISS trials). (This is now more explicit in lines 281-282, and in the caption to the figure
18 6). We explain why the L02 trial was only used in assessing safety outcomes on lines 194-198.
19 Problems in interpreting what is represented in the figures have been addressed in figure
20 captions and with more explicit description in the body of the text.(lines 212-218 and 237-243).

21
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25 22. On page 3 (in the conclusions paragraph) the fourth line states generalizability of 'pooled
26 results should be viewed with caution' and lines 5 and 6 mention possible 'hidden confounders'. Is
27 this saying that the pooled studies may have differed from one another in many respects
28 (confounders) and/or is it saying there are so many possibly uncontrolled confounders of clinical
29 relevance in these group comparisons that we are looking at group differences (the belimumab
30 treatment group vs the placebo group) that could be due to other clinically meaningful
31 confounding factors which differ between the treatment and placebo groups? The latter could be
32 a serious drawback to interpretability of any results whereas the former would, at least, preclude
33 an interpretable pooled estimate since we would be averaging over such disparate (and few)
34 populations which rather undermines the usefulness of a meta-analysis.

35
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37
38 **Reply:** Perhaps, it was not clear in the previous version of the paper. We have removed
39 reference to "hidden confounders" and have clarified the conclusion section (especially lines 361-
40 365). Please also see our reply in point 4 above.

41 42 43 44 References

45 Higgins, JP, Thompson SG, Deeks JJ and Altman DG (2003). Measuring inconsistency in meta-
46 analyses. *BMJ*, 327, 557-560.

47
48 Peters, J.L., Sutton, A.J., Jones, D.R. and Abrams K.R. (2010). Assessing publication bias in
49 meta-analyses in the presence of between-study heterogeneity. *Journal of the Royal Statistical*
50 *Society A*, 173(3), 575-591 There is an on-line copy of this paper at
51 <http://onlinelibrary.wiley.com/doi/10.1111/j.1467-985X.2009.00629.x/full>.

52 53 54 55 **Reviewer 2**

56 Ricard Cervera, MD, PhD, FRCP
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3 Head, Department of Autoimmune Diseases
4 Hospital Clínic
5 Barcelona, Catalonia, Spain
6
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8 Statement: I have no competing interests with the authors of this manuscript

9
10 Reviewer: This is an interesting systematic review and meta-analysis of the randomized
11 controlled trials of belimumab in patients with systemic lupus erythematosus. The study was well
12 designed, the results are interesting and the manuscript is well written with well balanced
13 discussion.
14

15
16 Reply: We would like to thank the reviewer for his kind comments on our manuscript.
17
18

19
20 Once more, we would like to thank the reviewers for thoughtful comments and suggestions. We
21 truly appreciate your interest in our work. We believe that as a result of the review process our
22 paper has greatly improved and hope that it is now acceptable for publication in BMJ Open.
23

24 Yours sincerely,
25

26 Ngianga-Bakwin Kandala, PhD
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FIGURE 1: Summary of the major clinical measures used in SLE trials

SELENA-SLEDAI: Encompasses 24 weighted items scored dichotomously as present or absent in the previous 10 days, thus improvement or worsening of a manifestation is not captured. Overall disease activity is scored over a range of 0 to 105 points. A minimum clinically meaningful score change = a decrease of 6 points (overall improvement) or an increase of 8 points (overall worsening). A designated change in score (≥ 4 points) between baseline and follow up can be used to dichotomise patients into responders or non-responders for overall disease.

BILAG: Includes 86 items grouped in eight organ systems to assess organ system involvement over the last four weeks compared to preceding four weeks based on physicians intention to treat using classifications ranging from A to E as follows: A = worsening usually requiring intensification of steroids or immunosuppressant treatments; B = worsening usually requiring antimalarials, nonsteroidal anti-inflammatory drugs (NSAIDs), or low dose steroids; C = stable disease (symptomatic therapy); D = improvement; E = system never involved. Unlike SELENA-SLEDAI it can detect worsening or improvement in individual organ system involvement.

PGA: Is employed to monitor change in patient overall disease activity; typically a visual analogue scale is used ranging between no disease = 0, mild disease = 1, moderate disease = 2, and severe disease = 3.

SRI: A composite instrument (combining elements of SELENA-SLEDAI, BILAG and PGA) developed by belimumab-trialists in conjunction with the US FDA. It allows patients to be dichotomised into responders or non-responders according to predefined assessment criteria in each of the component elements, such as: a SELENA-SLEDAI improvement of ≥ 4 points, plus no worsening in PGA score by > 0.3 points, plus no new BILAG organ system involvement scoring category A in one system or category B in two or more systems. An advantage of SRI, over any one of its components used alone, may be that it can detect SLE improvement in some initial manifestation(s) while guarding against the possibility that worsening in organ systems or overall disease activity might be masked.

FIGURE 2: PRISMA 2009 Flow Diagram for Belimumab in SLE RCTs and on-going trials

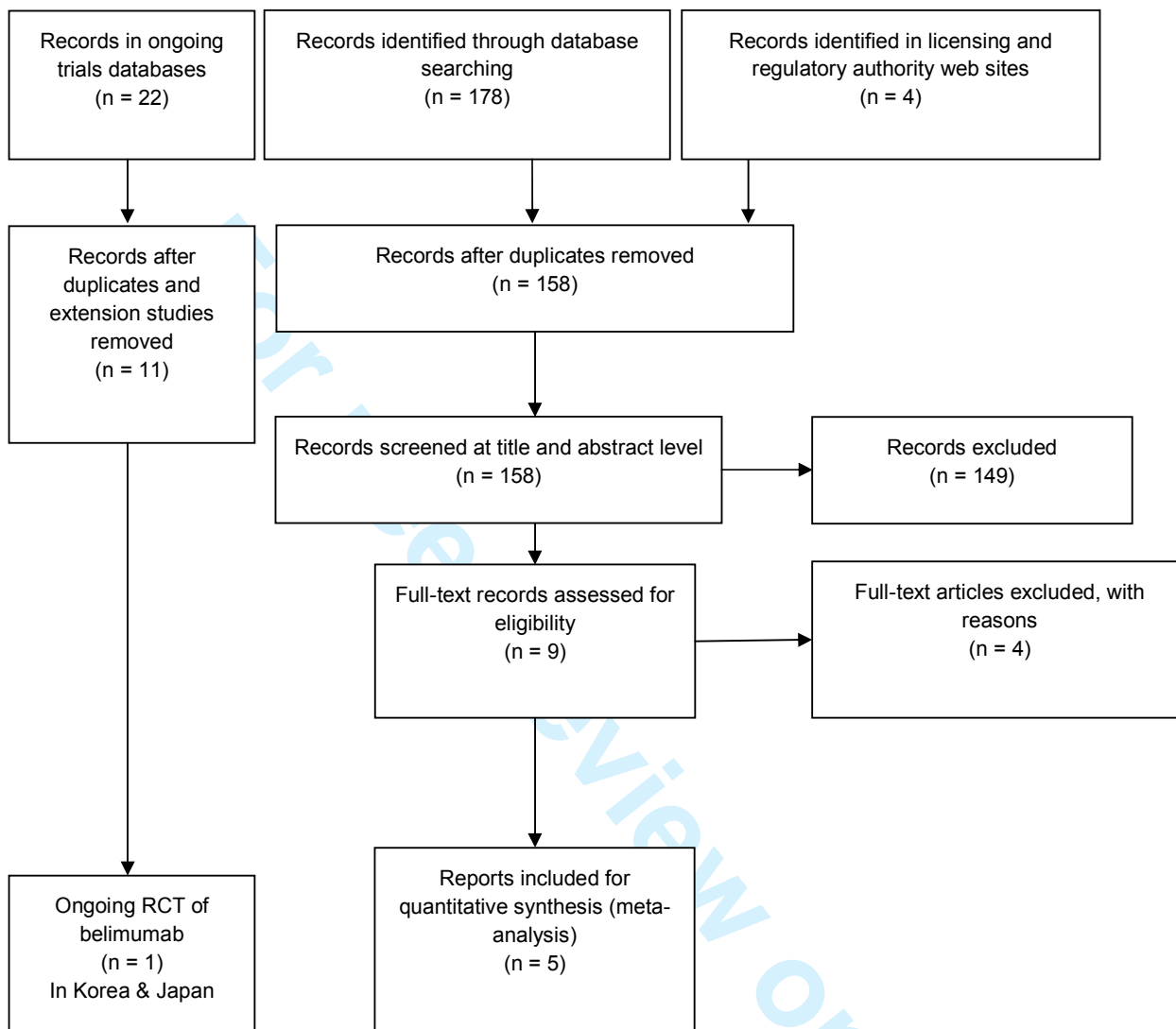


FIGURE 3: Differing centre locations in the BLISS 52 and BLISS 76 multicentre trials



FIGURE 4: Summary of results for major binary and time to event outcomes in belimumab RCTs

Except for safety outcomes the results shown are for the BLISS 52 and BLISS 76 trials. Odds ratios (OR) were calculated from the event rates reported in journal publications; hazard ratios are from data presented in the manufacturer's submission to the FDA. The BLISS trials were well balanced for baseline characteristics (disease, duration, Gender, race, baseline IgG, autoantibody, and complement levels, baseline SLEDAI and PGA scores, BILAG, organ domain involvement, SLICC Damage Index score, and Proteinuria). Safety outcomes are based on data presented in FDA documents.

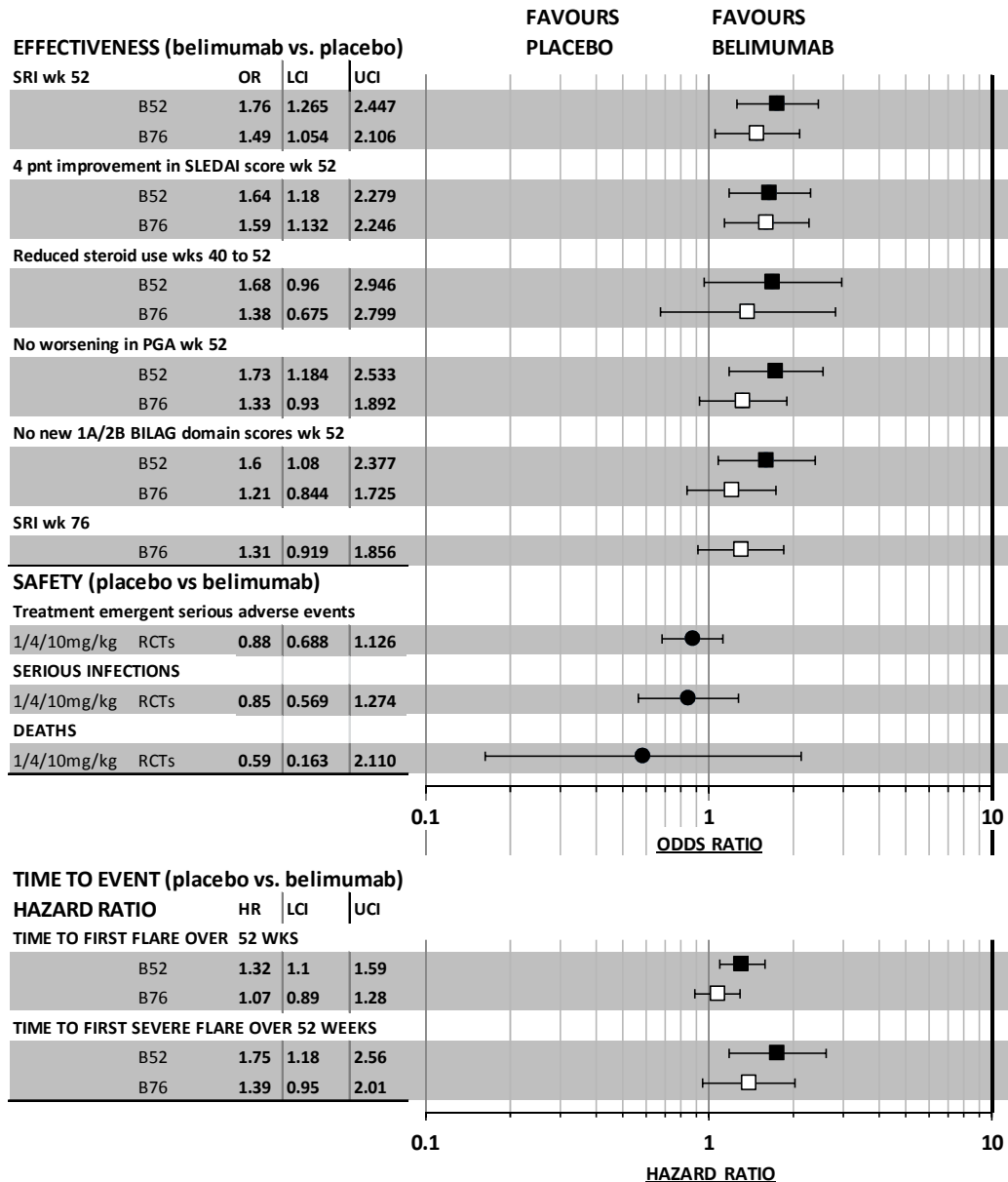
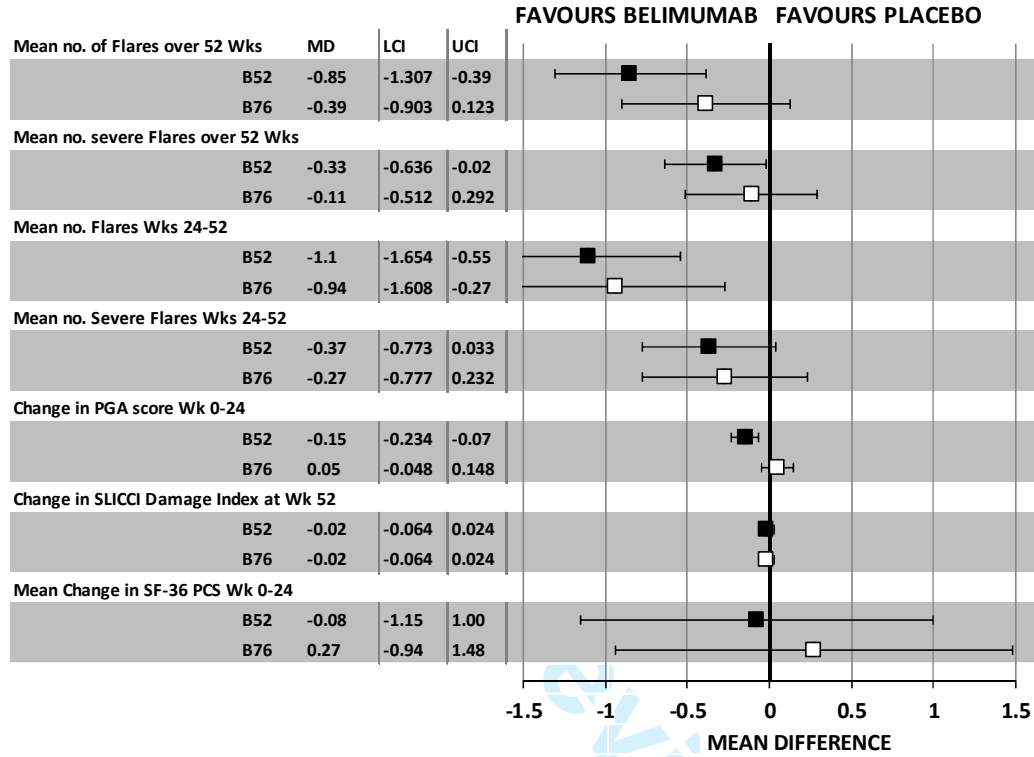


FIGURE 5: Summary of results for major continuous outcomes in BLISS 52 and BLISS 76 trials



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FIGURE 6: Meta-analysis of major outcomes in the two BLISS trials

Upper panel shows pooled estimates for binary and time to event outcomes (OR = odds ratio; HR = hazard ratio). Lower panel shows pooled estimates for continuous outcomes (MD = mean difference). SLICC = Systemic Lupus International Collaborating Clinics, the SLICC index is a measure of organ damage. Meta-analysis was conducted using random effects method (DerSimonian Laird).

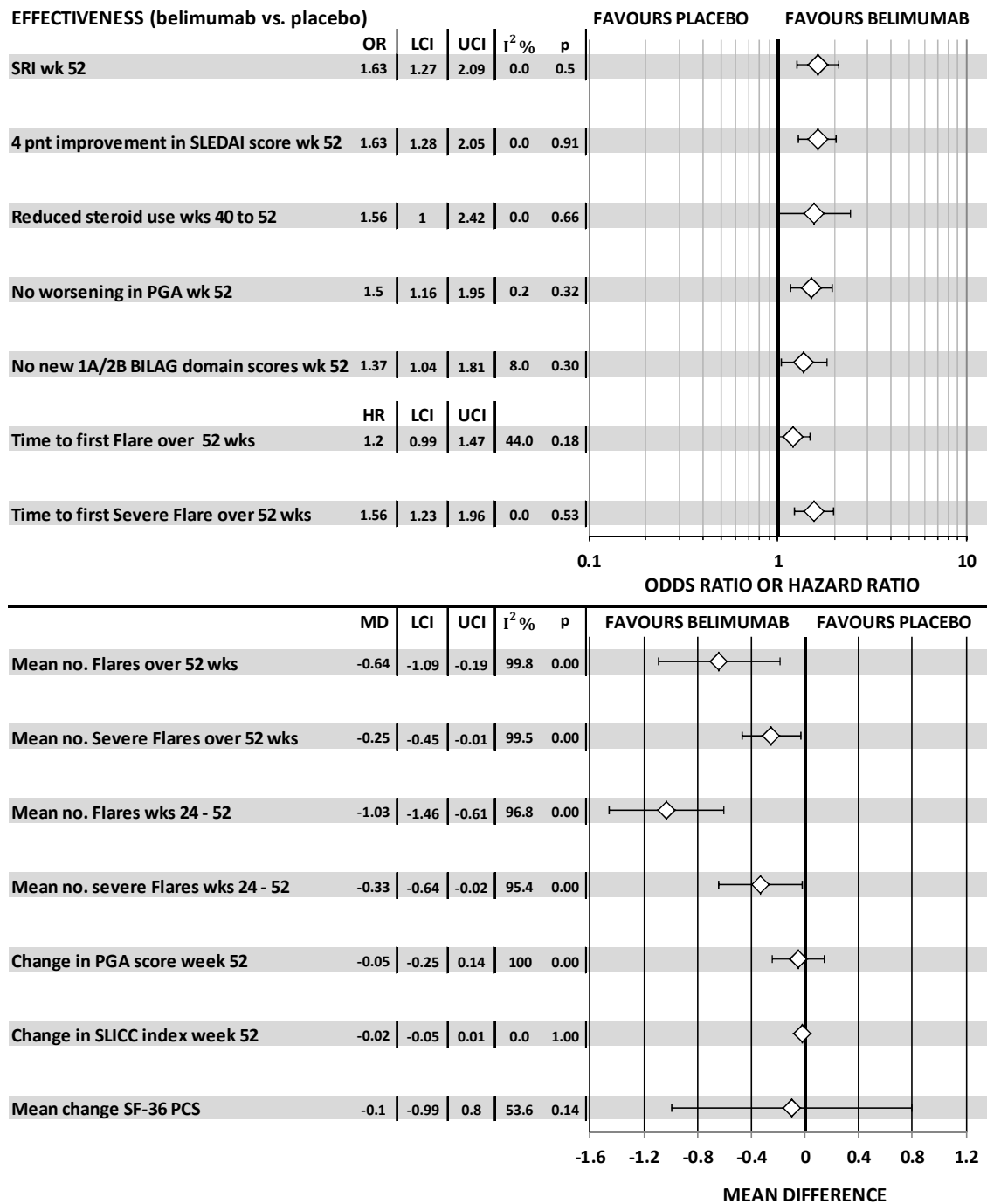


Table 1 Quality assessment of the included trials

QUALITY ITEMS	L02	BLISS-52	BLISS-76
Does reporting suggest that randomisation was carried out appropriately?	Yes	Yes	Yes
Does reporting suggest that the concealment of treatment allocation adequate?	Unclear	Unclear	Unclear
Were the groups reported as similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors reported as blind to treatment allocation?	Yes	Yes	Yes
Were any unexpected imbalances in drop-outs reported between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

Quality assessment used information presented in the study journal articles and the manufacturer's submission to the US FDA and was based on CRD guidance (2008)¹⁹ for undertaking systematic reviews in health care (CRD = Centre for Reviews and Dissemination, York: Centre for Reviews and Dissemination)

Table 2: Major characteristics of included studies

STUDY	Treatment (IV)	N	Mean Age (SD) yrs	SELENA-SLEDAI at entry	Geographical distribution of patients	Ethnic make-up of trial participants			Number and location of STUDY CENTRES
L02 2006 Phase II 52 week	Bel 1 mg/kg Bel 4 mg/kg Bel 10 mg/kg Placebo	114 111 111 113	42 (11)	> 4 points	US (98%), Canada (2%)	Caucasian	NR	69.9%	59 in N. America
						African American	NR	24.7%	
						Latino	NR	18.5%	
BLISS-52 2009 Phase III 52 week	Bel 1 mg/kg Bel 10 mg/kg Placebo	288 290 287	36 (11)	> 6 points	Latin America (50%), Asia (38%), E Europe & Australia (13%)	Caucasian	229	27%	90 in Pacific Asia. 11 in S. America & E. Europe
						Asian	327	38%	
						Black/African Am	30	4%	
						Alaskan Nat./Am Indian	279	32%	
						Nat. Hawaiian/Pacific Islander	0	0%	
Multiracial	5	1%							
BLISS-76 2009 Phase III 76 week	Bel 1 mg/kg Bel 10 mg/kg Placebo	271 273 275	40 (12)	> 6 points	US & Canada (53%), W Europe (25%) E Europe (11%) Latin America (11%)	Caucasian	569	70%	136 in N. America & Europe
						Asian	28	3%	
						Black/African Am	118	14%	
						Alaskan Nat./Am Indian	103	13%	
						Nat. Hawaiian/Pacific Islander	1	0%	
Multiracial	8	1%							

NR = not reported

Table 3: Outcomes defined and pre specified in the BLISS 52 and BLISS 76 trials and their accompanying designated status

Outcome	Measure	Outcome specification
SLE Responder Index (SRI*)	% responders at wk 52	Primary outcome
Reduction in SLEDAI score by ≥ 4 points	% responders at wk 52	Major secondary outcome
<i>Change in PGA score from baseline</i>	<i>Mean change at wk 24</i>	<i>Major secondary outcome</i>
Steroid reduction weeks 40 to 52	% responders	Major secondary outcome
<i>SF-36 Physical component summary score</i>	<i>Mean change at wk 24</i>	<i>Major secondary outcome</i>
SLE Responder Index	% responders at week 76	Major secondary outcome
<i>SLICC/ACR damage index</i>	<i>Mean change at wk 52</i>	<i>Secondary outcome</i>
<i>FACIT-fatigue scale mean change from baseline</i>	<i>Mean change at clinic visits</i>	<i>Secondary outcome</i>
<i>EQ-5D score</i>	<i>Mean change at clinic visits</i>	<i>Secondary outcome</i>
<i>Change in PGA score from baseline</i>	<i>Mean change at wk 52</i>	<i>Secondary outcome</i>
<i>SF-36 Physical component summary score</i>	<i>Mean change at wk 52</i>	<i>Secondary outcome</i>
SLEDAI SLE flare index over 52 wks	Time to first flare	Secondary outcome
SLE Responder Index (SRI)	% responders at timed clinic visits	Other outcome reported
Modified SLE responder index	% responders at wk 52	Other outcome reported
No worsening in PGA score by ≥ 0.3	% responders at wk 52	Other outcome reported
No new BILAG 1A/2B domain scores	% responders at wk 52	Other outcome reported
<i>Change in SLEDAI score from baseline</i>	<i>Mean change at week 52</i>	<i>Other outcome reported</i>
Death	Number during exposure	Safety outcome
Treatment emergent adverse events	Number during exposure	Safety outcome
Serious infections	Number during exposure	Safety outcome
* Composite outcome measure consisting of ≥ 4 points improvement in SLEDAI score, no worsening in PGA by ≥ 0.3 points and no new BILAG 1A or 2B domain scores; FACIT = Functional Assessment of Chronic Illness Therapy; EQ-5D = EuroQoL 5 dimensions; BILAG = British Isles Lupus Assessment Group; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SF-36 = Short Form 36-Item Health Survey; SLICC = Systemic Lupus International Collaborating Clinics; ACR = American College of Rheumatology.		

Continuous outcomes are in italics.

Appendix 1

Search Strategies

Cochrane Central Register of Controlled Trials (CENTRAL)

CENTRAL searched via Cochrane Library Interface on 18/05/11

1	MeSH descriptor Lupus Erythematosus, Systemic explode all trees	418
2	(lupus NEAR/3 erythematosus) or (systemic* NEAR/3 lupus) or (SLE)	630
3	(#1 OR #2)	703
4	belimumab OR benlysta	6
5	(#3 AND #4)	4

Medline

Medline searched via Ovid Interface on 19/05/11

1	exp Lupus Erythematosus, Systemic/	42025
2	(lupus adj3 erythematosus).tw.	35497
3	(systemic* adj3 lupus).tw.	31639
4	1 or 2 or 3	50358
5	belimumab.mp.	68
6	benlysta.mp.	3
7	5 or 6	68
8	4 and 7	48
9	randomized controlled trial.pt.	305892
10	controlled clinical trial.pt.	82328
11	randomized.ab.	212836
12	placebo.ab.	124063
13	clinical trials as topic.sh.	153987
14	randomly.ab.	154440
15	trial.ti.	91188
16	9 or 10 or 11 or 12 or 13 or 14 or 15	711420
17	exp animals/ not humans.sh.	3582822
18	16 not 17	656689
19	8 and 18	24

RCT search filter used: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format. Box 6.4.b in the Cochrane handbook. Reference: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Medline In-process

Medline In-Process searched via Ovid Interface on 19/05/11

1	exp Lupus Erythematosus, Systemic/	0
2	(lupus adj3 erythematosus).tw.	1213
3	(systemic* adj3 lupus).tw.	873
4	1 or 2 or 3	1236
5	belimumab.mp.	8
6	benlysta.mp.	4
7	5 or 6	10
8	4 and 7	6

Embase

1	belimumab.mp.orexpbelumumab/	427
2	benlysta.mp.	24
3	1 or 2	428
4	exp systemic lupus erythematosus/	50906
5	(lupus adj3 erythematosus).tw.	40637
6	(systemic: adj3 lupus).tw.	36554
7	4 or 5 or 6	59739
8	3 and 7	302
9	random:.tw.	632763
10	placebo:.mp.	250140
11	double-blind:.tw.	116148
12	9 or 10 or 11	796900
13	8 and 12	144

RCT search filter used: Wong, et al. (2006) Best optimization of sensitivity and specificity.
 Reference: Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for
 detecting clinically sound treatment studies in EMBASE. J Med Libr Assoc. 2006
 Jan;94(1):41-7. PubMed PMID: 16404468; PubMed Central PMCID: PMC1324770.



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1-2
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3-4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis. http://bmjopen.bmj.com/site/about/guidelines.xhtml)	5



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	5
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 2 and Figure 3
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 1 and Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	See Figure 6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	11

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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Exists, available from authors
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5-6
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RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 8-12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Discussion
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
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From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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**Belimumab: a technological advance for SLE patients?
Report of a systematic review and meta-analysis**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-002852.R2
Article Type:	Research
Date Submitted by the Author:	19-Jun-2013
Complete List of Authors:	Kandala, Ngianga-Bakwin; University of Warwick, Warwick Medical School; University of Oxford, KEMRI-University of Oxford-Wellcome Trust Collaborative Programme, Malaria Public Health and Epidemiology Group, Centre for Geographic Medicine Connock, Martin; University of Warwick, Division of Health Sciences, Warwick Medical School Grove, Amy; University of Warwick, Division of Health Sciences, Warwick Medical School Sutcliffe, Paul; University of Warwick, Division of Health Sciences, Warwick Medical School Mohiuddin, Syed; University of Warwick, Division of Health Sciences, Warwick Medical School Hartley, Louise; University of Warwick, Division of Health Sciences, Warwick Medical School Court, Rachel; Warwick University, Division of Health Sciences Cummis, Ewen; McMDCLtd, UK, G12 9TJ, McMaster Development Consultants Gordon, Caroline; University of Birmingham, School of Immunity and Infection, College of Medical and Dental Sciences Clarke, Aileen; University of Warwick, Division of Health Sciences
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Immunology (including allergy), Evidence based practice, Public health, Pharmacology and therapeutics
Keywords:	CLINICAL PHARMACOLOGY, EPIDEMIOLOGY, PREVENTIVE MEDICINE, PUBLIC HEALTH

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1 **Belimumab: a technological advance for Systemic Lupus Erythematosus patients?**
2 **Report of a systematic review and meta-analysis**

3
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34 **Short Title:**

35 Systematic review on belimumab for SLE

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ARTICLE SUMMARY

ARTICLE FOCUS

- SLE is a complex multi-organ auto-immune disease subject to relapse and remission.
- Patients almost always have fatigue, skin rashes and arthritis and there is a wide variety of other problems which the disease can cause.
- Belimumab is a new treatment specifically targeted against SLE.

KEY MESSAGES

1. Combining the results from two RCTs suggests that belimumab is clinically effective for SLE patients.
2. However, all outcomes were systematically superior in one trial compared with the other.
3. Different trial conduct and populations mean that it is too early to draw generalisable conclusions.

STRENGTHS AND LIMITATIONS

- At first sight combined meta analytic evidence suggests that belimumab is clinically effective for patients with severe SLE.
- We suggest that it is too early to draw strong conclusions because the two relevant trials cover different populations in different countries and there may be differences in trial conduct and outcome assessment.

Abstract:

Objectives: To undertake a systematic review and meta-analysis to investigate clinical effectiveness of belimumab for patients with SLE and anti-nuclear and/or anti-dsDNA autoantibodies.

Methods: We searched eight electronic databases and reference lists for randomised controlled trials (RCTs) of belimumab against placebo or best supportive care. Quality assessment and random effects meta-analysis were undertaken.

Design: A meta-Analysis of RCTs.

Setting: NA

Participants: 2133 SLE patients

Interventions: NA

Primary and secondary outcome measures: Responder Index (SRI) at week 52.

Results: Three double-blind placebo-controlled RCTs (L02, BLISS-52 BLISS-76) investigated 2133 SLE patients. BLISS-52 and BLISS-76 trials recruited patients with anti-nuclear and/or anti-dsDNA autoantibodies and demonstrated belimumab effectiveness for the SLE Responder Index (SRI) at week 52. Ethnicity and geographical location of participants varied considerably between BLISS trials. Although tests for statistical heterogeneity were negative, BLISS-52 results were systematically more favourable for all measured outcomes. Meta-analysis of pooled 52-week SRI BLISS results showed benefit for belimumab (OR 1.63, 95% CI 1.27-2.09). By week 76, the primary SRI outcome in BLISS-76 was not statistically significant (OR 1.31, 95% CI 0.919-1.855).

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an auto-immune disease subject to relapse and remission. Incidence is estimated at between 1.0 and 10.0 per hundred thousand person years using different measures, and prevalence at between 20-70 per 100,000.^{1;2} SLE is a complex multi-organ disease with a number of different manifestations.³ Patients almost always have fatigue, often have skin rashes and arthritis and there is a wide variety of other problems which the disease can cause.

The American College of Rheumatology has defined 11 classification criteria, including: rash; photosensitivity; oral ulcers; arthritis; serositis; renal and neurological disorder.^{4;5}

Assessment of the patient can be difficult, as flares of the disease have to be distinguished from its complications, from comorbidity especially infection, and from adverse effects of medications.⁶ SLE is more common in women (in most studies 90% or more of cases are women²) and in those from black and other ethnic groups. Recently age-adjusted incidence rates have been produced showing that rates are highest in women aged 40 years and

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3 109 over.⁷ Mortality rates show that five year survival is high, at over 90%^{8:9} and an overall SMR
4 110 has been calculated as 2.4.¹⁰
5
6

7 111
8 112 Antinuclear antibodies are present in virtually all patients with SLE.¹¹ Anti-ds DNA antibodies
9 113 are present in 50-60% patients at some point in their disease but often transiently with active
10 114 disease.¹¹ Corticosteroids are the mainstay of treatment, they suppress disease but they
11 115 may cause organ damage. The aim of treatment is to maintain normal function whilst
12 116 suppressing disease activity and preventing organ damage,⁶ achieving these conflicting
13 117 aims can be difficult. Other drugs used include antimalarials such as hydroxychloroquine,
14 118 and immunosuppressive drugs such as azathioprine and mycophenolatemofetil. More
15 119 recently rituximab (a monoclonal antibody which reacts with the CD20 antigen expressed on
16 120 B cells) has also been used, although the largest trial undertaken to date failed to reach its
17 121 end point.¹²
18 122

19 123 Belimumab (Benlysta®) is an IgG1 monoclonal antibody which inhibits the activity of the
20 124 soluble cytokine BLyS (B lymphocyte stimulator; also known as BAFF).¹³ In contrast to
21 125 earlier SLE treatments, belimumab is targeted at the fundamental pathology of SLE and has
22 126 been widely interpreted as representing a step change in treatment options.¹³
23 127

24 128 Belimumab was recently licensed in the USA and in Europe for treatment of autoantibody-
25 129 positive SLE and is the first drug to be so licensed for several decades. The European
26 130 indication is for severely affected SLE patients with active, autoantibody-positive disease
27 131 and a high degree of disease activity exemplified by positive anti-ds DNA and low
28 132 complement despite standard therapy.¹³ Belimumab is administered by IV infusion
29 133 recommended at 10 mg belimumab / kg on days 0, 14 and 28, and at 28 day intervals
30 134 thereafter. A course of belimumab treatment for a 64 kg patient using the US list price of
31 135 \$1,477 (£926.37) for a 400 mg vial¹⁴ would be \$56,527 (£35,454) per year, and according to
32 136 the US average whole sale price of \$4.432 (£2780) / 400 mg vial¹⁵ would be \$42,545
33 137 (£26,684) per year.
34 138

35 139 A number of clinical measures have been developed for tracking the progression of SLE¹⁶
36 140 and for estimating the effects of treatment.¹⁷ They include the Physician's Global
37 141 Assessment (PGA), the SELENA-SLEDAI (Safety of Estrogen in Lupus National
38 142 Assessment-Systemic Lupus Erythematosus Disease Activity Index), the BILAG Index
39 143 (British Isles Lupus Assessment Group Index), and the SRI index (SLE Response Index).
40 144 Their major features are summarised in Figure 1. Their complexity means that outside
41 145 specialised centres they may not be widely used in routine clinical practice. The multiplicity
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3 146 of SLE manifestations and of the systems developed to measure them has resulted in a
4 147 proliferation of outcome measures that can be reported in trials of interventions for SLE. This
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6 148 in turn means that by chance at least some outcome measures will generate favourable
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8 149 results for an intervention; hence the US Federal Drug agency (FDA) in conjunction with
9
10 150 belimumab-trialists developed the SRI aimed at guarding against the possibility that
11
12 151 worsening in overall disease might be masked by apparent improvement in a more narrowly
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14 152 defined manifestation.
15

153
154 **[Insert Figure 1 here]**
155

156 Our objective was to synthesise findings from randomised controlled trials (RCTs) of
157 belimumab for patients with SLE and anti-nuclear and /or anti-ds DNA autoantibodies, to
158 make an overall assessment of the performance of this drug in relation to comparator
159 treatments using the SRI and other outcomes (as listed in Figure 1) and to assess the
160 findings of trials in the light of population samples and geographical factors.¹⁸
161

162 **METHODS**

163
164 The study was undertaken as part of work for the National Institute for Health Research,
165 Health Technology Assessment programme (Grant funding reference 10/73/01. Further
166 information is available from:www.hta.ac.uk/).
167

168 **Search scope**

169 We searched for RCTs investigating belimumab administered i.v. for patients with SLE and
170 anti-nuclear and /or anti-ds DNA autoantibodies. Comparators considered were belimumab
171 versus placebo and belimumab versus best supportive care. Outcomes included all disease-
172 related or health-status-related measures. There was no publication year restriction, but the
173 search was restricted to English language references only.
174

175 **Search strategy**

176 The following eight databases were searched: Cochrane Database of Systematic Reviews;
177 the Cochrane Central Register of Controlled Trials (CENTRAL); DARE; EMBASE; HTA
178 Database; Medline; Pre-Medline and Science Citation Index. Search strategies for these
179 databases used a combination of terms related to the population and interventions listed
180 above; the specific search strategies are provided in Appendix 1. In Medline and EMBASE
181 the subject strategies were combined with search strategies designed to identify RCTs.
182 (Appendix 1).

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4 184 Unpublished studies were identified using: Clinical Trials, Current Controlled Trials, EU
5 185 Clinical Trials Register, UK Clinical Research Network Study Portfolio, National Research
6 186 Register, WHO Clinical Trials Search Portal, NHS Evidence, Conference Proceedings
7 187 Citation Index -Science and Google.
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11 189 In addition, specific websites were searched: Medicines and Healthcare products Regulatory
12 190 Agency (MHRA), European Medicines Agency (EMA), US Food and Drug Administration
13 191 (FDA) and the following specific conference proceedings: American College of
14 192 Rheumatology, British Society of Rheumatology and the European League Against
15 193 Rheumatism (EULAR).
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17 194

18 195 *Inclusion criteria:* Publications were included if they described results from RCTs of
19 196 belimumab for SLE patients with positive autoantibodies. Two reviewers independently
20 197 assessed retrieved publications for inclusion. There were no disagreements between
21 198 reviewers.
22
23 199

24 200 *Date extraction:* Potentially relevant publications were obtained in full text and assessed by
25 201 the same two reviewers. One reviewer extracted data for all specified primary and secondary
26 202 outcome measures, for adverse events and deaths. A second reviewer checked extracted
27 203 data.
28
29 204

30 205 *Quality evaluation:* Quality assessment and risk of bias was guided by the Centre for
31 206 Reviews and Dissemination (CRD) checklist¹⁹ based on all information in the included
32 207 publications which specifies reporting of randomisation, concealment of allocation, group
33 208 balance, blinding, drop-outs, outcome reporting bias, and whether intention to treat analysis
34 209 was used.
35
36 210

37 211 *Statistical analysis:* Unadjusted odds ratios (ORs) and mean differences were calculated for
38 212 binary and continuous outcomes respectively. Statistical heterogeneity was calculated using
39 213 the I^2 statistic.^{20,21} There were too few studies for an analysis of publication bias.²¹ Although
40 214 our thorough search found no further studies, we cannot completely rule out that any method
41 215 for combining the two trials may result in an over-estimate or under-estimate of effect sizes
42 216 due to publication bias. Adjusted outcome measures were tabulated where these were
43 217 reported. A random effects meta-analysis²² was undertaken using the DerSimonian Laird
44 218 method in STATA version 11..²³ All graphs were prepared in Microsoft Excel 2010.
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220

221 RESULTS

222

223 Characteristics of included studies

224 We identified three placebo controlled RCTs of belimumab versus standard care: the phase
225 III trials termed BLISS-52²⁴ and BLISS-76²⁵ and a phase II trial (study L02).²⁶ The PRISMA
226 flow chart shows the process of identification of publications (see Figure 2). We identified an
227 on-going trial in Asia.²⁷ All three completed trials appeared to be of good quality; however
228 details of allocation concealment were meagre (Table 1). In meta-analysis we included the
229 two phase III trials (BLISS-52 and BLISS-76) since the population, trial design and primary
230 outcome was different in the L02 trial.

231

232 **[Insert Table 1 here]**

233

234 **[Insert Figure 2 here]**

235

236 BLISS-52,²⁴ BLISS-76²⁵ and study L02²⁶ have been published in peer reviewed journals,
237 however the fullest accounts in the public domain are in the FDA licensing approval
238 documents^{28,29} and the manufacturer's 2011 submission to the UK National Institute of
239 Health and Clinical Excellence (NICE).³⁰ Each of these placebo-controlled randomised trials
240 was designed with multiple randomised groups. In the L02 trial, patients received 1 or 4 or
241 10 mg/kg of belimumab or placebo, while in the BLISS trials the belimumab dose regimens
242 were 1mg/kg or 10 mg/kg. Both US and European licensing is for the 10mg/kg dose
243 regimen. In this article we focus on efficacy results for the 10mg/kg licensed regimen relative
244 to placebo. We also consider the off licence 1 mg/kg and 4 mg/kg dose regimens for
245 investigation of adverse events.

246

247 Centralised, stratified randomisation was used in all three trials and arms were generally well
248 balanced. For the phase III trials, stratification was undertaken according to race, baseline
249 proteinuria and disease activity score (SELENA SLEDAI); for the phase I study, disease
250 activity only was used as a stratification factor. All three trials recruited predominantly
251 female patients (~90%) and were described as double blind. The two BLISS studies were
252 conducted according to similar protocols.

253

254 There were differences in geographical distribution of the study centres and in the resulting
255 ethnic racial make-up of the study populations (Table 2 and Figure 3). Thus in BLISS-76,

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3 256 70% were Caucasian, 13% Native American and 3% Asian, respectively, whereas in BLISS-
4 257 52, 27% were Caucasian, 32% native American and 38% were Asian. Table 3 lists the major
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6 258 protocol pre-specified outcomes in the BLISS trials.
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8 259

9 260 There were additional population differences between BLISS and L02 trials at recruitment.
10 261 Reporting of results for patients with anti-nuclear and /or anti-ds DNA autoantibodies in L02
11 262 was only included for a post-hoc subgroup and primary outcomes measured in L02 were not
12 263 comparable with those of the BLISS studies. For these reasons, L02 study results are
13 264 included here only with regard to safety outcomes. For the BLISS trials a composite novel
14 265 primary outcome measure was developed *a priori* from discussions between the FDA and
15 266 the manufacturer and termed the SLE Response Index (SRI) (see Figure 1 and Table 3).
16 267 The protocol pre-specified primary end point was the proportion of SRI responders at week
17 268 52. This is taken as the primary outcome in this systematic review.
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25 270 **[Insert Table 2 here]**
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28 272 **[Insert Figure 3 here]**
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31 274 **[Insert Table 3 here]**
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34 276 **[Insert Figure 4 here]**
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37 278 Efficacy results in the two BLISS trials for major binary effectiveness outcomes including the
38 279 time to first SLE flare and to first severe flare are summarised in Figure 4. ORs have been
39 280 calculated using the proportions of patients with and without events reported in the journal
40 281 articles for these trials.^{24,25} Safety outcomes shown in Figure 4 were calculated after
41 282 combining the number of events across the three trials (L02, BLISS-52 and BLISS-76) and
42 283 are taken from the FDA documents. The hazard ratios (HRs) for time to flares were poorly
43 284 reported in journal articles and the data presented are taken from the manufacturer's
44 285 submission to the FDA.^{28,29} As shown in Figure 4 both trials satisfied this primary end point
45 286 with a better result for BLISS-52. The difference in percentage responders in the belimumab
46 287 group relative to placebo group was larger in BLISS-52 (14%), than in in BLISS-76 (9.4%).
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54 289 For the other binary effectiveness outcomes, the BLISS-52 trial delivered results which were
55 290 more favourable to belimumab than did BLISS-76, with the latter results failing to reach a
56 291 conventional level of statistical significance except for the ≥ 4 point improvement in SLEDAI

292 score at week 52. The journal articles and manufacturer's submissions to the FDA and to
293 NICE used a logistic regression model and reported ORs adjusted according to the
294 stratification factors employed at randomisation. Adjusted ORs for a response in BLISS-52
295 and in BLISS-76 were respectively 1.83 (95% CI: 1.30-2.59; $p = 0.0006$) and 1.52 (95% CI:
296 1.07-2.15; $p = 0.0207$). Again a superior response was found for the BLISS-52 trial. By
297 week 76, the unadjusted OR for the SRI response in the BLISS-76 trial ceased to reach
298 statistical significance (Figure 4); this also held for the reported OR adjusted by logistic
299 regression (OR 1.31, 95% CI: 0.92 – 1.87, $p = 0.1323$).²⁹

300
301 With regard to time to first flare or to first severe flare (each estimated over 52 weeks follow
302 up) the responses reported in the FDA submission are again superior for BLISS-52. Each
303 outcome failed to reach conventional statistical significance for BLISS-76. The FDA
304 submission additionally reported more mature results estimated over 76 weeks of follow up
305 for BLISS-76, and again these indicate lack of statistical significance for both outcomes (HR
306 for first flare: 1.05, 95% CI: 0.88 – 1.27; HR for first severe flare 1.30, 95% CI: 0.92 – 1.85).

307
308 Figure 4 shows the results for major safety outcomes. Although there were more serious
309 adverse events, more serious infections and more deaths associated with belimumab than
310 with placebo, none of the ORs for these outcomes reached statistical significance. There
311 were 14 deaths during the controlled phase of the three trials; three in the placebo group
312 ($n=675$), and 11 in the belimumab groups ($n=1458$) with six in the 10mg/kg and five in the
313 1mg/kg groups, respectively (odds ratio 11.7; 95% CI 0.474 to 6.124). The causes of death
314 were various: five were infection-related, three were strokes, three cardiovascular events,
315 two suicides, one cancer, one from SLE-related complications, and two were of unknown
316 cause.

317
318 Results for continuous outcomes are summarised in Figure 5. Mean changes from baseline
319 reported in the BLISS journal articles and in the manufacturer's submissions to the FDA and
320 NICE have been used to generate a mean difference statistic (sometimes termed "weighted
321 mean difference"³¹). These revealed superiority of response in BLISS-52 relative to BLISS-
322 76 for all reported outcomes, a pattern similar to that for binary outcomes. Mean changes
323 from baseline for FACIT-fatigue scores and for EQ-5D utility scores (not pictured) did not
324 reach statistical significance and again improvement seen in BLISS-52 for these was
325 superior to that seen in BLISS-76.

326
327 In summary, BLISS-52 showed a systematic superiority over BLISS-76 in apparent benefit of
328 belimumab across the full range of test responses (binary, time to event and continuous),

329 which may reflect geographical differences between the trials (Table 2 and Figure 3). The
330 primary outcome in BLISS-76 was achieved (adjusted OR 1.52, 95% CI 1.07 to 2.15) but
331 large geographical differences within BLISS-76 were striking: rates of 32% (46 out of 145),
332 and 35% (47 out of 136), for placebo and belimumab respectively, were reported for patients
333 from North America and Canada (a < 3% greater response for belimumab), whereas for
334 BLISS-76 patients outside these regions a > 15% greater response for belimumab over
335 placebo was reported, 71 of 137 (51.8%) for belimumab and 47 of 130 (36.1%) for placebo.
336 In comparison, the corresponding rates for patients from Latin America in BLISS-52 were
337 49% placebo (71 out of 145), and 61% belimumab (85 out of 140).

338

339 **[Insert Figure 5 here]**

340

341 The manufacturer's submissions to the FDA and to NICE combined results from the two
342 BLISS trials by pooling the patients and applying the logistic regression model described
343 above; for the primary outcome (proportion of SRI responders at week 52), the difference
344 between the belimumab and placebo groups was 11.8%.²⁸

345

346 An alternate method of combining trials by meta-analysis of study level results from the two
347 BLISS trials showed a statistically significant benefit of belimumab for most main outcomes
348 including SRI, SELENA-SLEDAI, worsening in PGA, steroid use, BILAG score or, time to
349 first severe flare, and mean number of flares and severe flares over 52 weeks and weeks 24
350 to 52 (Figure 6). Tests for statistical heterogeneity of ORs and HR outcomes were not
351 significant. This Meta-analysis offers an alternative to the manufacturer logistic regression
352 and it is justified for two trials of substantial size (N=577 and N=548), however, these results,
353 and those from pooling individual patient data from the two trials prior to logistic regression,
354 mask the systematic difference between trials across all outcomes.

355

356 **[Insert Figure 6 here]**

357

358 **DISCUSSION**

359 We undertook a systematic review of the clinical effectiveness of belimumab, a new
360 treatment targeted at systemic lupus erythematosus (SLE) patients with anti-nuclear and /or
361 anti-ds DNA autoantibodies. We performed an extensive search and systematic review of
362 both completed and on-going trials using a number of databases and by checking reference
363 lists. Data were extracted independently and studies were quality assessed. Random effects
364 meta-analysis was undertaken.

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4 366 We identified three RCTs (L02, BLISS-52, BLISS-76) reporting data on over 2000 patients.
5
6 367 In contrast to the BLISS trials, L02 recruited patients who were not necessarily current
7
8 368 carriers of anti-nuclear or anti ds DNA antibodies at study commencement. L02 failed to
9
10 369 demonstrate clinical effectiveness for its primary end points.²⁶ Meta-analysis of the BLISS
11
12 370 studies showed a benefit of belimumab with the main primary outcome (SRI), showing
13
14 371 improvement at 52 weeks (OR 1.63; 95% CI: 1.27-2.09 p<0.001) although by week 76, the
15
16 372 proportion of SRI responders in the BLISS-76 trial ceased to reach statistical significance
17
18 373 (OR 1.31; 95% CI: 0.92–1.87 p=0.1323). There were no significant differences between
19
20 374 placebo and intervention groups in quality of life or adverse events.
21
22 375
23 376 We found that the benefits of belimumab were systematically greater across the board
24
25 377 (although not significantly so) in the BLISS-52 trial and although tests for statistical
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27 378 heterogeneity were negative, geographical location of study centres and the racial
28
29 379 background and ethnicity of participants varied considerably. If the two BLISS trials were
30
31 380 drawn from the same underlying populations, whilst one might expect outcomes to differ, we
32
33 381 would anticipate that this would occur randomly between trials– some better some worse
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35 382 than the other.
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37 383
38 384 A few studies have directly assessed the existence of and importance of geographical
39
40 385 differences in trial outcomes.³²⁻³⁴ Key factors contributing to such differences are variation in
41
42 386 underlying patient population characteristics and variation in study execution. Vickers et al,³³
43
44 387 found that Eastern Asian and Eastern European studies had a higher proportion of positive
45
46 388 trial results when compared to other countries. This is seen in the present case for the
47
48 389 primary outcome where both the belimumab and placebo response rates in BLISS 52 study
49
50 390 were greater than those in BLISS-76 and, remarkably, the placebo response rate in BLISS-
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52 391 52 (49%) was greater than that for the belimumab arm of BLISS-76 (43%). O’Shea and
53
54 392 DeMets also report that within the Beta-Blocker Heart Attack Trial (BHAT), not only was
55
56 393 there a difference in the direction, but also in the size of treatment effect between Canada
57
58 394 and the US, although it should be noted that the original aim of that trial was not
59
60 395 investigation of international differences in treatment effect.³⁵ One study found that 96-99%
396
397 of the total variance in the “*Global utilisation of strategies to open occluded coronary arteries*
398
399 *IV acute coronary syndromes*” (GUSTO IV ACS) trial could be accounted for by patient-level
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401 factors.³⁶
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402 endpoints and, by implication, results of interest³⁷⁻⁴⁴ since it is possible that in centres in
403 different countries these factors may differ systematically.³⁷ Equally, underlying differences
404 in populations and countries (ethnicity, genetics, socio-economic status and health-care
405 systems), and the nature and epidemiology of SLE according to ethnic background may
406 result in differences in reporting of outcomes and pooled results.

407
408 The outcomes used in the BLISS trials would be unfamiliar to most of the investigators and it
409 is possible that criteria may have differed between countries. In particular the Physician
410 Global Assessment (PGA) is an important element of the outcomes measured (see Figure
411 1). PGA was measured as an outcome in itself, and it is also incorporated in SRI. PGA is of
412 concern because as a global physician assessment of a patient's SLE status, it is subjective.
413 The investigators reported a nearly 10% difference between the BLISS-52 and BLISS-76
414 studies in estimates of percentage change in PGA score in intervention groups at week 24
415 compared to baseline and this single result in one of the two trials is likely to have had an
416 important influence on findings of the effectiveness of belimumab in SLE patients.

417
418 The latest results of belimumab in patients with SLE (phase II study design, uncontrolled
419 extension study) reported that of 449 patients with active SLE (USA/Canada) 177 (39.4%)
420 patients remained on treatment after 7 years of therapy (i.e. approximately 1746 cumulative
421 patients-years) and that this subgroup exhibited durable sustained improvement in SLE
422 disease activity (SRI and PGA).³⁰

423 424 **CONCLUSIONS**

425 In conclusion, systematic review and random effects meta-analysis of two RCTs of
426 belimumab for patients with autoantibody positive SLE demonstrated positive results in the
427 main outcome at week 52. However, in view of the different populations studied at different
428 locations in the BLISS trials and the consistently superior results from one trial compared to
429 the other, we consider that population heterogeneity, geographical differences and variation
430 in trial conduct and outcome assessment may have played a role in influencing outcomes.
431 However the generalisability of results pooled meta-analytically or by logistic regression
432 should be viewed with caution and we suggest that it is too early to draw strong conclusions
433 in this case.

434 435 436 **Acknowledgements**

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438 Technology Assessment programme for funding this work.

439

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443

Competing interest statement

No conflicts of interest.

446

Contributions:

N-BK: Conception and design. Data analysis and interpretation. Drafting the article. Critical revisions for important intellectual content. Approval of final article for submission.

MC: Conception and design. Data analysis and interpretation. Literature review. Interpretation of results. Drafting the article. Critical revisions for important intellectual content. Approval of final article for submission.

AG: Interpretation of results. Critical revisions for important intellectual content.

PS: Literature review. Interpretation of results. Critical revisions for important intellectual content.

SM: Data analysis and interpretation. Interpretation of results. Critical revisions for important intellectual content.

LH: Literature review. Interpretation of results. Critical revisions for important intellectual content.

RC: Literature review. Critical revisions for important intellectual content.

EC: Interpretation of results. Critical revisions for important intellectual content.

CG: Interpretation of results. Critical revisions for important intellectual content.

AC: Conception and design. Interpretation of results. Drafting the article. Critical revisions for important intellectual content. Approval of final article for submission.

All authors read and approved the final manuscript.

466

Data sharing

No additional data available.

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3 469 Figure legends:
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6 470

7 471 **FIGURE 1: Summary of the major clinical measures used in SLE trials**

8 472 **FIGURE 2: PRISMA 2009 Flow Diagram for Belimumab in SLE RCTs and on-going**
9 473 **trials**

10 474 **FIGURE 3: Differing centre locations in the BLISS 52 and BLISS 76 multicentre trials**

11 475 **FIGURE 4: Summary of results for major binary and time to event outcomes in**
12 476 **belimumab RCTs**

13
14 477 **FIGURE 5: Summary of results for major continuous outcomes in BLISS 52 and BLISS**
15 478 **76 trials**

16
17 479 **FIGURE 6: Meta-analysis of major outcomes in the two BLISS trials**

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631 **Table 1 Quality assessment of the included trials**

QUALITY ITEMS	L02	BLISS-52	BLISS-76
Does reporting suggest that randomisation was carried out appropriately?	Yes	Yes	Yes
Does reporting suggest that the concealment of treatment allocation adequate?	Unclear	Unclear	Unclear
Were the groups reported as similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors reported as blind to treatment allocation?	Yes	Yes	Yes
Were any unexpected imbalances in drop-outs reported between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes	Yes

632 Quality assessment used information presented in the study journal articles and the manufacturer's
 633 submission to the US FDA and was based on CRD guidance (2008)¹⁹ for undertaking systematic
 634 reviews in health care (CRD = Centre for Reviews and Dissemination, York: Centre for Reviews and
 635 Dissemination)

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638 **Table 2: Major characteristics of included studies**

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STUDY	Treatment (IV)	N	Mean Age (SD) yrs	SELENA-SLEDAI at entry	Geographical distribution of patients	Ethnic make-up of trial participants			Number and location of STUDY CENTRES
L02 2006 Phase II 52 week	Bel 1 mg/kg Bel 4 mg/kg Bel 10 mg/kg Placebo	114 111 111 113	42 (11)	> 4 points	US (98%), Canada (2%)	Caucasian	NR	69.9%	59 in N. America
						African American	NR	24.7%	
						Latino	NR	18.5%	
BLISS-52 2009 Phase III 52 week	Bel 1 mg/kg Bel 10 mg/kg Placebo	288 290 287	36 (11)	> 6 points	Latin America (50%), Asia (38%), E Europe & Australia (13%)	Caucasian	229	27%	90 in Pacific Asia. 11 in S. America & E. Europe
						Asian	327	38%	
						Black/African Am	30	4%	
						Alaskan Nat./Am Indian	279	32%	
						Nat. Hawaiian/Pacific Islander	0	0%	
BLISS-76 2009 Phase III 76 week	Bel 1 mg/kg Bel 10 mg/kg Placebo	271 273 275	40 (12)	> 6 points	US & Canada (53%), W Europe (25%) E Europe (11%) Latin America (11%)	Caucasian	569	70%	136 in N. America & Europe
						Asian	28	3%	
						Black/African Am	118	14%	
						Alaskan Nat./Am Indian	103	13%	
						Nat. Hawaiian/Pacific Islander	1	0%	
Multiracial	8	1%							

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642 NR = not reported

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646 **Table 3: Outcomes defined and pre specified in the BLISS 52 and BLISS 76 trials and**
647 **their accompanying designated status**

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Outcome	Measure	Outcome specification
SLE Responder Index (SRI*)	% responders at wk 52	Primary outcome
Reduction in SLEDAI score by ≥ 4 points	% responders at wk 52	Major secondary outcome
<i>Change in PGA score from baseline</i>	<i>Mean change at wk 24</i>	<i>Major secondary outcome</i>
Steroid reduction weeks 40 to 52	% responders	Major secondary outcome
<i>SF-36 Physical component summary score</i>	<i>Mean change at wk 24</i>	<i>Major secondary outcome</i>
SLE Responder Index	% responders at week 76	Major secondary outcome
<i>SLICC/ACR damage index</i>	<i>Mean change at wk 52</i>	<i>Secondary outcome</i>
<i>FACIT-fatigue scale mean change from baseline</i>	<i>Mean change at clinic visits</i>	<i>Secondary outcome</i>
<i>EQ-5D score</i>	<i>Mean change at clinic visits</i>	<i>Secondary outcome</i>
<i>Change in PGA score from baseline</i>	<i>Mean change at wk 52</i>	<i>Secondary outcome</i>
<i>SF-36 Physical component summary score</i>	<i>Mean change at wk 52</i>	<i>Secondary outcome</i>
SLEDAI SLE flare index over 52 wks	Time to first flare	Secondary outcome
SLE Responder Index (SRI)	% responders at timed clinic visits	Other outcome reported
Modified SLE responder index	% responders at wk 52	Other outcome reported
No worsening in PGA score by ≥ 0.3	% responders at wk 52	Other outcome reported
No new BILAG 1A/2B domain scores	% responders at wk 52	Other outcome reported
<i>Change in SLEDAI score from baseline</i>	<i>Mean change at week 52</i>	<i>Other outcome reported</i>
Death	Number during exposure	Safety outcome
Treatment emergent adverse events	Number during exposure	Safety outcome
Serious infections	Number during exposure	Safety outcome
* Composite outcome measure consisting of ≥ 4 points improvement in SLEDAI score, no worsening in PGA by ≥ 0.3 points and no new BILAG 1A or 2B domain scores; FACIT = Functional Assessment of Chronic Illness Therapy; EQ-5D = EuroQoL 5 dimensions; BILAG = British Isles Lupus Assessment Group; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SF-36 = Short Form 36-Item Health Survey; SLICC = Systemic Lupus International Collaborating Clinics; ACR = American College of Rheumatology.		

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650 Continuous outcomes are in italics.

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3 1 **Belimumab: a technological advance for Systemic Lupus Erythematosus patients?**
4 **Report of a systematic review and meta-analysis**
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37 34 **Short Title:**

38 35 Systematic review on belimumab for SLE
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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is an auto-immune disease subject to relapse and remission. Incidence is estimated at between 1.0 and 10.0 per hundred thousand person years using different measures, and prevalence at between 20-70 per 100,000.^{1,2} SLE is a complex multi-organ disease with a number of different manifestations.³ Patients almost always have fatigue, often have skin rashes and arthritis and there is a wide variety of other problems which the disease can cause.

The American College of Rheumatology has defined 11 classification criteria, including: rash; photosensitivity; oral ulcers; arthritis; serositis; renal and neurological disorder.^{4,5} Assessment of the patient can be difficult, as flares of the disease have to be distinguished from its complications, from comorbidity especially infection, and from adverse effects of medications.⁶ SLE is more common in women (in most studies 90% or more of cases are women²) and in those from black and other ethnic groups. Recently age-adjusted incidence rates have been produced showing that rates are highest in women aged 40 years and over.⁷ Mortality rates show that five year survival is high, at over 90%^{8,9} and an overall SMR has been calculated as 2.4.¹⁰

Antinuclear antibodies are present in virtually all patients with SLE.¹¹ Anti-ds DNA antibodies are present in 50-60% patients at some point in their disease but often transiently with active disease.¹¹ Corticosteroids are the mainstay of treatment, they suppress disease but they may cause organ damage. The aim of treatment is to maintain normal function whilst suppressing disease activity and preventing organ damage,⁶ achieving these conflicting aims can be difficult. Other drugs used include antimalarials such as hydroxychloroquine, and immunosuppressive drugs such as azathioprine and mycophenolatemofetil. More recently rituximab (a monoclonal antibody which reacts with the CD20 antigen expressed on B cells) has also been used, although the largest trial undertaken to date failed to reach its end point.¹²

Belimumab (Benlysta®) is an IgG1 monoclonal antibody which inhibits the activity of the soluble cytokine BLyS (B lymphocyte stimulator; also known as BAFF).¹³ In contrast to earlier SLE treatments, belimumab is targeted at the fundamental pathology of SLE and has been widely interpreted as representing a step change in treatment options.¹³

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3 72 Belimumab was recently licensed in the USA and in Europe for treatment of autoantibody-
4 73 positive SLE and is the first drug to be so licensed for several decades. The European
5 74 indication is for severely affected SLE patients with active, autoantibody-positive disease
6 75 and a high degree of disease activity exemplified by positive anti-ds DNA and low
7 76 complement despite standard therapy.¹³ Belimumab is administered by IV infusion
8 77 recommended at 10 mg belimumab / kg on days 0, 14 and 28, and at 28 day intervals
9 78 thereafter. A course of belimumab treatment for a 64 kg patient using the US list price of
10 79 \$1,477 (£926.37) for a 400 mg vial¹⁴ would be \$56,527 (£35,454) per year, and according to
11 80 the US average whole sale price of \$4.432 (£2780) / 400 mg vial¹⁵ would be \$42,545
12 81 (£26,684) per year.
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20 83 A number of clinical measures have been developed for tracking the progression of SLE¹⁶
21 84 and for estimating the effects of treatment.¹⁷ They include the Physician's Global
22 85 Assessment (PGA), the SELENA-SLEDAI (Safety of Estrogen in Lupus National
23 86 Assessment-Systemic Lupus Erythematosus Disease Activity Index), the BILAG Index
24 87 (British Isles Lupus Assessment Group Index), and the SRI index (SLE Response Index).
25 88 Their major features are summarised in Figure 1. Their complexity means that outside
26 89 specialised centres they may not be widely used in routine clinical practice. The multiplicity
27 90 of SLE manifestations and of the systems developed to measure them has resulted in a
28 91 proliferation of outcome measures that can be reported in trials of interventions for SLE. This
29 92 in turn means that by chance at least some outcome measures will generate favourable
30 93 results for an intervention; hence the US Federal Drug agency (FDA) in conjunction with
31 94 belimumab-trialists developed the SRI aimed at guarding against the possibility that
32 95 worsening in overall disease might be masked by apparent improvement in a more narrowly
33 96 defined manifestation.
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46 100 Our objective was to synthesise findings from randomised controlled trials (RCTs) of
47 101 belimumab for patients with SLE and anti-nuclear and /or anti-ds DNA autoantibodies, to
48 102 make an overall assessment of the performance of this drug in relation to comparator
49 103 treatments using the SRI and other outcomes (as listed in Figure 1) and to assess the
50 104 findings of trials in the light of population samples and geographical factors.¹⁸
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55 106 **METHODS**

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3 108 The study was undertaken as part of work for the National Institute for Health Research,
4 109 Health Technology Assessment programme (Grant funding reference 10/73/01. Further
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6 110 information is available from:www.hta.ac.uk/).
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9 112 **Search scope**

10 113 We searched for RCTs investigating belimumab administered i.v. for patients with SLE and
11 114 anti-nuclear and /or anti-ds DNA autoantibodies. Comparators considered were belimumab
12 115 versus placebo and belimumab versus best supportive care. Outcomes included all disease-
13 116 related or health-status-related measures. There was no publication year restriction, but the
14 117 search was restricted to English language references only.
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17 119 **Search strategy**

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20 120 The following eight databases were searched: Cochrane Database of Systematic Reviews;
21 121 the Cochrane Central Register of Controlled Trials (CENTRAL); DARE; EMBASE; HTA
22 122 Database; Medline; Pre-Medline and Science Citation Index. Search strategies for these
23 123 databases used a combination of terms related to the population and interventions listed
24 124 above; the specific search strategies are provided in Appendix 1. In Medline and EMBASE
25 125 the subject strategies were combined with search strategies designed to identify RCTs.
26 126 (Appendix 1).
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29 128 Unpublished studies were identified using: Clinical Trials, Current Controlled Trials, EU
30 129 Clinical Trials Register, UK Clinical Research Network Study Portfolio, National Research
31 130 Register, WHO Clinical Trials Search Portal, NHS Evidence, Conference Proceedings
32 131 Citation Index -Science and Google.
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35 133 In addition, specific websites were searched: Medicines and Healthcare products Regulatory
36 134 Agency (MHRA), European Medicines Agency (EMA), US Food and Drug Administration
37 135 (FDA) and the following specific conference proceedings: American College of
38 136 Rheumatology, British Society of Rheumatology and the European League Against
39 137 Rheumatism (EULAR).
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42 139 *Inclusion criteria:* Publications were included if they described results from RCTs of
43 140 belimumab for SLE patients with positive autoantibodies. Two reviewers independently
44 141 assessed retrieved publications for inclusion. There were no disagreements between
45 142 reviewers.
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3 144 *Date extraction:* Potentially relevant publications were obtained in full text and assessed by
4 145 the same two reviewers. One reviewer extracted data for all specified primary and secondary
5 146 outcome measures, for adverse events and deaths. A second reviewer checked extracted
6 147 data.
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11 149 *Quality evaluation:* Quality assessment and risk of bias was guided by the Centre for
12 150 Reviews and Dissemination (CRD) checklist¹⁹ based on all information in the included
13 151 publications which specifies reporting of randomisation, concealment of allocation, group
14 152 balance, blinding, drop-outs, outcome reporting bias, and whether intention to treat analysis
15 153 was used.
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20 155 *Statistical analysis:* Unadjusted odds ratios (ORs) and mean differences were calculated for
21 156 binary and continuous outcomes respectively. Statistical heterogeneity was calculated using
22 157 the I² statistic.^{20;21} There were too few studies for an analysis of publication bias.²¹ Although
23 158 our thorough search found no further studies, we cannot completely rule out that any method
24 159 for combining the two trials may result in an over-estimate or under-estimate of effect sizes
25 160 due to publication bias. Adjusted outcome measures were tabulated where these were
26 161 reported. A random effects meta-analysis²² was undertaken using the DerSimonian Laird
27 162 method in STATA version 11..²³ All graphs were prepared in Microsoft Excel 2010.
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35 165 RESULTS

36 166 37 38 167 **Characteristics of included studies**

39 168 We identified three placebo controlled RCTs of belimumab versus standard care: the phase
40 169 III trials termed BLISS-52²⁴ and BLISS-76²⁵ and a phase II trial (study L02).²⁶ The PRISMA
41 170 flow chart shows the process of identification of publications (see Figure 2). We identified an
42 171 on-going trial in Asia.²⁷ All three completed trials appeared to be of good quality; however
43 172 details of allocation concealment were meagre (Table 1). In meta-analysis we included the
44 173 two phase III trials (BLISS-52 and BLISS-76) since the population, trial design and primary
45 174 outcome was different in the L02 trial.
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180 BLISS-52,²⁴ BLISS-76²⁵ and study L02²⁶ have been published in peer reviewed journals,
181 however the fullest accounts in the public domain are in the FDA licensing approval
182 documents^{28;29} and the manufacturer's 2011 submission to the UK National Institute of
183 Health and Clinical Excellence (NICE).³⁰ Each of these placebo-controlled randomised trials
184 was designed with multiple randomised groups. In the L02 trial, patients received 1 or 4 or
185 10 mg/kg of belimumab or placebo, while in the BLISS trials the belimumab dose regimens
186 were 1mg/kg or 10 mg/kg. Both US and European licensing is for the 10mg/kg dose
187 regimen. In this article we focus on efficacy results for the 10mg/kg licensed regimen relative
188 to placebo. We also consider the off licence 1 mg/kg and 4 mg/kg dose regimens for
189 investigation of adverse events.

190
191 Centralised, stratified randomisation was used in all three trials and arms were generally well
192 balanced. For the phase III trials, stratification was undertaken according to race, baseline
193 proteinuria and disease activity score (SELENA SLEDAI); for the phase I study, disease
194 activity only was used as a stratification factor. All three trials recruited predominantly
195 female patients (~90%) and were described as double blind. The two BLISS studies were
196 conducted according to similar protocols.

197
198 There were differences in geographical distribution of the study centres and in the resulting
199 ethnic racial make-up of the study populations (Table 2 and Figure 3). Thus in BLISS-76,
200 70% were Caucasian, 13% Native American and 3% Asian, respectively, whereas in BLISS-
201 52, 27% were Caucasian, 32% native American and 38% were Asian. Table 3 lists the major
202 protocol pre-specified outcomes in the BLISS trials.

203
204 There were additional population differences between BLISS and L02 trials at recruitment.
205 Reporting of results for patients with anti-nuclear and /or anti-ds DNA autoantibodies in L02
206 was only included for a post-hoc subgroup and primary outcomes measured in L02 were not
207 comparable with those of the BLISS studies. For these reasons, L02 study results are
208 included here only with regard to safety outcomes. For the BLISS trials a composite novel
209 primary outcome measure was developed *a priori* from discussions between the FDA and
210 the manufacturer and termed the SLE Response Index (SRI) (see Figure 1 and Table 3).
211 The protocol pre-specified primary end point was the proportion of SRI responders at week
212 52. This is taken as the primary outcome in this systematic review.

213
214 **[Insert Table 2 here]**

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3 216 **[Insert Figure 3 here]**

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6 218 **[Insert Table 3 here]**

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9 220 **[Insert Figure 4 here]**

10 221

11 222 Efficacy results in the two BLISS trials for major binary effectiveness outcomes including the
12 223 time to first SLE flare and to first severe flare are summarised in Figure 4. ORs have been
13 224 calculated using the proportions of patients with and without events reported in the journal
14 225 articles for these trials.^{24;25} Safety outcomes shown in Figure 4 were calculated after
15 226 combining the number of events across the three trials (L02, BLISS-52 and BLISS-76) and
16 227 are taken from the FDA documents. The hazard ratios (HRs) for time to flares were poorly
17 228 reported in journal articles and the data presented are taken from the manufacturer's
18 229 submission to the FDA.^{28;29} As shown in Figure 4 both trials satisfied this primary end point
19 230 with a better result for BLISS-52. The difference in percentage responders in the belimumab
20 231 group relative to placebo group was larger in BLISS-52 (14%), than in in BLISS-76 (9.4%).
21 232

22 233 For the other binary effectiveness outcomes, the BLISS-52 trial delivered results which were
23 234 more favourable to belimumab than did BLISS-76, with the latter results failing to reach a
24 235 conventional level of statistical significance except for the ≥ 4 point improvement in SLEDAI
25 236 score at week 52. The journal articles and manufacturer's submissions to the FDA and to
26 237 NICE used a logistic regression model and reported ORs adjusted according to the
27 238 stratification factors employed at randomisation. Adjusted ORs for a response in BLISS-52
28 239 and in BLISS-76 were respectively 1.83 (95% CI: 1.30-2.59; $p = 0.0006$) and 1.52 (95% CI:
29 240 1.07-2.15; $p = 0.0207$). Again a superior response was found for the BLISS-52 trial. By
30 241 week 76, the unadjusted OR for the SRI response in the BLISS-76 trial ceased to reach
31 242 statistical significance (Figure 4); this also held for the reported OR adjusted by logistic
32 243 regression (OR 1.31, 95% CI: 0.92 – 1.87, $p = 0.1323$).²⁹
33 244

34 245 With regard to time to first flare or to first severe flare (each estimated over 52 weeks follow
35 246 up) the responses reported in the FDA submission are again superior for BLISS-52. Each
36 247 outcome failed to reach conventional statistical significance for BLISS-76. The FDA
37 248 submission additionally reported more mature results estimated over 76 weeks of follow up
38 249 for BLISS-76, and again these indicate lack of statistical significance for both outcomes (HR
39 250 for first flare: 1.05, 95% CI: 0.88 – 1.27; HR for first severe flare 1.30, 95% CI: 0.92 – 1.85).
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252 Figure 4 shows the results for major safety outcomes. Although there were more serious
253 adverse events, more serious infections and more deaths associated with belimumab than
254 with placebo, none of the ORs for these outcomes reached statistical significance. There
255 were 14 deaths during the controlled phase of the three trials; three in the placebo group
256 (n=675), and 11 in the belimumab groups (n=1458) with six in the 10mg/kg and five in the
257 1mg/kg groups, respectively (odds ratio 11.7; 95% CI 0.474 to 6.124). The causes of death
258 were various: five were infection-related, three were strokes, three cardiovascular events,
259 two suicides, one cancer, one from SLE-related complications, and two were of unknown
260 cause.

261
262 Results for continuous outcomes are summarised in Figure 5. Mean changes from baseline
263 reported in the BLISS journal articles and in the manufacturer's submissions to the FDA and
264 NICE have been used to generate a mean difference statistic (sometimes termed "weighted
265 mean difference"³¹). These revealed superiority of response in BLISS-52 relative to BLISS-
266 76 for all reported outcomes, a pattern similar to that for binary outcomes. Mean changes
267 from baseline for FACIT-fatigue scores and for EQ-5D utility scores (not pictured) did not
268 reach statistical significance and again improvement seen in BLISS-52 for these was
269 superior to that seen in BLISS-76.

270
271 In summary, BLISS-52 showed a systematic superiority over BLISS-76 in apparent benefit of
272 belimumab across the full range of **test responses** (binary, time to event and continuous),
273 which may reflect geographical differences between the trials (Table 2 and Figure 3). The
274 primary outcome in BLISS-76 was achieved (adjusted OR 1.52, 95% CI 1.07 to 2.15) but
275 large geographical differences within BLISS-76 were striking: rates of 32% (46 out of 145),
276 and 35% (47 out of 136), for placebo and belimumab respectively, were reported for patients
277 from North America and Canada (a < 3% greater response for belimumab), whereas for
278 BLISS-76 patients outside these regions a > 15% greater response for belimumab over
279 placebo was reported, 71 of 137 (51.8%) for belimumab and 47 of 130 (36.1%) for placebo.
280 In comparison, the corresponding rates for patients from Latin America in BLISS-52 were
281 49% placebo (71 out of 145), and 61% belimumab (85 out of 140).

282

283 **[Insert Figure 5 here]**

284

285 The manufacturer's submissions to the FDA and to NICE combined results from the two
286 BLISS trials by pooling the patients and applying the logistic regression model described
287 above; for the primary outcome (proportion of SRI responders at week 52), the difference
288 between the belimumab and placebo groups was 11.8%.²⁸

289
290 An alternate method of combining trials by meta-analysis of study level results from the two
291 BLISS trials showed a statistically significant benefit of belimumab for most main outcomes
292 including SRI, SELENA-SLEDAI, worsening in PGA, steroid use, BILAG score or, time to
293 first severe flare, and mean number of flares and severe flares over 52 weeks and weeks 24
294 to 52 (Figure 6). Tests for statistical heterogeneity of ORs and HR outcomes were not
295 significant. **This Meta-analysis offers an alternative to the manufacturer logistic regression
296 and it is justified for two trials of substantial size (N=577 and N=548), however, these results,
297 and those from pooling individual patient data from the two trials prior to logistic regression,
298 mask the systematic difference between trials across all outcomes.**

299
300 **[Insert Figure 6 here]**

302 DISCUSSION

303 We undertook a systematic review of the clinical effectiveness of belimumab, a new
304 treatment targeted at systemic lupus erythematosus (SLE) patients with anti-nuclear and /or
305 anti-ds DNA autoantibodies. We performed an extensive search and systematic review of
306 both completed and on-going trials using a number of databases and by checking reference
307 lists. Data were extracted independently and studies were quality assessed. Random effects
308 meta-analysis was undertaken.

309
310 We identified three RCTs (L02, BLISS-52, BLISS-76) reporting data on over 2000 patients.
311 In contrast to the BLISS trials, L02 recruited patients **who** were not necessarily current
312 carriers of anti-nuclear or anti ds DNA antibodies at study commencement. L02 failed to
313 demonstrate clinical effectiveness for its primary end points.²⁶ **Meta-analysis of the BLISS
314 studies showed a benefit of belimumab with the main primary outcome (SRI), showing
315 improvement at 52 weeks (OR 1.63; 95% CI: 1.27-2.09 p<0.001) although by week 76, the
316 proportion of SRI responders in the BLISS-76 trial ceased to reach statistical significance
317 (OR 1.31; 95% CI: 0.92–1.87 p=0.1323). There were no significant differences between
318 placebo and intervention groups in quality of life or adverse events.**

319
320 We found that the benefits of belimumab were systematically greater across the board
321 (although not significantly so) in the BLISS-52 trial and although tests for statistical
322 heterogeneity were negative, geographical location of study centres and the racial
323 background and ethnicity of participants varied considerably. If the two BLISS trials were
324 drawn from the same underlying populations, whilst one might expect outcomes to differ, we

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3 325 would anticipate that this would occur randomly between trials– some better some worse
4 326 than the other.
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8 328 A few studies have directly assessed the existence of and importance of geographical
9 329 differences in trial outcomes.³²⁻³⁴ Key factors contributing to such differences are variation in
10 330 underlying patient population characteristics and variation in study execution. Vickers et al,³³
11 331 found that Eastern Asian and Eastern European studies had a higher proportion of positive
12 332 trial results when compared to other countries. This is seen in the present case for the
13 333 primary outcome where both the belimumab and placebo response rates in BLISS 52 study
14 334 were greater than those in BLISS-76 and, remarkably, the placebo response rate in BLISS-
15 335 52 (49%) was greater than that for the belimumab arm of BLISS-76 (43%). O’Shea and
16 336 DeMets also report that within the Beta-Blocker Heart Attack Trial (BHAT), not only was
17 337 there a difference in the direction, but also in the size of treatment effect between Canada
18 338 and the US, although it should be noted that the original aim of that trial was not
19 339 investigation of international differences in treatment effect.³⁵ One study found that 96-99%
20 340 of the total variance in the “*Global utilisation of strategies to open occluded coronary arteries*
21 341 *IV acute coronary syndromes*” (GUSTO IV ACS) trial could be accounted for by patient-level
22 342 factors.³⁶
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32 344 International trials need to harmonise training of investigators, patient selection, treatment
33 345 management, thresholds to centre admission, access to facilities, ascertainment of
34 346 endpoints and, by implication, results of interest³⁷⁻⁴⁴ since it is possible that in centres in
35 347 different countries these factors may differ systematically.³⁷ Equally, underlying differences
36 348 in populations and countries (ethnicity, genetics, socio-economic status and health-care
37 349 systems), and the nature and epidemiology of SLE according to ethnic background may
38 350 result in differences in reporting of outcomes and pooled results.
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44 352 The outcomes used in the BLISS trials would be unfamiliar to most of the investigators and it
45 353 is possible that criteria may have differed between countries. In particular the Physician
46 354 Global Assessment (PGA) is an important element of the outcomes measured (see Figure
47 355 1). PGA was measured as an outcome in itself, and it is also incorporated in SRI. PGA is of
48 356 concern because as a global physician assessment of a patient’s SLE status, it is subjective.
49 357 The investigators reported a nearly 10% difference between the BLISS-52 and BLISS-76
50 358 studies in estimates of percentage change in PGA score in intervention groups at week 24
51 359 compared to baseline and this single result in one of the two trials is likely to have had an
52 360 important influence on findings of the effectiveness of belimumab in SLE patients.
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3 362 The latest results of belimumab in patients with SLE (phase II study design, uncontrolled
4 363 extension study) reported that of 449 patients with active SLE (USA/Canada) 177 (39.4%)
5
6 364 patients remained on treatment after 7 years of therapy (i.e. approximately 1746 cumulative
7
8 365 patients-years) and that this subgroup exhibited durable sustained improvement in SLE
9 366 disease activity (SRI and PGA).³⁰

10 367

11 368 **CONCLUSIONS**

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13 369 In conclusion, systematic review and random effects meta-analysis of two RCTs of
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15 370 belimumab for patients with autoantibody positive SLE demonstrated positive results in the
16
17 371 main outcome at week 52. However, in view of the different populations studied at different
18
19 372 locations in the BLISS trials and the consistently superior results from one trial compared to
20
21 373 the other, we consider that population heterogeneity, geographical differences and variation
22
23 374 in trial conduct and outcome assessment may have played a role in influencing outcomes.
24
25 375 However the generalisability of results pooled meta-analytically or by logistic regression
26
27 376 should be viewed with caution and we suggest that it is too early to draw strong conclusions
28
29 377 in this case.
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32 379 **ARTICLE FOCUS**

- 33 380
- 34 381 • SLE is a complex multi-organ auto-immune disease subject to relapse and remission.
 - 35 382 • Patients almost always have fatigue, skin rashes and arthritis and there is a wide
36 383 variety of other problems which the disease can cause.
 - 37 384 • Belimumab is a new treatment specifically targeted against SLE.
- 38
39 384

40 385 **KEY MESSAGES**

- 41 386
- 42 387 1. Combining the results from two RCTs suggests that belimumab is clinically effective
43 388 for SLE patients.
 - 44 389 2. However, all outcomes were systematically superior in one trial compared with the
45 390 other.
 - 46 391 3. Different trial conduct and populations mean that it is too early to draw generalisable
47 392 conclusions.
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53 394 **STRENGTHS AND LIMITATIONS**

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3 395 • At first sight combined meta analytic evidence suggests that belimumab is clinically
4 396 effective for patients with severe SLE.
5
6 397 • We suggest that it is too early to draw strong conclusions because the two relevant
7 398 trials cover different populations in different countries and there may be differences in
8 399 trial conduct and outcome assessment.

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11 400

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19 408

20 409 **Competing interest statement**

21 410 No conflicts of interest.

22 411

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24 413 N-BK: Conception and design. Data analysis and interpretation. Drafting the article. Critical
25 414 revisions for important intellectual content. Approval of final article for submission.

26 415 MC: Conception and design. Data analysis and interpretation. Literature review.
27 416 Interpretation of results. Drafting the article. Critical revisions for important intellectual
28 417 content. Approval of final article for submission.

29 418 AG: Interpretation of results. Critical revisions for important intellectual content.

30 419 PS: Literature review. Interpretation of results. Critical revisions for important intellectual
31 420 content.

32 421 SM: Data analysis and interpretation. Interpretation of results. Critical revisions for important
33 422 intellectual content.

34 423 LH: Literature review. Interpretation of results. Critical revisions for important intellectual
35 424 content.

36 425 RC: Literature review. Critical revisions for important intellectual content.

37 426 EC: Interpretation of results. Critical revisions for important intellectual content.

38 427 CG: Interpretation of results. Critical revisions for important intellectual content.

39 428 AC: Conception and design. Interpretation of results. Drafting the article. Critical revisions
40 429 for important intellectual content. Approval of final article for submission.

41 430 All authors read and approved the final manuscript.

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FIGURE 1: Summary of the major clinical measures used in SLE trials

SELENA-SLEDAI: Encompasses 24 weighted items scored dichotomously as present or absent in the previous 10 days, thus improvement or worsening of a manifestation is not captured. Overall disease activity is scored over a range of 0 to 105 points. A minimum clinically meaningful score change = a decrease of 6 points (overall improvement) or an increase of 8 points (overall worsening). A designated change in score (≥ 4 points) between baseline and follow up can be used to dichotomise patients into responders or non-responders for overall disease.

BILAG: Includes 86 items grouped in eight organ systems to assesses organ system involvement over the last four weeks compared to preceding four weeks based on physicians intention to treat using classifications ranging from A to E as follows: A = worsening usually requiring intensification of steroids or immunosuppressant treatments; B = worsening usually requiring antimalarials, nonsteroidal anti-inflammatory drugs (NSAIDs), or low dose steroids; C = stable disease (symptomatic therapy); D = improvement; E = system never involved. Unlike SELENA-SLEDAI it can detect worsening or improvement in individual organ system involvement.

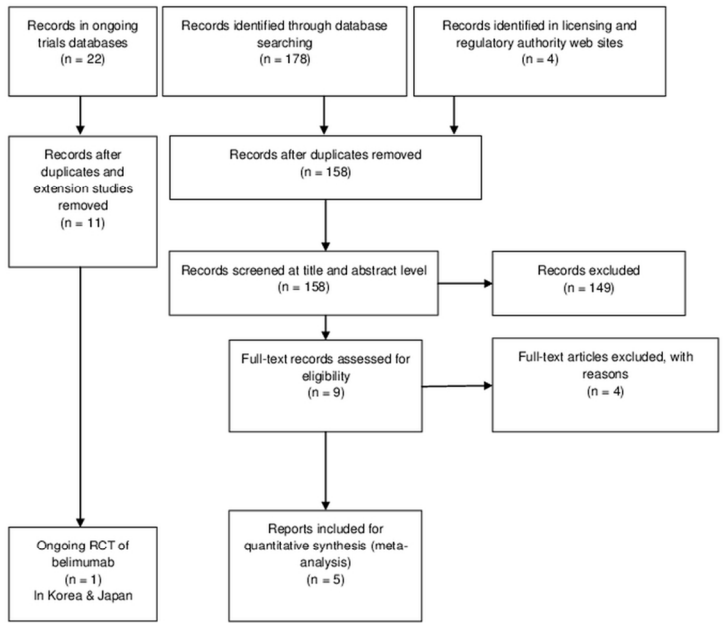
PGA: Is employed to monitor change in patient overall disease activity; typically a visual analogue scale is used ranging between no disease = 0, mild disease = 1, moderate disease = 2, and severe disease = 3.

SRI: A composite instrument (combining elements of SELENA-SLEDAI, BILAG and PGA) developed by belimumab-trialists in conjunction with the US FDA. It allows patients to be dichotomised into responders or non-responders according to predefined assessment criteria in each of the component elements, such as: a SELENA-SLEDAI improvement of ≥ 4 points, plus no worsening in PGA score by > 0.3 points, plus no new BILAG organ system involvement scoring category A in one system or category B in two or more systems. An advantage of SRI, over any one of its components used alone, may be that it can detect SLE improvement in some initial manifestation(s) while guarding against the possibility that worsening in organ systems or overall disease activity might be masked.

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FIGURE 2: PRISMA 2009 Flow Diagram for Belimumab in SLE RCTs and on-going trials



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FIGURE 3: Differing centre locations in the BLISS 52 and BLISS 76 multicentre trials



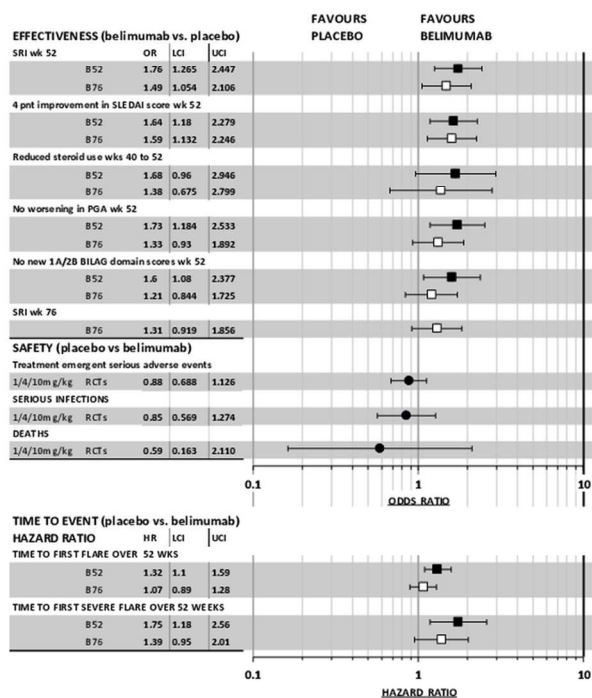
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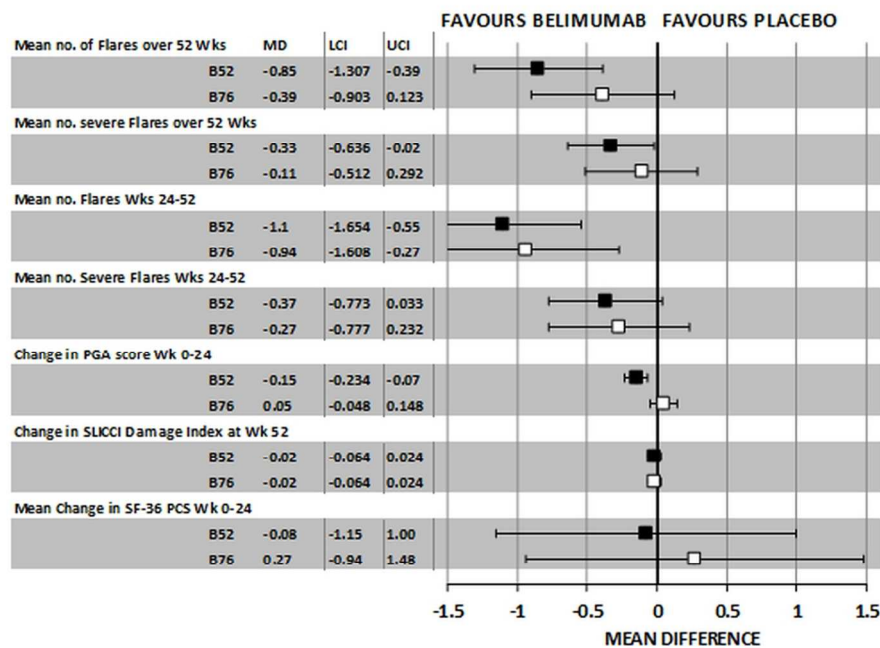
FIGURE 4: Summary of results for major binary and time to event outcomes in belimumab RCTs

Except for safety outcomes the results shown are for the BLISS 52 and BLISS 76 trials. Odds ratios (OR) were calculated from the event rates reported in journal publications; hazard ratios are from data presented in the manufacturer's submission to the FDA. The BLISS trials were well balanced for baseline characteristics (disease, duration, Gender, race, baseline IgG, autoantibody, and complement levels, baseline SLEDAI and PGA scores, BILAG, organ domain involvement, SLICC Damage Index score, and Proteinuria). Safety outcomes are based on data presented in FDA documents.



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FIGURE 5: Summary of results for major continuous outcomes in BLISS 52 and BLISS 76 trials

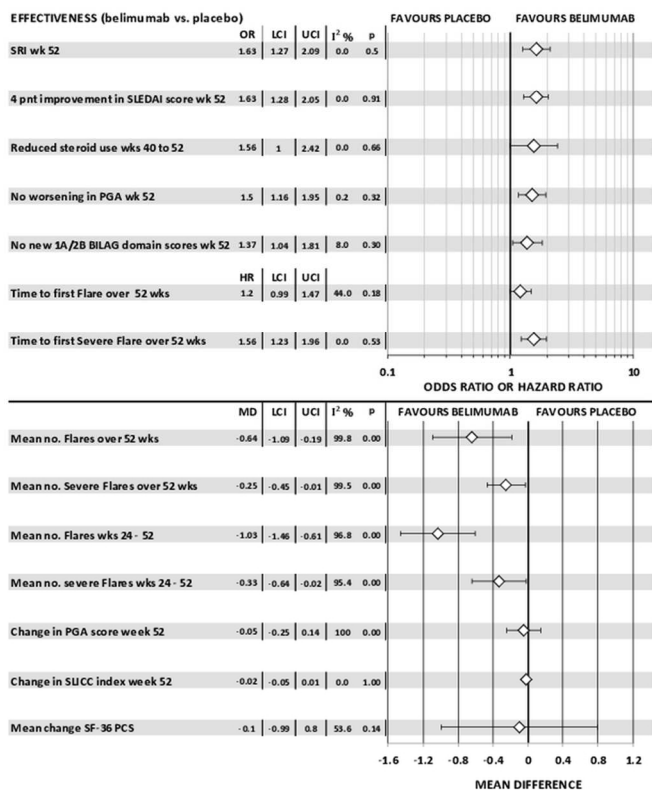


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FIGURE 6: Meta-analysis of major outcomes in the two BLISS trials

Upper panel shows pooled estimates for binary and time to event outcomes (OR = odds ratio; HR = hazard ratio). Lower panel shows pooled estimates for continuous outcomes (MD = mean difference). SLICC = Systemic Lupus International Collaborating Clinics, the SLICC index is a measure of organ damage. Meta-analysis was conducted using random effects method (DerSimonian Laird).



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Appendix 1

Search Strategies

Cochrane Central Register of Controlled Trials (CENTRAL)

CENTRAL searched via Cochrane Library Interface on 18/05/11

1	MeSH descriptor Lupus Erythematosus, Systemic explode all trees	418
2	(lupus NEAR/3 erythematosus) or (systemic* NEAR/3 lupus) or (SLE)	630
3	(#1 OR #2)	703
4	belimumab OR benlysta	6
5	(#3 AND #4)	4

Medline

Medline searched via Ovid Interface on 19/05/11

1	exp Lupus Erythematosus, Systemic/	42025
2	(lupus adj3 erythematosus).tw.	35497
3	(systemic* adj3 lupus).tw.	31639
4	1 or 2 or 3	50358
5	belimumab.mp.	68
6	benlysta.mp.	3
7	5 or 6	68
8	4 and 7	48
9	randomized controlled trial.pt.	305892
10	controlled clinical trial.pt.	82328
11	randomized.ab.	212836
12	placebo.ab.	124063
13	clinical trials as topic.sh.	153987
14	randomly.ab.	154440
15	trial.ti.	91188
16	9 or 10 or 11 or 12 or 13 or 14 or 15	711420
17	exp animals/ not humans.sh.	3582822
18	16 not 17	656689
19	8 and 18	24

RCT search filter used: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format. Box 6.4.b in the Cochrane handbook. Reference: Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org

Medline In-process

Medline In-Process searched via Ovid Interface on 19/05/11

1	exp Lupus Erythematosus, Systemic/	0
2	(lupus adj3 erythematosus).tw.	1213
3	(systemic* adj3 lupus).tw.	873
4	1 or 2 or 3	1236
5	belimumab.mp.	8
6	benlysta.mp.	4
7	5 or 6	10
8	4 and 7	6

Embase

1	belimumab.mp.orexpbelumab/	427
2	benlysta.mp.	24
3	1 or 2	428
4	exp systemic lupus erythematosus/	50906
5	(lupus adj3 erythematosus).tw.	40637
6	(systemic: adj3 lupus).tw.	36554
7	4 or 5 or 6	59739
8	3 and 7	302
9	random:.tw.	632763
10	placebo:.mp.	250140
11	double-blind:.tw.	116148
12	9 or 10 or 11	796900
13	8 and 12	144

RCT search filter used: Wong, et al. (2006) Best optimization of sensitivity and specificity. Reference: Wong SS, Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. J Med Libr Assoc. 2006 Jan;94(1):41-7. PubMed PMID: 16404468; PubMed Central PMCID: PMC1324770.



PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Exists, available from authors
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 8-10
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 8-12
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis)	Page 5-6

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PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 5-6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 8-12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figures
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Tables
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Discussion
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	End of paper

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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