

#### INTRODUCTION

- Systemic lupus erythematosus (SLE) is a chronic, inflammatory, autoimmune disease that can affect virtually every organ system. Symptoms can range from mild to severe, and vary from patient to patient. The disease course of SLE is characterized by remissions and relapses (*Gladman 2017*).
- Approximately 170,000 to 200,000 adults are estimated to have SLE in the United States. It is typically diagnosed between the ages of 14 and 50 years, and is more common in female and non-white populations (*Benlysta dossier 2017*). SLE is associated with organ damage, morbidity, increased mortality, and decreased quality of life (*Navarra et al 2011, Thong et al 2017*).
- Clinical manifestations of SLE in adults may include the following (*Gladman 2017*):
  - constitutional symptoms (fatigue, fever, myalgia, weight loss)
  - arthritis and arthralgias
  - skin and mucous membrane involvement (facial eruption [“butterfly rash”], discoid lesions, photosensitivity, oral/nasal ulcers, alopecia)
  - vascular abnormalities (Raynaud phenomenon, vasculitis, thromboembolic disease)
  - renal involvement (nephritis)
  - gastrointestinal involvement (esophagitis, intestinal pseudo-obstruction, protein-losing enteropathy, hepatitis, pancreatitis, mesenteric vasculitis or ischemia, peritonitis)
  - pulmonary involvement (pleuritis, pneumonitis, interstitial lung disease, pulmonary hypertension, shrinking lung syndrome, alveolar hemorrhage)
  - cardiac disease (pericarditis is the most common; may also involve the myocardium, valves, conduction system, and coronary arteries)
  - hematologic abnormalities (anemia of chronic disease, autoimmune hemolytic anemia, leukopenia, thrombocytopenia)
  - lymphadenopathy and splenomegaly
  - ophthalmic involvement
  - neuropsychiatric involvement
- SLE in children has similar manifestations as in adults, although the frequency of specific manifestations varies, and the disease may be worse in children if the diagnosis is delayed (*Lehman et al 2016*).
- Several disease activity indices have been developed for SLE (See Appendix). These indices, which are used for research purposes, use a combination of history, physical examination, and laboratory data (*Wallace 2016*).
  - Examples of scoring systems include the SLE Disease Activity Index (SLEDAI), the Safety of Estrogens in Lupus Erythematosus National Assessment version of the SLEDAI (SELENA-SLEDAI), and the British Isles Lupus Assessment Group (BILAG) index, among others.
  - Clinical trials are also using combinations of indices as composite measures. An example is the SLE responder index (SRI).
- Although there is no consensus on what constitutes an SLE disease flare, most clinicians agree that that a moderate or severe flare refers to a measureable disease activity increase that is significant enough to result in a change in therapy (*Wallace 2016*).
- Effective management of SLE varies based on the patient’s disease manifestations, disease severity, and comorbidities. Patients are generally managed by a rheumatologist, but may require multidisciplinary care. The overall goals of treatment are to achieve the lowest possible disease activity, prevent organ damage, minimize drug toxicity, ensure long-term survival, and improve quality of life (*Wallace et al 2016*).
- Medications used in the treatment of SLE include (*Thong et al 2017, Wallace et al 2016*):
  - Antimalarials: hydroxychloroquine, chloroquine
    - Used routinely in most SLE patients; have broad benefits on many SLE manifestations and may reduce disease flares, organ damage, and mortality
  - Corticosteroids: prednisone, methylprednisolone

- Used orally in patients with active manifestations, and intravenously (IV) in acute situations (eg, onset of nephritis, cerebritis, or myocarditis)
- Immunosuppressants: azathioprine, mycophenolate mofetil, cyclophosphamide
  - Used in lupus nephritis and other significant organ involvement
- Biologics: rituximab (off-label), belimumab
  - Used in selected patients with active disease
- Many of the treatments in use have not been specifically Food and Drug Administration (FDA)-approved to treat SLE (*Clinical Pharmacology 2017*).
- The role of rituximab in SLE is uncertain. Most of the data supporting its efficacy for reducing disease activity is observational, and significant benefit has not been conclusively shown in randomized trials (*Cobo-Ibáñez 2014, Wallace 2016*). Efficacy in lupus nephritis has also not been conclusively demonstrated; however, it is supported by consensus opinion for use in selected patients failing to benefit from established therapies (*Hahn et al 2012, Thong et al 2017*).
- Benlysta (belimumab) is the only biologic FDA-approved to treat SLE. It is a monoclonal antibody that acts as a specific inhibitor of B lymphocyte stimulator protein (BLyS), a survival cytokine for B lymphocytes that is overexpressed in patients with SLE and other autoimmune diseases.
- Benlysta was initially approved by the FDA in 2011 as an IV formulation. A new subcutaneous (SC) formulation was FDA approved in July 2017.
- Medispan class: SLE Agents; BLyS-Specific Inhibitors

## INDICATIONS

- Belimumab is indicated for the treatment of adult patients with active, autoantibody-positive SLE who are receiving standard therapy (*Benlysta prescribing information 2017*).
  - Limitations of use: The efficacy of belimumab has not been evaluated in patients with severe active lupus nephritis or severe active central nervous system (CNS) lupus. Belimumab has not been studied in combination with other biologics or IV cyclophosphamide. Use of belimumab is not recommended in these situations.
- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

## CLINICAL EFFICACY SUMMARY

- Two Phase 3, double-blind (DB), randomized trials, BLISS-52 (N = 865) and BLISS-76 (N = 819), compared IV belimumab to placebo in adults meeting the American College of Rheumatology (ACR) criteria for SLE (*Furie et al 2011, Navarra et al 2011*). Enrolled patients had active disease and a baseline score of  $\geq 6$  on the SELENA-SLEDAI. Patients were also required to have a positive antinuclear antibody (ANA) or double-stranded deoxyribonucleic acid (dsDNA) antibody, and to be on a stable regimen of SLE medications (prednisone, nonsteroidal anti-inflammatory drug [NSAID], antimalarial, and/or immunosuppressive agent). Patients with severe active lupus nephritis or CNS lupus were excluded.
  - The primary endpoint for both studies was the response rate at week 52 assessed with the SRI, a composite index for disease activity and response.
    - In BLISS-52, this endpoint was reached by 58% and 44% of patients in the belimumab 10 mg/kg and placebo groups, respectively (odds ratio [OR], 1.83; 95% confidence interval [CI], 1.30 to 2.59;  $p = 0.0006$ ).
    - In BLISS-76, this endpoint was reached by 43.2% and 33.5%, respectively (OR not reported;  $p = 0.017$ ).
  - Some (but not all) key secondary endpoints were met in these studies at their primary assessments (week 24, 52, or 76). Notably:
    - In BLISS-52, components of the SRI measuring disease activity (SELENA-SLEDAI) and the physician's global assessment (PGA) demonstrated superiority of belimumab 10 mg/kg vs placebo. However, a quality of life measure was not improved, and reductions in prednisone dose did not reach statistical significance.
    - In BLISS-76, a higher percentage of patients achieved a clinically meaningful reduction on the SELENA-SLEDAI, but most other secondary endpoints, such as the PGA, quality of life, and reduction in prednisone dose, were not significantly improved.
- More recently, a Phase 3, DB, randomized trial, BLISS-SC, compared belimumab 200 mg SC once weekly to placebo in 836 patients with SLE (*Stohl et al 2017*). Inclusion and exclusion criteria were similar to the BLISS-52 and BLISS-76 trials, but patients were required to have a slightly more severe baseline disease activity (score  $\geq 8$  on the SELENA-SLEDAI, described as moderate to severe).

- The primary endpoint, the SRI at week 52, was achieved by 61.4% and 48.4% of patients in the belimumab and placebo groups, respectively (OR, 1.68; 95% CI, 1.25 to 2.25;  $p = 0.0006$ ).
  - In a subgroup analysis, patients with SELENA-SLEDAI scores  $\geq 10$  had significant treatment responses with belimumab, whereas those with less severe disease (scores  $\leq 9$ ) did not.
- Notable results for secondary endpoints were as follows:
  - Belimumab-treated patients were less likely to experience a severe flare compared to placebo-treated patients.
  - Patients treated with belimumab had a greater reduction in fatigue than those in the placebo group.
  - In patients with baseline proteinuria, fewer patients had a renal flare in the belimumab group compared to the placebo group.
  - Differences between groups were not significant for corticosteroid dose reduction or reduction in renal flare in the overall population.
- In the belimumab IV trials, the SRI response rate was lower for black patients receiving belimumab relative to black patients receiving placebo (both with concomitant standard therapy). In the SC trial, the SRI response was slightly higher for black patients receiving belimumab relative to black patients receiving placebo (both with concomitant standard therapy), but the treatment difference was not as large as that observed in the overall population. No definitive conclusion can be drawn from this subgroup analysis. Caution should be used when considering treatment with belimumab in black/African-American patients.

## CLINICAL GUIDELINES

- Clinical guidelines from the ACR and the European League Against Rheumatism (EULAR) provide background information and general guidance of management of patients with SLE. However, in most cases the guidelines do not provide specific recommendations or algorithms for drug selection and dosing. Neither guideline has been updated to include the place in therapy for belimumab.
- **American College of Rheumatology.** Guidelines for referral and management of SLE in adults (*ACR 1999*).
  - These guidelines were developed to improve the quality of care for SLE patients by primary care physicians. Recommendations were evidence-based when possible; where evidence is unavailable, the guidelines were based on recommendations of SLE specialists.
  - Referral to a rheumatologist and/or other appropriate specialist is recommended for the following:
    - Establishment of the diagnosis
    - Assessment of disease activity and severity
    - Establishment of a disease management plan
    - Management of uncontrolled disease
    - Management of disease with major organ damage
    - Management/prevention of complications of therapies
    - Management of special clinical situations (eg, antiphospholipid antibody syndrome, pregnancy, surgery)
  - Lifelong monitoring is required for most patients with SLE in order to detect flares of disease early and institute appropriate therapy. This monitoring should consist of targeted history-taking, physical examination, and laboratory tests.
  - Particular care should be taken to assure the safe use of medications in SLE.
  - Treatment of mild SLE may appropriately incorporate the following:
    - Topical sunscreens
    - Topical glucocorticoid preparations
    - NSAIDs
    - Antimalarial agents (eg, hydroxychloroquine)
      - Antimalarial agents are useful for skin and joint involvement, constitutional symptoms, and preventing flares. Additionally, they may reduce fatigue and decrease low-density lipoprotein levels.
    - Oral glucocorticoids
      - Systemic glucocorticoids are not usually needed for mild SLE. Patients should be referred to a specialist for initiation of therapy.
  - Considerations in the treatment of serious, life-threatening, or organ-threatening SLE:
    - Organ involvement may lead to irreversible damage.
    - High-dose glucocorticoids are used for refractory SLE manifestations and severe organ-threatening disease.

- Immunosuppressive/cytotoxic agents that have been used to treat SLE include azathioprine, cyclophosphamide, methotrexate, chlorambucil, cyclosporine, and nitrogen mustard. Choice of therapy depends on the nature and severity of the condition (eg, methotrexate for severe arthritis, azathioprine or cyclophosphamide for nephritis).
- **European League Against Rheumatism.** EULAR recommendations for the management of systemic lupus erythematosus. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (*Bertsias et al 2008*).
  - Guideline development used an evidence-based approach followed by expert consensus.
  - In the treatment of SLE without major organ manifestations, antimalarials and/or glucocorticoids are of benefit and may be used.
  - NSAIDs may be used judiciously for limited periods of time in patients at low risk for their complications.
  - In non-responsive patients or patients not able to reduce corticosteroids below doses acceptable for chronic use, immunosuppressive agents such as azathioprine, mycophenolate mofetil and methotrexate should be considered.
  - SLE patients with major neuropsychiatric manifestations considered to be of inflammatory origin (optic neuritis, acute confusional state/coma, cranial or peripheral neuropathy, psychosis, and transverse myelitis/myelopathy) may benefit from immunosuppressive therapy.
  - In patients with proliferative lupus nephritis, glucocorticoids in combination with immunosuppressive agents are effective against progression to end-stage renal disease. Long-term efficacy has been demonstrated only for cyclophosphamide-based regimens; however, these are associated with considerable adverse effects (AEs). In short- and medium-term trials, mycophenolate mofetil has demonstrated at least similar efficacy compared with pulse cyclophosphamide and a more favorable toxicity profile. Small, non-controlled trials suggest that up to 50% of patients refractory to cyclophosphamide may have a clinically significant response to rituximab. Flares following remission are not uncommon and require careful follow-up.

## SAFETY SUMMARY

### • Contraindications

- Prior anaphylaxis with belimumab

### • Key warnings/precautions

- Mortality: There were more deaths reported with belimumab than with placebo during the controlled period of clinical trials with IV belimumab.
  - Out of 2133 patients in 3 clinical trials of IV belimumab, a total of 14 deaths occurred during the DB, placebo-controlled treatment periods: 3/675 (0.4%), 5/673 (0.7%), 0/111 (0%), and 6/674 (0.9%) in the groups receiving placebo and belimumab 1 mg/kg, 4 mg/kg, and 10 mg/kg, respectively. No single cause of death predominated. Etiologies included infection, cardiovascular disease, and suicide.
  - In the controlled trial of SC belimumab (N = 836), a total of 5 deaths occurred during the DB, placebo-controlled treatment period: 2/280 (0.7%) and 3/556 (0.5%) in the placebo and belimumab groups, respectively. Infection was the most common cause of death.
- Serious infections: Serious and sometimes fatal infections have been reported in patients receiving immunosuppressive agents, including belimumab. Belimumab should be used cautiously in patients with severe or chronic infections. Interruption of therapy should be considered if patients develop a new infection during belimumab treatment.
  - In the controlled clinical trials of IV belimumab, the overall incidence of infections was 71% in patients treated with belimumab and 67% of patients treated with placebo, and the incidence of serious infections was 6.0% and 5.2%, respectively.
  - In the controlled trial of SC belimumab, the overall incidence of infections was 55% in patients treated with belimumab and 57% in patients treated with placebo, and the incidence of serious infections was 4.1% and 5.4%, respectively.
- Progressive multifocal leukoencephalopathy (PML): Cases of PML resulting in neurological deficits, including fatal cases, have been reported in patients with SLE receiving immunosuppressants, including belimumab. Patients presenting with new-onset or deteriorating neurological signs and symptoms should be evaluated for PML by an appropriate specialist. If PML is confirmed, discontinuation of immunosuppressant therapy, including belimumab, should be considered.
- Hypersensitivity reactions, including anaphylaxis: Serious and fatal reactions have been reported.



- In the controlled clinical trials of IV belimumab, hypersensitivity reactions occurring on the same day as the infusion were reported in 191/1458 (13%) of patients receiving belimumab and 76/675 (11%) of patients receiving placebo, and anaphylaxis was observed in 0.6% and 0.4% of patients, respectively. Due to overlap in signs and symptoms, it was not possible to distinguish between hypersensitivity reactions and infusion reactions in all cases. IV belimumab should be administered by healthcare providers prepared to manage anaphylaxis.
    - In the controlled trials of SC belimumab, systemic hypersensitivity reactions were similar to those observed in the IV clinical trials.
  - Depression: Depression and suicidality have been reported in trials with belimumab. Patients should be instructed to contact their healthcare provider if they experience new or worsening depression, suicidal thoughts, or other mood changes.
    - In the controlled clinical trials of IV belimumab, psychiatric events were reported more frequently with belimumab than placebo (16% and 12%, respectively). These were primarily related to depression-related events (6.3% vs 4.7%), insomnia (6.0% vs 5.3%), and anxiety (3.9% vs 2.8%). Serious psychiatric events were reported in 0.8% of patients receiving belimumab (0.6% and 1.2% with 1 mg/kg and 10 mg/kg, respectively) and 0.4% of patients receiving placebo. Serious depression was reported in 0.4% and 0.1% of patients receiving belimumab and placebo, respectively, and 2 suicides (0.1%) were reported in patients receiving belimumab.
    - In the controlled trial of SC belimumab, psychiatric events were reported in 6% and 11% of patients receiving belimumab and placebo, respectively, and depression-related events were reported in 2.7% and 3.6%, respectively. Serious psychiatric events were reported in 0.2% of patients receiving belimumab and in no patients receiving placebo. There were no serious depression-related events or suicides in either group.
- **Adverse effects**
  - Common AEs (≥ 5%) with IV belimumab were nausea, diarrhea, pyrexia, nasopharyngitis, bronchitis, insomnia, pain in extremity, depression, migraine, and pharyngitis. The safety profile observed for SC belimumab was consistent with the safety profile of IV belimumab, with the addition of local injection site reactions.
- **Drug Interactions**
  - Formal drug interaction studies have not been performed with belimumab.
  - Live vaccines should not be given for 30 days before or concurrently with belimumab because clinical safety has not been established. Additionally, because of its mechanism of action, belimumab may interfere with the response to immunizations.
  - Belimumab has not been studied in combination with other biologic therapies or IV cyclophosphamide, and concomitant use with these agents is not recommended.

## DOSING AND ADMINISTRATION

**Table 1. Dosing and Administration**

Drug	Available Formulations	Usual Recommended Frequency	Comments
Benlysta (belimumab)	Injection for IV use	Every 2 weeks for 3 doses, then every 4 weeks	<ul style="list-style-type: none"> <li>● Should be administered by healthcare providers prepared to manage anaphylaxis</li> </ul>
	Injection for SC use	Once weekly	<ul style="list-style-type: none"> <li>● The first dose should be administered under supervision of a healthcare professional; thereafter, a patient or caregiver may administer when deemed appropriate</li> </ul>

See the current prescribing information for full details

## CONCLUSION

- Belimumab is a unique agent in that it is the only biological agent FDA-approved to treat SLE. Clinical trials have demonstrated efficacy, but effects on key endpoints have been somewhat limited. Across the Phase 3, placebo-controlled trials with IV and SC belimumab, the percentage of patients classified as responders ranged from approximately 43% to 61% for FDA-approved doses of belimumab and 34% to 48% for placebo, and belimumab has not conclusively shown improvements in quality of life or reductions in the need for corticosteroids. Belimumab is well-

tolerated in most patients; however, warnings/precautions note potential risks of infections, PML, hypersensitivity, depression/suicidality, and increased mortality (which was observed with the IV formulation).

- Belimumab may have a role in patients with moderate to severe SLE who have failed to respond adequately to more well-established therapies.
- The SC formulation provides a more convenient administration route compared to the IV formulation, and allows for the option of self-administration. Safety and efficacy appear to be comparable for the 2 formulations, but they have not been directly compared to each other.

## APPENDIX

### Study Endpoint Descriptions

- **British Isles Lupus Assessment Group (BILAG) and BILAG-2004** (*Lam et al 2005, Mikdashi et al 2015*)
  - The BILAG index provides disease activity scores across 8 organ systems on an ordinal scale (A to E).
    - Organ systems assessed include general, mucocutaneous, neurological, musculoskeletal, cardiovascular and respiratory, vasculitis, renal, and hematological.
  - Disease activity occurring over the past 4 weeks is recorded. Questions within each system are answered as 0 (not present), 1 (improving), 2 (same), 3 (worse), or 4 (new). Based on these items, each system is given a score of A (most active), B (moderate activity), C (minor activity), D (stable), or E (never present).
  - In an updated version (BILAG-2004), the original system of vasculitis was removed and 2 systems, ophthalmic and abdominal, were added. In this version, the total number of items is increased from 86 to 97.
- **Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue)** (*Kosinski et al 2013, Strand et al 2014*)
  - A health-related quality of life questionnaire measuring fatigue in patients with chronic illness.
  - Contains 13 items that measure an individual's level of fatigue during the past week on a 5-point scale (4 = not at all fatigued to 0 = very much fatigued).
  - Scores range from 0 to 52, with lower scores representing more severe disease.
  - An improvement of  $\geq 4$  is considered clinically important.
- **Physician's Global Assessment (PGA)** (*Benlysta dossier 2017, Furie et al 2011*)
  - The PGA used in the BLISS trials used a visual analog scale, with markings of 0 (none), 1 (mild), 2 (moderate), and 3 (severe).
- **Renal Flare Measurement** (*Stohl et al 2017*)
  - In the BLISS-SC trial, a renal flare was defined as confirmed development of  $\geq 1$  of the following 3 features:
    - Increase in 24-hour urinary protein to  $> 1000$  mg if baseline was  $< 200$  mg, or to  $> 2000$  mg if baseline was 200 mg to 1000 mg, or to more than twice a baseline value of  $> 1000$  mg
    - Decrease in the glomerular filtration rate of  $> 20\%$ , accompanied by proteinuria ( $> 1000$  mg/24 hours), hematuria ( $\geq 4$  red blood cells per high-power field), and/or cellular (red blood cell or white blood cell) casts
    - New hematuria ( $\geq 11$  to 20 red blood cells per high-power field) or a 2-grade increase in hematuria compared with baseline, associated with  $> 25\%$  dysmorphic red blood cells, glomerular in origin, and accompanied by an 800 mg increase in 24 hour urinary protein level or new red blood cell casts
- **Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)** (*Benlysta dossier 2017, Bombardier et al 1992, Castrejón et al 2014, Petri et al 2005*)
  - SELENA-SLEDAI is a measure of global improvement in SLE.
  - This index assesses disease activity by scoring 24 weighted disease activity descriptors of SLE as present or absent in the preceding 10 days. Items include: seizure, psychosis, organic brain syndrome, visual disturbance, cranial nerve disorder, lupus headache, cerebrovascular accident, vasculitis, arthritis, myositis, urinary casts, hematuria, proteinuria, pyuria, rash, alopecia, mucosal ulcers, pleurisy, pericarditis, low complement, increased DNA binding, fever, thrombocytopenia, and leukopenia.
  - Scores range from 0 to 105, with higher numbers indicating increased disease activity. In practice, few patients have scores  $> 45$ .
  - Although interpretation of scores varies slightly among publications, activity categories can be generalized to the following approximate ranges: mild (1 to 5), moderate (6 to 10), high (11 to 19), and very high ( $\geq 20$ ).

- A reduction in the SELENA-SLEDAI score of 2 to 3 is considered clinically meaningful; however, a higher threshold of a  $\geq 4$ -point reduction from baseline may be important to demonstrate a desired treatment effect over and above another therapy.
- **SELENA-SLEDAI Flare Index (or SLE Flare Index)** (*Petri 1999, Petri 2005*)
  - An index used to measure SLE flare activity and identify the severity of flares.
  - A mild/moderate flare is defined as the presence of 1 or more of the following:
    - A change in SELENA-SLEDAI score of  $\geq 3$  (but not to more than 12)
    - New or worsened:
      - skin manifestations (discoid, photosensitive, profundus, cutaneous vasculitis, bullous lupus)
      - nasopharyngeal ulcers
      - pleuritis
      - pericarditis
      - arthritis
      - fever (SLE)
    - Increase in prednisone, but not to  $> 0.5$  mg/kg/day
    - Added NSAID or hydroxychloroquine for SLE activity
    - $\geq 1.0$  increase in PGA score, but not to  $> 2.5$
  - A severe flare is defined as:
    - Change in SELENA-SLEDAI score to  $> 12$
    - New or worsened of the following, requiring doubling of the prednisone dose, prednisone increase to  $> 0.5$  mg/kg/day, or hospitalization:
      - CNS SLE
      - vasculitis
      - nephritis
      - myositis
      - platelets  $< 60,000$
      - hemolytic anemia (hemoglobin  $< 70$  g/L or decrease in hemoglobin  $> 30$  g/L)
    - Increase in prednisone to  $> 0.5$  mg/kg/day
    - New cyclophosphamide, azathioprine, or methotrexate for SLE activity
    - Hospitalization for SLE activity
    - Increase in PGA score to  $> 2.5$
  - Note: In the *modified* SLE flare index, the criterion of increased SELENA-SLEDAI score to  $> 12$  for identification of a severe flare is excluded.
- **36-item Short Form Health Survey (SF-36)** (*Strand et al 2014*)
  - The SF-36 is a set of generic (not disease-specific) quality of life measures. It includes a total of 36 questions across 8 domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.
  - Two overall summary scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS), can be computed. For each summary score, the raw domain scores are converted to a 0 to 100 scale, with higher scores indicating better quality of life.
  - The minimum clinically important differences for the summary scores are +2.5 for improvement and -0.8 for deterioration.
- **SLE Responder Index (SRI)** (*Stohl et al 2017*)
  - A composite index requiring all of the following, compared to baseline:
    - A  $\geq 4$ -point reduction in the SELENA-SLEDAI scale
    - No worsening (increase  $< 0.3$  from baseline) in the PGA
    - No new BILAG A organ domain score
    - $\leq 1$  new BILAG B organ domain scores

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