TRANSPARENCY COMMITTEE
Opinion
25 June 2014

BENLYSTA 120 mg, powder for concentrate for solution for infusion
B/1 vial of 120 mg (CIP: 34009 580 875 8 5)

BENLYSTA 400 mg, powder for concentrate for solution for infusion
B/1 vial of 400 mg (CIP: 34009 580 876 4 6)

Applicant: GLAXOSMITHKLINE

<table>
<thead>
<tr>
<th>INN</th>
<th>Belimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code (2014)</td>
<td>L04AA26 (selective immunosuppressants)</td>
</tr>
<tr>
<td>Reason for the review</td>
<td>Re-assessment of the Actual Benefit at the Transparency Committee's request. Re-assessment of the IAB at the company’s request</td>
</tr>
<tr>
<td>List concerned</td>
<td>Hospital use (French Public Health Code L.5123 2)</td>
</tr>
<tr>
<td>Indication concerned</td>
<td>&quot;BENLYSTA (belimumab) is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy.&quot;</td>
</tr>
<tr>
<td>Actual Benefit</td>
<td>Substantial</td>
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<td>----------------</td>
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</tr>
<tr>
<td>Improvement in Actual Benefit</td>
<td>Given a modest efficacy and the lack of data in severe forms of renal and neurological involvement and the uncertainties regarding long term safety, the improvement in actual benefit provided by BENLYSTA, as an add-on to the usual treatment, remains minor (IAB IV) in the treatment of adult patients with active, autoantibody positive systemic lupus erythematosus with a high degree of disease activity despite treatment with synthetic antimalarials, NSAIDs, corticosteroids and possibly immunosuppressants, depending on the specific organ involvement.</td>
</tr>
<tr>
<td>Therapeutic use</td>
<td>Second line treatment in the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) as an add-on to standard treatment with synthetic antimalarials, NSAIDs, corticosteroids and possibly immunosuppressants, depending on the specific organ involvement, after failing or being intolerant to properly conducted treatment.</td>
</tr>
</tbody>
</table>
## 01 ADMINISTRATIVE AND REGULATORY INFORMATION

<table>
<thead>
<tr>
<th>Marketing Authorisation</th>
<th>13/07/2011 (centralised procedure)</th>
</tr>
</thead>
</table>
| Prescribing and dispensing conditions /special status | List I  
Medicinal product reserved for hospital use. Prescription by specialists in internal medicine, rheumatology, nephrology or dermatology only.  
RMP: long-term safety studies |

<table>
<thead>
<tr>
<th>ATC Classification</th>
</tr>
</thead>
</table>
| 2014 L Antineoplastic and immunomodulating agents  
L04 Immunosuppressants  
L04A Immunosuppressants  
L04AA Selective immunosuppressants  
L04AA26 belimumab |

## 02 BACKGROUND

During the initial assessment of BENLYSTA for listing, the Transparency Committee concluded a substantial actual benefit (AB) and a minor improvement in actual benefit (IAB IV) in the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite treatment with synthetic antimalarials, NSAIDs, corticosteroids and/or immunosuppressants, depending on the specific organ systems involved, given the lack of data in severe forms of renal and neurological involvement and uncertainties regarding long-term safety (see opinion of 29 February 2012).

In its recommendations, the Committee wished:
- to re-assess BENLYSTA within 2 years
- to have a significant number of French patients included in the long-term placebo-controlled study provided in the RMP and with the aim of evaluating the long-term infectious and carcinogenic risks.

In its current application, the company has submitted the available new efficacy and safety data and is requesting re-assessment of the IAB on the basis of data relating to corticosteroid sparing, reduced fatigue and reduced flare-ups.

## 03 THERAPEUTIC INDICATIONS

"BENLYSTA (belimumab) is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy."
"BENLYSTA (belimumab) treatment should be initiated and supervised by a qualified physician experienced in the diagnosis and treatment of SLE. BENLYSTA (belimumab) infusions should be administered by a qualified healthcare professional trained to give infusion therapy. Administration of BENLYSTA (belimumab) may result in hypersensitivity reactions and infusion reactions. Therefore, BENLYSTA (belimumab) should be administered in an environment where resources for managing such reactions are immediately available. There are no or insufficient data available on the effects of BENLYSTA (belimumab) in patients with severe active lupus nephritis or severe active central nervous system lupus. Therefore, BENLYSTA (belimumab) cannot be recommended to treat these conditions.

**Posology**

Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of BENLYSTA (belimumab). The recommended dose regimen is 10 mg/kg BENLYSTA (belimumab) on Days 0, 14 and 28, and at 4-week intervals thereafter. The patient's condition should be evaluated continuously. Discontinuation of treatment with BENLYSTA (belimumab) should be considered if there is no improvement in disease control after 6 months of treatment.

**Special populations**

*Older people (>65 years)*

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

*Renal impairment*

Belimumab has been studied in a limited number of SLE patients with renal impairment. On the basis of the available information, dose adjustment is not required in patients with mild, moderate or severe renal impairment. Caution is however recommended in patients with severe renal impairment due to the lack of data in this population.

*Hepatic impairment*

No specific studies with BENLYSTA (belimumab) have been conducted in patients with hepatic impairment. Patients with hepatic impairment are unlikely to require dose adjustment.

*Paediatric population*

The safety and efficacy of BENLYSTA (belimumab) in children (less than 18 years of age) has not been established. No data are available.

**Method of administration**

BENLYSTA (belimumab) is administered intravenously by infusion, and must be reconstituted and diluted before administration. For instructions on reconstitution, dilution, and storage of the medicinal product before administration, see section 6.6 (of the SPC). BENLYSTA (belimumab) should be infused over a 1-hour period.

BENLYSTA (belimumab) must not be administered as an intravenous bolus. The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life-threatening adverse reaction."
05 CLINICALLY RELEVANT COMPARATORS

05.1 Medicinal products

BENLYSTA is the only treatment indicated in SLE after failure of standard treatment (synthetic antimalarials, NSAIDs, corticosteroids and immunosuppressants).

05.2 Other health technologies

Not applicable.

> Conclusion
There is no clinically relevant comparator for BENLYSTA in this indication.

06 SUMMARY OF PREVIOUS ASSESSMENTS

<table>
<thead>
<tr>
<th>Date of opinion</th>
<th>29/02/2012 (listing for hospital use)</th>
</tr>
</thead>
</table>
| Indication      | "BENLYSTA (belimumab) is indicated as add-on therapy in adult patients with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy."
| AB              | SLE is a protean and polymorphic autoimmune disease mainly affecting women during ovulatory activity (9 women for every man), progressing via flare-ups of variable severity that may become life threatening. This proprietary medicinal product is intended as symptomatic therapy. Public health benefit SLE is a rare disease. The burden of this disease is therefore low, as is the one covered by the indication. There is a public health need (Second Plan "Rare Diseases 2011-2014"). In view of the available data, the impact of BENLYSTA on the morbidity and mortality of treated patients is low and there is no impact on quality of life. Furthermore, BENLYSTA is not expected to have any impact on the organisation of care. The transposability of trial results to everyday practice is debatable, especially due to the fact that patients with severe renal and neurological involvement were excluded from the trials and to concerns regarding the long-term safety (especially the risk of cancer) of this monoclonal antibody. Therefore the proprietary medicinal product BENLYSTA provides only a partial response to the public health need expressed. Consequently, it is not expected that BENLYSTA will benefit public health in this indication. The efficacy adverse effects ratio is modest. |
This medicinal product is a second-line therapy in the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (e.g., positive anti-dsDNA and low complement) as an add-on to standard treatment, after failing or being intolerant to properly conducted treatment (synthetic antimalarials, NSAIDs, corticosteroids and/or immunosuppressants, depending on the specific organ system involvement). In the absence of data in patients with severe renal and neurological involvement, belimumab prescription is not recommended in these forms of lupus.

There is no validated therapeutic alternative in the event of failure of or intolerance to a treatment consisting of synthetic antimalarials, NSAIDs, corticosteroids and immunosuppressants.

The actual benefit of BENLYSTA 120 mg and 400 mg, powder for concentrate for solution for infusion is substantial.

IAB

Given a modest efficacy and the lack of data in severe forms of renal and neurological involvement and the uncertainties regarding long-term safety, the improvement in actual benefit provided by BENLYSTA, as an add-on to the usual treatment, is minor (IAB IV) in the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite treatment with synthetic antimalarials, NSAIDs, corticosteroids and/or immunosuppressants, depending on the specific organ system involvement.

Studies requested

The Committee asks to have a significant number of French patients included in the long-term placebo-controlled study provided in the RMP and with the aim of evaluating the long-term infectious and carcinogenic risks. The number of patients included should be sufficient to be representative of the French situation.
07 ANALYSIS OF AVAILABLE DATA

07.1 Efficacy

7.1.1 Review of previously assessed data

The efficacy and safety of belimumab were evaluated in two phase III comparative, placebo-controlled, randomised studies (BLISS 52 and BLISS 76) in patients with active SLE at baseline according to the diagnostic criteria of the American College of Rheumatology (ACR) and characterised by:
- a SELENA-SLEDAI score of 6 during the screening visit,
- and positive antinuclear antibodies (ANA) (ANA titre ≥ 1:80),
- and/or positive anti-dsDNA antibodies (≥ 30 units/ml) at two independent measurements before randomisation,
- and receiving standard treatment for lupus (including at least one of the following treatments: NSAIDS, antimalarials, corticosteroids, immunosuppressants) unchanged and at a stable dose for at least 30 days. This treatment may be adjusted during the study according to a regimen predefined in the protocol. Patients requiring a change to the standard treatment for their SLE other than those authorised by the protocol were declared treatment failures/non-responders.

A total of 1684 patients were included and divided into three groups, belimumab 10 mg/kg, belimumab 1 mg/kg (dosage not included in the marketing authorisation) and placebo. The study treatments were administered by IV infusion for one hour every 28 days up to 48 weeks in BLISS 52 and up to 72 weeks in BLISS 76. The primary efficacy endpoint was the SLE responder index (SRI), a composite endpoint, measured at 52 weeks in both studies.

The SRI is defined by the percentage of patients simultaneously satisfying the following three conditions:
- reduction by at least 4 points of the SELENA-SLEDAI score,
- absence of any new involvement of a system or organ defined by one BILAG A item or two BILAG B items,
- no worsening of the overall health status of the patient as judged by the physician, worsening being defined by an increase >0.30 on the PGA scale.

The SRI at 52 weeks was higher with belimumab 10 mg/kg than with the placebo:
- BLISS 52: 57.6% versus 43.6%, i.e. a difference of 14.03% (p = 0.0006)
- BLISS 76: 43.2% versus 33.8%, i.e. a difference of 9.41% (p = 0.0207)
- pooled analysis of the two studies: 50.6% versus 38.8%, i.e. a difference of 11.8% (p < 0.0001)

These differences observed in favour of belimumab, although statistically significant, are modest.

A pooled analysis of two studies, conducted post hoc at the request of the EMA, was done in three subgroups of patients whose characteristics could define severe disease. In these three subgroups, differences in terms of SRI at 52 weeks in favour of belimumab versus placebo were greater than in the total study population:
- SELENA-SLEDAI score ≥ 10: 18.9%
- taking corticosteroids and low C3/C4 levels at baseline: 21.1%
- low C3/C4 levels and anti-dsDNA autoantibodies: 19.8%

On the basis of these results, the indication of the marketing authorisation is limited to patients with active lupus with autoantibodies and with a high degree of disease activity despite standard treatment.

1 See TC opinion of 29 February 2012
2 See the definition in Appendix 1.
3 See the definition in Appendix 2.
A phase II, randomised, double-blind, placebo controlled study was also provided in the dossier (study LSBL02). The objective of this study was to evaluate the efficacy of three doses (1.4 and 10 m/kg) of belimumab as an add-on to the standard treatment in 449 adults with SLE according to the 1997 ACR criteria and active defined by:

- a SELENA-SLEDAI score ≥ 4
- a history of measurable antinuclear, anti-dsDNA, anti-Sm, anti-RNP, anti-Ro or antiphospholipid autoantibodies.

Patients had to be on stable treatment for their lupus including (alone or in combination):
- prednisone (5-40 mg/day)
- antimalarials
- NSAIDs
- Immunosuppressant (methotrexate, azathioprine, leflunomide or mycophenolate mofetil).

This study included a 48-week double-blind treatment phase with an evaluation of the efficacy at weeks 24 and 52 and an extension phase (from 56 to 76 weeks), during which all patients received belimumab at a dose of 10 mg/kg (n = 345).

The co-primary efficacy endpoints were:
- the percentage of change in the SELENA-SLEDAI score at 24 weeks,
- and the time to onset of the first mild/moderate or severe lupus flare (defined by the SLE Flare Index (SFI) over 52 weeks).

No significant difference was observed between belimumab and placebo on the two co-primary efficacy endpoints for any of the dosages studied.

A post-hoc analysis showed the superiority of belimumab (all doses combined) relative to placebo at 52 weeks on the change in the SELENA-SLEDAI score in the population of autoantibody positive patients (ANA titre > 1:80 and/or anti-dsDNA antibodies ≥ 30 IU/ml) and a SELENA-SLEDAI score ≥ 8 (pre-defined subgroup) at baseline: -28.8% with belimumab versus -14.2% with placebo (p = 0.04335).

7.1.2 New clinical efficacy data

The company has provided a post-hoc analysis of BLISS 52 and BLISS 76 combined and the 7 year results of study LSBL99, the extension phase of the phase II study LSBL02 on corticosteroid sparing, fatigue (FACIT-Fatigue score⁴) and lupus flare-ups. These endpoints were secondary endpoints.

Given that patients included in study LSBL99 may have a mild to moderate form of SLE, which does not comply with the indication of the marketing authorisation, limited to severe forms of the disease, and that the methodology of the extension phase was non comparative, the results of this study will not be considered.

The results of the observational study (OBSErve) conducted in the United States and Germany will not be presented insofar as they do not reflect French clinical practice.

⁴ FACIT-Fatigue: A questionnaire including 13 items clinically evaluating fatigue associated with chronic diseases. The score ranges from 0 (the worst score) to 52 (the best score), a positive difference indicating an improvement. A difference of 3-4 points is considered to be clinically relevant.
Impact of belimumab on oral corticosteroid administration:

**BLISS 52 and BLISS 76 studies:**
In BLISS 52, the percentage of patients whose mean prednisone dose was reduced by ≥ 25% from baseline to ≤ 7.5 mg/day during weeks 40 to 52 was greater with belimumab, but only at the dose of 1 mg/kg, than with the placebo (difference of 8.61%, p = 0.0252).

In BLISS 76, no difference was demonstrated between the belimumab and placebo groups in terms of corticosteroid sparing.

The post-hoc analysis combining the results of both studies shows a difference in favour of the 10 mg/kg dose of belimumab relative to placebo on this same endpoint: 17.9% versus 12.3%, p=0.0451.

In this pooled analysis, a difference in favour of belimumab 10 mg/kg is also observed on the following endpoints (see Table 1):
- Mean of the reductions in total cumulative doses of corticosteroids
- Mean of the increases in total cumulative doses of corticosteroids
- Change in the mean cumulative doses of corticosteroids relative to baseline
- Change in the mean daily doses of corticosteroids relative to baseline

In the subgroups of patients with severe active disease characterised by a SELENA-SLEDAI score ≥ 10, corticosteroid use and low C3/C4 levels at baseline or low C3/C4 levels and anti-dsDNA autoantibodies, a significant difference versus placebo in the percentage of patients whose mean dose of prednisone was reduced by at least 25% from baseline to a level ≤ 7.5 mg/day during weeks 40 to 52 appears only for the subgroup of patients with a SELENA SLEDAI score ≥10 (see Table 1).

1684 patients were included in this analysis. In all, 86.3% of patients were treated for their lupus by corticosteroids, including 58% at a prednisone or equivalent dose > 7.5 mg/day.

**Table 1:** Combined analysis of BLISS 52 and BLISS 76 on the percentage of patients whose mean dose of prednisone was reduced by at least 25% from baseline to a level ≤ 7.5 mg/day during weeks 40 to 52

<table>
<thead>
<tr>
<th>Combined analysis of BLISS-52/76</th>
<th>Placebo N = 562</th>
<th>Belimumab 10 mg/kg N = 563</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose of corticosteroids ± SD at baseline, mg/day</td>
<td>12.3 ± 7.9</td>
<td>12.8 ± 8.5</td>
</tr>
<tr>
<td>Prednisone reduction ≥ 25% versus baseline to reach a dose ≤ 7.5 mg/day between weeks 40 and 52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>318</td>
<td>324</td>
</tr>
<tr>
<td>Response (number, %)</td>
<td>39 (12.3%)</td>
<td>58 (17.9%)</td>
</tr>
<tr>
<td>p (versus placebo)</td>
<td></td>
<td>0.0451</td>
</tr>
<tr>
<td>Post-hoc analyses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean of the reductions in total cumulative doses of corticosteroids, mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p (versus placebo)</td>
<td>542</td>
<td>741</td>
</tr>
<tr>
<td>Mean of the increases in total cumulative doses of corticosteroids, mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p (versus placebo)</td>
<td>1458</td>
<td>1272</td>
</tr>
<tr>
<td>Change in the mean cumulative doses of corticosteroids relative to baseline, mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p (versus placebo)</td>
<td>916</td>
<td>531</td>
</tr>
<tr>
<td>Change in the mean daily doses of corticosteroids relative to baseline, mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p (versus placebo)</td>
<td>+2.51</td>
<td>+1.46</td>
</tr>
</tbody>
</table>

Subgroup analysis: SELENA-SLEDAI score ≥ 10:

<p>| Prednisone reduction ≥ 25% versus baseline to reach a dose of ≤ 7.5 mg/day between weeks 40 and 52 |
|---------------------------------|----------------|----------------|
| N | 298 | 296 |</p>
<table>
<thead>
<tr>
<th>Response (number, %)</th>
<th>6.6%</th>
<th>17.2%</th>
<th>p (versus placebo)</th>
<th>0.026</th>
</tr>
</thead>
</table>

**Subgroup analysis: Taking corticosteroids and low C3/C4 levels at baseline:**

<table>
<thead>
<tr>
<th>Prednisone reduction ≥ 25% versus baseline to reach a dose of ≤ 7.5 mg/day between weeks 40 and 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
</tr>
<tr>
<td>Response (number, %)</td>
</tr>
<tr>
<td>p (versus placebo)</td>
</tr>
</tbody>
</table>

**Subgroup analysis: Low C3/C4 and anti-dsDNA autoantibodies present**

<table>
<thead>
<tr>
<th>Prednisone reduction ≥ 25% versus baseline to reach a dose of ≤ 7.5 mg/day between weeks 40 and 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
</tr>
<tr>
<td>Response (number, %)</td>
</tr>
<tr>
<td>p (versus placebo)</td>
</tr>
</tbody>
</table>

- **Impact of belimumab on fatigue:**

  **BLISS 52 and BLISS 76 studies:**

  In BLISS 52, the mean change in the FACIT-Fatigue score at week 52 compared with baseline was greater in the belimumab 10 mg/kg (4.8 points, p <0.001) and 1 mg/kg (3.9 points, p <0.01) groups compared with placebo (2.1 points).

  In BLISS 76, the mean change in the FACIT-Fatigue score at week 52 relative to baseline was higher compared with placebo (2.9) only in the belimumab 1 mg/kg group (5.7, p < 0.001).

  However, in both studies, the differences observed in each of these analyses did not reach a clinically relevant minimum difference threshold (≥ 3 points).

  Post-hoc analysis combining the results of both studies showed a greater mean change in the FACIT-Fatigue score at week 52 relative to baseline in the belimumab 10 mg/kg group compared with placebo (4.70 versus 2.46, p = 0.0006).

  In the subgroups of patients with severe active disease characterised by a SELENA-SLEDAI score ≥ 10, corticosteroid use and a low baseline C3/C4 level or a low C3/C4 level and anti dsDNA autoantibodies, a significant difference in favour of belimumab 10 mg/kg was demonstrated relative to placebo; however this difference was clinically relevant only in the subgroup of patients with corticosteroid use and a low C3/C4 count at baseline: 4.98 versus 1.82 or a difference of 3.16 points (p < 0.0001).

- **Impact of belimumab on the occurrence of lupus flare-ups:**

  **BLISS 52 and BLISS 76:**

  In BLISS 52, the medium time to onset of the first flare was extended in the belimumab 10 mg/kg group (119 days; p = 0.0036) and 1 mg/kg group (126 days; p = 0.0026) compared with placebo (84 days).

  The percentage of patients with severe flare-ups was lower in the belimumab 10 mg/kg group relative to placebo (13.8% versus 23%, p = 0.0055).

  In BLISS 76, no difference was observed after 52 weeks between the belimumab and placebo groups in terms of mean time to onset of the first flare and percentage of patients with a severe flare.

  Post-hoc analysis combining the results of both studies shows an extended mean time to onset of the first flare in patients receiving belimumab 10 mg/kg compared with those receiving placebo (110 versus 84 days; RR = 0.84; p = 0.012).

  However, no significant difference was observed in the mean number of severe flare-ups at 52 weeks between belimumab (0.79 flare-ups) and placebo (1.01 flare-ups).
The percentage of patients with a severe lupus flare during the 52 weeks of treatment was smaller in the belimumab 10 mg/kg group compared with the placebo group (15.6% versus 23.7%; \( p = 0.0011 \)).

In the subgroups of patients with severe active disease characterised by a SELENA-SLEDAI score \( \geq 10 \), corticosteroid use and low C3/C4 level at baseline or a low C3/C4 level and anti dsDNA autoantibodies, a significant difference in favour of belimumab 10 mg/kg was demonstrated relative to placebo after 52 weeks in:
- the mean number of flare-ups,
- the mean time to onset of the first severe flare and
- the percentage of patients with a severe flare (see Table 2).

**Table 2:** Combined analysis of BLISS 52 and BLISS 76 on lupus flare-ups

<table>
<thead>
<tr>
<th>Combined analysis of BLISS 52/76 (post hoc)</th>
<th>Placebo n = 562</th>
<th>Belimumab 10 mg/kg n = 563</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients: n</td>
<td>557</td>
<td>556</td>
</tr>
<tr>
<td>Mean number of severe flare-ups per subject between baseline and week 52 ± SD</td>
<td>1.01 ± 0.09</td>
<td>0.79 ± 0.09</td>
</tr>
<tr>
<td>( p )</td>
<td>0.0754</td>
<td></td>
</tr>
<tr>
<td>Mean time to onset of the first severe flare</td>
<td>( p )</td>
<td>( p )</td>
</tr>
<tr>
<td>Relative risk</td>
<td>0.70</td>
<td>0.00244</td>
</tr>
<tr>
<td>Risk of severe lupus flare-ups during the 52 weeks of treatment</td>
<td>23.7%</td>
<td>15.6%</td>
</tr>
<tr>
<td>( p )</td>
<td>0.0011</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SELENA-SLEDAI score ( \geq 10 ) subgroup</th>
<th>n = 298</th>
<th>n = 296</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of severe flare-ups per subject between baseline and week 52</td>
<td>1.32</td>
<td>0.84</td>
</tr>
<tr>
<td>( p )</td>
<td>0.0124</td>
<td></td>
</tr>
<tr>
<td>Mean time to onset of the first severe flare over 52 weeks</td>
<td>( HR )</td>
<td>( p )</td>
</tr>
<tr>
<td>( p )</td>
<td>0.58 (0.41; 0.81)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Patients presenting a severe flare over 52 weeks of treatment (%)</td>
<td>26.9%</td>
<td>17.9%</td>
</tr>
<tr>
<td>( p )</td>
<td>0.0017</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low C3/C4 and corticosteroid use at baseline subgroup</th>
<th>n = 309</th>
<th>n = 327</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of severe flare-ups per subject between baseline and week 52</td>
<td>3.83</td>
<td>2.68</td>
</tr>
<tr>
<td>( p )</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Mean time to onset of the first severe flare over 52 weeks</td>
<td>( HR )</td>
<td>( p )</td>
</tr>
<tr>
<td>( p )</td>
<td>0.63 (0.45; 0.87)</td>
<td>0.0047</td>
</tr>
<tr>
<td>Patients presenting a severe flare over 52 weeks of treatment (%)</td>
<td>28.5%</td>
<td>19.0%</td>
</tr>
<tr>
<td>( p )</td>
<td>0.0047</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low C3/C4 and anti-dsDNA autoantibodies present subgroup</th>
<th>n = 287</th>
<th>n = 305</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of severe flare-ups per subject between baseline and week 52</td>
<td>3.99</td>
<td>2.73</td>
</tr>
<tr>
<td>( p )</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
<tr>
<td>Mean time to onset of the first severe flare over 52 weeks</td>
<td>( HR )</td>
<td>( p )</td>
</tr>
<tr>
<td>( p )</td>
<td>0.61 (0.44; 0.85)</td>
<td>0.0038</td>
</tr>
<tr>
<td>Patients presenting a severe flare over 52 weeks of treatment (%)</td>
<td>29.6%</td>
<td>19.0%</td>
</tr>
<tr>
<td>( p )</td>
<td>0.0038</td>
<td></td>
</tr>
</tbody>
</table>
7.2 Safety/Adverse effects

7.2.1 Safety data from BLISS 52 and BLISS 76

In BLISS 52 and BLISS 76, the most common adverse events with belimumab were: diarrhoea (12.2% versus 9.9% with placebo), nausea (15.1% vs 12.6%), infections (70% versus 67%), fever (9.6% versus 7.9%), infusion-related reactions including hypersensitivity reactions (16.9% versus 14.7%), psychiatric disorders (insomnia, depression, anxiety), leukopenia, and extremity pain.

7.2.2 PSUR data

Pharmacovigilance data led to changing the SPC with regard to hypersensitivity reactions and infections.

Hypersensitivity reactions:
Hypersensitivity reactions have been mentioned in the SPC since marketing authorisation was obtained, with a warning recommending that BENLYSTA be administered by a qualified healthcare professional trained to give infusion therapy and in an environment with access to resources for treating this type of potentially severe reaction. During clinical studies, the reactions occurred immediately and had a favourable outcome.

Since marketing, five cases of hypersensitivity reaction (including a fatal one) occurred within a period from 4 hours to several hours post-infusion and three cases of a delayed reaction 7 days after the infusion. Delayed hypersensitivity reactions were rash, nausea, fatigue and facial oedema and had a favourable outcome.

After these events, the SPC was changed in March 2012 to indicate the risk of hypersensitivity reactions after several hours following administration of belimumab with a recommendation for medical monitoring for an extended period (several hours) at least after the first two infusions and for informing patients about this risk.

The SPC was changed to include a warning regarding the risk of delayed hypersensitivity (time to onset > 72 hours) in December 2013.

Infections:
Infections are among the adverse events frequently reported during belimumab treatment. They are related to the belimumab treatment as well as to the disease itself and to the other immunosuppressant treatments.

Classification of the infections reported during phase II and III studies led to changing the SPC in May 2012 to specify bacterial infections as very common adverse effects.

The rate of sepsis was stable (0.54/100 patient-years, 95% CI = [0.37, 0.74]) and does not appear greater than that observed in the placebo group (0.52/100 patient-years, 95% CI = [0.14, 1.33]).

The rate of opportunistic infections remained stable and did not increase relative to the literature data in lupus patients. Cases were reported after marketing, which led to changing the SPC in July 2013 to broaden the experience to post-marketing data.

7.2.3 Long-term safety data

Study LBSL99, the open-label, non-comparative extension phase of the phase II study LBSL02, provides 7-year safety data. All the patients included in this extension phase had received belimumab at the dose of 10 mg/kg every 28 days in compliance with the marketing authorisation.

After 7 years of study, 190 patients were still enrolled in the study out of the 296 initially enrolled and treated with belimumab in the extension phase.

The incidence of adverse events was calculated per one-year period. The incidence of these events (all adverse events combined, serious adverse events, overall infections, serious infections, cancer and death) remained stable throughout the study (see Table 3).
**Table 3: Change in incidence of adverse events (AEs) on belimumab up to 7 years**

<table>
<thead>
<tr>
<th>Type of AE</th>
<th>Number of patients with an AE per time interval (incidence rate per 100 patient-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-1 years N = 424</td>
</tr>
<tr>
<td></td>
<td>1-2 years N = 339</td>
</tr>
<tr>
<td></td>
<td>2-3 years N = 274</td>
</tr>
<tr>
<td></td>
<td>3-4 years N = 248</td>
</tr>
<tr>
<td></td>
<td>4-5 years N = 223</td>
</tr>
<tr>
<td></td>
<td>5-6 years N = 208</td>
</tr>
<tr>
<td></td>
<td>6-7 years N = 190</td>
</tr>
<tr>
<td>All AEs</td>
<td>413 (110)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>70 (18.7)</td>
</tr>
<tr>
<td>Discontinuation due to an AE</td>
<td>24 (6.4)</td>
</tr>
<tr>
<td>All infections</td>
<td>313 (83.7)</td>
</tr>
<tr>
<td>Serious infections</td>
<td>22 (5.9)</td>
</tr>
<tr>
<td>AEs due to injection*</td>
<td>87 (23.3)</td>
</tr>
<tr>
<td>Serious AEs due to injection</td>
<td>0 (0.4)</td>
</tr>
<tr>
<td>Malignant tumours**</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Mortality ***</td>
<td>3 (0.8)</td>
</tr>
</tbody>
</table>

*: including hypersensitivity reactions

**: including defined and undefined solid organs, cutaneous or other melanomas and malignant haematological tumour.

***: two patients on belimumab died during the 52-week double-blind period as did one patient treated with placebo during the double blind period and then with belimumab, after around 232 days of exposure to belimumab.

**7.2.4 Risk management plan (RMP)**

No change in the identified and potential risk profile has occurred since marketing authorisation was obtained.

The identified risks are hypersensitivity reactions and infections.

The potential risks are cancer, immunogenicity, effects on immunisation including interactions with living vaccines and psychiatric events (depression, suicidal behaviour).

Conducting a long-term (5 years) placebo-controlled comparative study that was to include 5000 patients to evaluate the longer-term risks of infection and cancer initially provided in the RMP was replaced by two post-marketing safety studies (European Commission decision of 24 October 2012):

- a double-blind, placebo-controlled study in 5000 patients. The study will evaluate the incidences of all-cause mortality and adverse events of special interest in SLE patients over a minimum period of 1 year. These include serious infections (including serious and non-serious opportunistic infections and PMLE), malignant tumours (including non-melanoma skin cancer), serious hypersensitivity and infusion related reactions and serious psychiatric events including mood disorders, anxiety and suicide.

- a prospective observational follow-up long-term safety study in which 2000 patients treated with belimumab will be followed for a minimum duration of 5 years. This registry, including a control group of 1000 patients, will permit evaluating the incidence of all-cause mortality and adverse events of special interest in patients with SLE such as serious infections (including opportunistic infections and PMLE), certain serious psychiatric events and malignant tumours (including non-melanoma skin cancer).

**07.3 Summary & discussion**
The new data provided by the company mainly rely on a post hoc analysis of BLISS 52 and BLISS 76 combined, on corticosteroid sparing, fatigue (FACIT-Fatigue score\(^5\)) and lupus flare-ups, the secondary endpoints for these studies.

The phase III studies, BLISS 52 and BLISS 76, were comparative, placebo-controlled, randomised studies, in patients with active SLE at baseline according to the diagnostic criteria of the American College of Rheumatology (ACR)\(^6\) and characterised by:
- a SELENA-SLEDAI\(^7\) ≥ score of 6 during the screening visit,
- and the presence of antinuclear antibodies (ANA) (ANA titre ≥ 1:80),
- and/or the presence of anti-dsDNA antibodies (≥ 30 units/ml) at two independent measurements before randomisation,

and receiving standard treatment for lupus (including at least one of the following treatments: NSAIDS, antimalarials, corticosteroids, immunosuppressants) unchanged and at a stable dose for at least 30 days. This treatment may be adjusted during the study according to a regimen predefined in the protocol. Patients requiring a change to the standard treatment for their SLE other than those authorised by the protocol were declared treatment failures/non-responders.

In these studies, an analysis was done of the various patient subgroups defined post hoc with severe active disease characterised by:
1. a SELENA-SLEDAI score ≥ 10
2. taking corticosteroids and a low C3/C4 level at baseline
3. a low C3/C4 level and anti-dsDNA autoantibodies:

As a reminder, the primary endpoint for these studies was a composite endpoint, the SRI (SLE Responder Index) measured at 52 weeks, defined by the percentage of patients simultaneously meeting the following three conditions:
- reduction by at least 4 points of the SELENA-SLEDAI score,
- absence of any new involvement of a system or organ defined by one BILAG A item or two BILAG B items,
- no worsening of the overall health status of the patient as judged by the physician, worsening being defined by an increase >0.30 on the PGA scale.

The results showed a modest difference in favour of belimumab 10 mg/kg in terms of SRI at 52 weeks (14.03% in BLISS 52 and 9.41% in BLISS 76). This difference was doubled in the three subgroups with severe active disease defined post hoc.

The new results presented showed:

- **In terms of corticosteroid sparing**, a difference in favour of belimumab 10 mg/kg relative to placebo on the percentage of patients whose mean prednisone dose was reduced by at least 25% since inclusion to reach a level ≤ 7.5 mg/day during weeks 40 to 52 (17.9% versus 12.3%, \(p = 0.0451\)). In the subgroups of patients with severe active disease, a difference versus placebo was observed only in the subgroup of patients with a SELENA-SLEDAI score ≥ 10 (17.2% versus 6.6%, \(p = 0.026\)).

- **In terms of fatigue**, a mean change in the FACIT Fatigue score at week 52 relative to baseline which was larger in the belimumab 10 mg/kg group compared with the placebo group (4.70 versus 2.46; \(p = 0.0006\)), however, the difference is not clinically relevant (< 3 points).

In the subgroup of patients with severe active disease, a clinically relevant difference in favour of belimumab 10 mg/kg was demonstrated relative to placebo only in the subgroup of patients

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\(^5\) FACIT-Fatigue: A questionnaire including 13 items clinically evaluating fatigue associated with chronic diseases. The score ranges from 0 (the worst score) to 52 (the best score), a positive difference indicating an improvement. A difference of 3-4 points is considered to be clinically relevant.
\(^6\) See the definition in Appendix 1.
\(^7\) See the definition in Appendix 2.
using corticosteroids and having a low C3/C4 level at baseline: 4.98 versus 1.82 or a difference of 3.16 points (p < 0.0001).

- **In terms of lupus flare-ups**, the superiority of belimumab 10 mg/g compared with placebo on the mean time to first flare (110 versus 84 days, RR = 0.84, p = 0.012) and the percentage of patients with severe lupus flare-ups over the 52 weeks of treatment (15.6% versus 23.7%, p = 0.0011).
  However, no significant difference was observed between belimumab and placebo in the mean number of severe flare-ups at 52 weeks (0.79 versus 1.01 flare-ups).
  In the subgroup of patients with severe active disease, a difference in favour of belimumab 10 mg/kg was demonstrated relative to placebo on these three criteria.

- **In terms of safety**, an unchanged safety profile since marketing of belimumab.
  The 7-year open-label extension phase of a phase II study, during which all patients received belimumab at the dose of 10 mg/kg every 28 days showed that the incidence of adverse events (all adverse events combined, serious adverse events, overall infections, serious infections, cancers and deaths) remained stable throughout the study.
  Pharmacovigilance data allowed specifying the nature of the hypersensitivity reactions that could occur within 4 hours of administration or in a delayed manner 7 days after administration.
  Monitoring for several hours after administration is recommended in the SPC. The identified risks (hypersensitivity and infections) and potential risks (cancer, immunogenicity, effects on immunisation including interactions with living vaccines and psychiatric events including depression and suicidal behaviour) remain to be monitored in the RMP. Two safety studies (one randomised, double-blind, placebo controlled clinical study and one observational study for at least 5 years) should be conducted to clarify the safety of belimumab.

In all, the new results presented by the company show a statistically significant and clinically-relevant superiority of belimumab 10 mg/kg relative to placebo on corticosteroid sparing and lupus flare-ups (increase in the time to onset of the first flare and reduced percentage of patients who had a severe flare) but not in terms of fatigue.

In the subgroups of patients with active and severe disease defined post hoc, belimumab was superior to placebo at 52 weeks regarding the mean number of severe lupus flare-ups with treatment, the percentage of patients who had at least one severe flare and the mean time to onset of the first severe flare. In terms of corticosteroid sparing and fatigue reduction, the uneven results from one subgroup to another did not allow drawing conclusions on the benefit of belimumab versus placebo on these endpoints in this subpopulation.

The safety profile remains unchanged, but with clarifications regarding the occurrence of hypersensitivity reactions from within a few hours to several days following administration. These additional long-term data are necessary, especially to evaluate the risk of cancer and psychiatric and immunity disorders.

**07.4 Planned studies**

Two studies are planned in the RMP (see above, section 7.2.4) in order to study belimumab safety, especially the risks of serious and opportunistic infections, malignant tumours and hypersensitivity reactions.

**08 THERAPEUTIC USE**
The basic treatment for SLE, which aims to prevent relapse, uses synthetic antimalarials (chloroquine, hydroxychloroquine) and/or low-dose corticosteroids (if corticosteroid treatment was introduced during a flare).

Immunosuppressant or immunomodulatory agents, with a marketing authorisation in SLE, such as azathioprine and cyclophosphamide, or without a marketing authorisation for this indication, such as leflunomide, methotrexate, mycophenolate mofetil and cyclosporine, are used in more severe or more active forms of the disease, poorly controlled by antimalarials and low-dose corticosteroids or forms requiring prolonged corticosteroid administration. The choice of treatment depends on the type and severity of damage (see PNDS-ALD [National Protocol for Diagnosis and Care - Chronic Conditions] 21 January 2010).

In the most severe forms, high-dose corticosteroids are usually prescribed. Local corticosteroids may be used in cutaneous forms.

NSAIDs and analgesics may be beneficial in the less severe bone and joint forms.

Thalidomide has an authorisation for special reimbursement regimen under Article L162-17-2-1 of the French Social Security Code (Official Gazette of 20/10/09) in the treatment of cutaneous lupus erythematosus resistant to conventional treatments.

When the disease is severe or refractory, it is common to resort to treatment combinations.

Belimumab, an anti-BLYS (human protein activating B cells) antibody, is a second-line treatment in the treatment of adults with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity as an add-on to standard treatment, after failing or being intolerant to properly conducted treatment with synthetic antimalarials, NSAIDs, corticosteroids and possibly immunosuppressants, depending on the specific organ system involvement.

Belimumab has not been studied in severe renal and neurological involvement. Consequently, its prescription is not recommended in these forms of lupus.

09 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

09.1 Actual benefit

- SLE is a protean and polymorphic autoimmune disease mainly affecting women during ovulatory activity (9 women for every man), progressing via flare-ups of variable severity that may become life-threatening.

- These medicinal products are in the symptomatic therapy category.

- The efficacy/adverse effects ratio is modest.

- These medicinal products are a second-line therapy in the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) as an add-on to standard treatment, after failing or being intolerant to properly conducted treatment with synthetic antimalarials, NSAIDs, corticosteroids and possibly immunosuppressants, depending on the specific organ system involvement. In the absence of data in patients with severe renal and neurological involvement, belimumab prescription is not recommended in these forms of lupus.

- There is no validated therapeutic alternative in the event of failure of or intolerance to a treatment consisting of synthetic antimalarials, NSAIDS, corticosteroids and immunosuppressants.
Public health benefit:
Because of its rarity, SLE that failed standard treatments is a low public health burden. There is a public health need (Second Plan "Rare Diseases 2011-2014"). In view of the available data, the impact of BENLYSTA on the morbidity and mortality of treated patients is low and there is no demonstrated impact on quality of life. Furthermore, BENLYSTA is not expected to have any impact on the organisation of care. The transposability of trial results to everyday practice is debatable, especially due to difficulties in evaluating the response to treatment, as the composite SRI score used in the studies was not suited to clinical practice, due to exclusion of patients with severe renal and neurological involvement in the trials and concerns regarding long term safety (especially on the cancer risk) of this monoclonal antibody. Therefore the proprietary medicinal product BENLYSTA provides only a partial response to the public health need expressed. Consequently, BENLYSTA is not expected to have any impact on public health in this indication.

Taking account of these points, the Committee considers that the actual benefit of BENLYSTA 120 mg and 400 mg, powder for concentrate for solution for infusion is substantial in the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (e.g positive anti-dsDNA and low complement) as an add-on to standard treatment, after failing or being intolerant to properly conducted treatment with synthetic antimalarials, NSAIDs, corticosteroids and possibly immunosuppressants, depending on the specific organ involvement.

The Committee recommends continued inclusion on the list of medicinal products approved for hospital use for treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity (e.g positive anti-dsDNA and low complement) as an add-on to standard treatment, after failing or being intolerant to properly conducted treatment with synthetic antimalarials, NSAIDs, corticosteroids and possibly immunosuppressants, depending on the specific organ involvement and at the dosages in the marketing authorisation.

Proposed reimbursement rate: 65%

09.2 Improvement in actual benefit (IAB)

Given a modest efficacy, the lack of data in severe forms of renal and neurological involvement and the uncertainties regarding long-term safety, the improvement in actual benefit provided by BENLYSTA, as an add-on to the usual treatment, remains minor (IAB IV) in the treatment of adult patients with active, autoantibody-positive systemic lupus erythematosus with a high degree of disease activity despite treatment with synthetic antimalarials, NSAIDs, corticosteroids and possibly immunosuppressants, depending on the specific organ involvement.

010 TRANSPARENCY COMMITTEE RECOMMENDATIONS

Packaging
Appropriate for the prescribing conditions.

Request for data
The Committee regrets the lack of clinical data in active and severe forms of systemic lupus erythematosus with kidney and neurological involvement, which are the forms most likely to benefit from second-line treatment in the event of failure of standard treatment with synthetic antimalarials,
NSAIDs, corticosteroids and possibly immunosuppressants depending on the specific organ involvement.
APPENDIX 1: Classification criteria of the American College of Rheumatology for SLE

According to the guidelines of the ACR (1999), adult SLE should be suspected when the patient has two or more of the characteristics in the table below. SLE is diagnosed if at least four of these criteria are present.

APPENDIX 2: SLEDAI/SELENA-SLEDAI

The SLEDAI is a validated and weighted index to assess the activity of systemic lupus. The disease activity is assessed in nine organ systems depending on clinical signs and symptoms, laboratory tests and the physician's assessment. The tool does not count subjective symptoms, such as fatigue, which is one of the most common constitutional symptoms of the disease. The clinical signs are taken into consideration if they are present at the time of the visit or within 10 days prior to it (Griffiths, 2005⁸). The scores weighted by organ (24 items in all) are added as follows:

- central nervous system and vascular involvement: score of 8 for each item.
- renal system and musculoskeletal system: score of 4 for each item.
- skin, mucosa and immunological testing system: score of 2 for each item.
- constitutional symptoms and haematological system: score of 1 for each item.

SELENA-SLEDAI is a modified version of SLEDAI. The description of some parameters is slightly modified, but the systems/organs and weighted scores are the same as for the SLEDAI. The SELENA-SLEDAI measures whether or not clinical signs, symptoms or laboratory abnormalities indicating SLE are present. It does not consider changes in signs and symptoms (improvement or worsening) relative to the prior visit. Consequently, SELENA-SLEDAI is not very sensitive to changes because the complete resolution of signs or symptoms is necessary to indicate a change in disease activity. Moreover, SELENA-SLEDAI only includes assessments for two biomarkers related to SLE (complement level and presence of anti-dsDNA antibodies). Neither the other autoantibodies nor the BLyS levels (correlated to the disease activity and its clinical manifestations) are assessed in SELENA-SLEDAI (Bombardier, 1992⁹).

The maximum theoretical score for the SLEDAI is 105 (if the patient simultaneously presents 24 clinical or laboratory manifestations – a situation which is inconceivable in practice). A score ≥ 20 corresponds to a "very high" SLE activity.

The categories of disease activity were defined from the SLEDAI scores as follows (Petri, 1999¹⁰):
- SLEDAI 0 = no activity
- SLEDAI 1-5 = mild activity
- SLEDAI 6-10 = moderate activity
- SLEDAI 11-19 = high activity
- SLEDAI 20+ = very high activity

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A disease flare was defined as an increase of 3 points or more in the SLEDAI or SELENA-SLEDAI score. An increase of more than 5 points is associated with the introduction of a new therapy or a change in the treatment in more than 50% of cases. 

A reduction of 4 points or more in the SELENA-SLEDAI score was defined in the studies as a clinically relevant reduction of disease activity.

Note: there is currently no consensus on this limit of clinical relevance.

APPENDIX 3 : BILAG

The BILAG index is a clinical measurement of SLE activity. It is a validated score on the basis of expert opinion. Unlike SELENA-SLEDAI, the activity of the disease in eight different systems/organs is counted separately (constitutional, mucocutaneous, neurological, musculoskeletal, cardio respiratory, vascular, renal, and haematological). The index consists of 86 items including renal and haematological results, but not immunological tests (Griffiths, 2005).

The score is based on the principle of the intention of a physician to treat a pathological process:

- **BILAG A (ACTION)**: serious manifestations of the disease requiring high doses of corticosteroids (prednisone or equivalent ≥ 20 mg/day) and/or cytotoxic agents.
- **BILAG B (BEWARE)**: more moderate manifestations of the disease requiring low doses of corticosteroids, antimalarials or non-steroidal anti-inflammatory drugs (NSAIDs).
- **BILAG C (CONTENTMENT)**: mild symptoms only requiring symptomatic treatment (i.e. analgesics or NSAIDs).
- **BILAG D (DISCOUNT)**: no symptoms in an organ system that was affected previously.
- **BILAG E (No EVIDENCE)**: no symptoms in an organ system that was not affected previously.

Weighted numerical scores were assigned to each of the scores above (A = 9, B = 3, C = 1 and D / E = 0); it is therefore also possible to calculate an overall score ranging from 0 to 72. However, the index was not initially designed to be used this way.

In this system, a severe flare (1A) is defined as an increase of any prior score to a BILAG A in one or more organs/systems and a moderate flare (2B) is an increase from a BILAG score of C, D or E to a score B in two or more systems/organs.

The development of a 1A or 2B flare is a clinically relevant change reflecting a sufficient deterioration of the activity of the disease to justify an increase in therapeutic pressure (Furie, 2009).

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<table>
<thead>
<tr>
<th>Criteria</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malar rash</td>
<td>Fixed erythema, flat or raised, mainly on the cheeks and nose, sparing the nasolabial folds and the eyelids.</td>
</tr>
<tr>
<td>Discoid lupus</td>
<td>Erythematous plaque covered with fine telangiectasia, thick scales plugging follicles, scarring and atrophy.</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>Skin rash following unusual reaction to the sun, such as determined by patient history or physician observation</td>
</tr>
<tr>
<td>Oral or nasopharyngeal ulcers</td>
<td>Oral or nasopharyngeal ulcers, usually not painful, observed by the physician.</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Non-erosive arthritis affecting at least two peripheral joints, characterised by swelling, tenderness or effusion.</td>
</tr>
<tr>
<td>Serositis</td>
<td>Pleurisy, following a history of pleural pain, auscultation abnormalities or evidence of pleural effusion or Pericarditis documented by electrocardiogram, auscultation abnormalities, or evidence of pericardial effusion.</td>
</tr>
<tr>
<td>Renal abnormalities</td>
<td>Persistent proteinuria &gt; 0.5 g/day (or +++ or Urinary casts.</td>
</tr>
<tr>
<td>Neurological abnormalities</td>
<td>Convulsions or psychosis in the absence of inducing medicines or Known metabolic abnormalities (for example, uraemia, ketoacidosis, electrolyte imbalance).</td>
</tr>
<tr>
<td>Haematological involvement</td>
<td>Haemolytic anaemia or Leukocytopenia &lt; 4000/µl observed on two occasions or Lymphocytopenia &lt; 1500/µl observed on two occasions or Thrombocytopenia &lt; 100,000/µl in the absence of inducing medicines.</td>
</tr>
<tr>
<td>Immunological disorder</td>
<td>Presence of anti-double strand DNA or anti-Sm or antiphospholipid antibodies Positive anti-double strand DNA at an abnormal level or Presence of anti-Sm antibodies or Abnormal titre of anticardiolipin IgG or IgM antibody or Presence of an anti-prothrombin or False positive syphilitic serology known for at least 6 months (VDRL+/TPHA-)</td>
</tr>
<tr>
<td>ANAs</td>
<td>Abnormal titre of antinuclear factors in the absence of inducing medicines (by immunofluorescence or equivalent assay)</td>
</tr>
</tbody>
</table>

APPENDIX 4: Definition of a flare according to the SELENA (Safety of Estrogen in Lupus Erythematosus National Assessment) study

<table>
<thead>
<tr>
<th>Mild to moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 or more of the following items:</td>
<td>1 or more of the following items:</td>
</tr>
<tr>
<td>• Change in SLEDAl ≥3 points or New involvement or worsening of skin involvement, stomatitis, serositis, arthritis, fever or Increase in the prednisolone dose (&lt;0.5 mg/kg/day), or Addition of an NSAID or antimalarial, or Increase of ≥1.0 on the PGA scale</td>
<td>• Change in SLEDAl &gt;12 points or New or worsening involvement of the central nervous system, vasculitis, myositis, nephritis, platelets &lt;60,000, haemolytic anaemia with Hb &lt;7 mg/dl requiring doubling the dose or &gt; 0.5 mg/kg/day of prednisolone, hospitalisation for SLE or Addition of an immunosuppressant Increase of ≥2.5 on the PGA scale</td>
</tr>
</tbody>
</table>