Systemic lupus erythematosus (SLE)—commonly known as lupus—is an inflammatory autoimmune disorder that occurs in women of childbearing age. It is more common among African-Americans and Asians than among whites. SLE is the predominant form of lupus; other types affect only the skin or are triggered by certain medications. Because SLE is relatively uncommon and not a reportable disease, recent estimates of prevalence and incidence in the United States are unavailable. A study published in 2008 estimated a U.S. prevalence of 161,000 people with definite SLE and 322,000 with definite or probable SLE.

SLE is classified as either mild or severe. Mild disease is characterized by fever, arthritis, pleurisy, pericarditis, headache, and/or rash, whereas patients with severe disease may present with hemolytic anemia, thrombocytopenic purpura, pleural and pericardial involvement, renal damage, acute vasculitis of the extremities or gastrointestinal tract, and/or central nervous system involvement. Mild SLE is treated with nonsteroidal anti-inflammatory drugs and antimalarials. Severe disease is treated with corticosteroids (predominantly prednisone); the antimalarial drug hydroxychloroquine; and immunosuppressants.

Analysts have identified several unmet needs in the SLE marketplace, including:

- Drugs with superior efficacy and safety profiles, particularly for LN
- Better drug formulations for improved compliance
- Reduction of SLE-associated morbidity and mortality.

With these needs in mind, pharmaceutical companies are working to develop novel immunomodulatory treatments for patients with SLE and/or LN (Table 1). Some of these agents are more promising than others. Here we discuss—in alphabetical order—that are anticipated to reach Food and Drug Administration (FDA) review.

Abatacept (Orencia, Bristol-Myers Squibb), a selective T-cell costimulation modulator, is currently approved for the treatment of patients with adult rheumatoid arthritis (RA) or juvenile idiopathic arthritis. It is also being evaluated as a potential treatment for patients with LN. The product is a soluble fusion protein consisting of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 linked to the modified Fc portion of human immunoglobulin G1. Abatacept inhibits T-cell activation by binding to proteins CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T cells, which have been implicated in the pathogenesis of RA.

Bristol-Myers Squibb initially investigated abatacept as a potential treatment for patients with SLE, but disappointing phase 2b data led the company to shift its attention to patients with LN. A subsequent phase 2 trial, however, found no difference in response rates between abatacept and placebo in patients with class III or class IV LN. Nevertheless, a phase 3 randomized, double-blind, placebo-controlled study is evaluating the efficacy and safety of abatacept versus placebo, both administered on a background of mycophenolate mofetil and prednisone, in patients with active class III or class IV LN. A total of 400 adults (18 years of age and older) are expected to participate in the study, which began in January 2013, with an estimated completion date of May 2021. The study’s primary endpoint is the proportion of patients achieving a complete response of renal disease—defined as a composite endpoint based on renal function, proteinuria, urine sediment, and corticosteroid dose—after 52 weeks of treatment. Top-line results from this study are expected in May 2019, potentially resulting in expanded labeling for abatacept the following year. The new label would include patients with class III or class IV LN in the nephrotic range.

Anifrolumab (AstraZeneca/MedImmune) is an antagonist human monoclonal antibody that targets interferon-alpha receptor 1 (IFNAR1). Anifrolumab inhibits the binding of IFN ligands to IFNAR1, thereby blocking the formation of the ternary IFN/IFNAR1/IFNAR2 signaling complex. It is believed that dysregulation of IFN activity and/or signaling is implicated in SLE.

Anifrolumab is being evaluated as a potential SLE treatment in two phase 3 studies; both are expected to be completed in May 2018. In the first study, an estimated 360 adults (18 to 70 years of age) with moderately to severely active, autoantibody-positive SLE are being treated with anifrolumab or placebo every four weeks from week 0 to week 48 for a total of 13 doses. The primary outcome measure is the difference in the proportion of patients who achieve an SLE Responder Index score of 4 (SRI-4) or greater at week 52. The second study is following the same design in the same age group, but involves two unspecified doses of anifrolumab in an estimated 450 patients.

A phase 2b trial (TULIP-LN1) is also evaluating anifrolumab as a potential treatment for patients with LN.
Anifrolumab (AstraZeneca/ MedImmune) is a selective peptibody antagonist of the BAFF cytokine (human mAb targeting IFNAR1) and is critical to the development, maintenance, and survival of B cells and plasma cells. It interacts with three receptor subtypes expressed primarily on B cells and plasma cells: BAFF receptor, B-cell maturation antigen, and transmembrane activator and cyclophilin ligand interactor. Blisibimod was developed as an alternative to antibodies and is produced in Escherichia coli.15

The pivotal phase 3 CHABLIS-SC1 trial was designed to evaluate the efficacy and safety of subcutaneous (SC) blisibimod administered in addition to standard therapy in patients with active SLE despite ongoing stable corticosteroid therapy.16 In November 2016, Anthera Pharmaceuticals announced that the study had failed to meet its primary endpoint: the proportion of patients achieving an SRI-6 response at week 52. This endpoint was reached in 47% of patients in the blisibimod arm compared with 42% of patients in the placebo arm, but the difference was not statistically significant. An SRI-6 response requires a reduction of at least six points in Safety of Estrogens in Lupus Erythematosus National Assessment/Systemic Lupus Erythematosus Disease Activity Index (SELENA–SLEDAI) scores. The magnitude of blisibimod treatment effects for other SRI scores (SRI-4 and SRI-8) also did not reach statistical significance.17

Another pivotal phase 3 trial of SC blisibimod in patients with SLE (with or without LN) is currently under way. The primary objective of the CHABLIS 7.5 trial is to evaluate the clinical efficacy of blisibimod, as measured by the SRI, in a population of patients who, despite corticosteroid use, continue to have clinically active SLE. The primary endpoint is the SRI-6 response at week 52. The study began recruiting participants in June 2016, and its estimated completion date is December 2018.18,19 The U.S. patent for blisibimod is scheduled to expire in November 2023.6

If approved by the FDA, blisibimod is expected to be launched in 2020 as a third-line treatment for patients with SLE and/or in SLE patients who are refractory to standard-of-care therapy.6

Lupuzor (ImmuPharma)—also known as P140 peptide—is a 21-mer linear peptide (sequence 131–151) derived from the spliceosomal small nuclear ribonucleoprotein U1-70K, a major anti-

### Table 1 Immunotherapies in Late-Stage Development for SLE and/or Lupus Nephritis6

<table>
<thead>
<tr>
<th>Drug Developer(s)</th>
<th>Mechanism of Action</th>
<th>Targeted Indication</th>
<th>Route of Administration</th>
<th>Expected Pricing Strategy</th>
<th>Estimated Average Cost per Year in U.S.</th>
<th>Anticipated U.S. Launch Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abatacept (Orencia)  Bristol-Myers Squibb</td>
<td>Immuno modulator (T-cell costimulation modulator)</td>
<td>Adults with class III or IV LN in nephrotic range (third line)</td>
<td>IV</td>
<td>Likely to retain price as marketed for RA</td>
<td>$65,930</td>
<td>2020 (expanded label)</td>
</tr>
<tr>
<td>Anifrolumab AstraZeneca/ MedImmune</td>
<td>Immuno modulator (human mAb targeting IFNAR1)</td>
<td>Adults with SLE or moderate-to-severe LN (second line)</td>
<td>IV</td>
<td>Likely to be priced at 25% premium to belimumab (Benlysta, GlaxoSmithKline)</td>
<td>$54,390</td>
<td>2021 (SLE) 2022 (LN; expanded label)</td>
</tr>
<tr>
<td>Blisibimod Anthera/Amgen</td>
<td>Immuno modulator (peptibody antagonist of BAFF cytokine)</td>
<td>Adults with moderate-to-severe SLE and/or SLE patients refractory to SoC (third line)</td>
<td>SC</td>
<td>Likely to be priced at approximately 10% discount to belimumab</td>
<td>$36,680</td>
<td>2020</td>
</tr>
<tr>
<td>Lupuzor ImmuPharma</td>
<td>Immuno modulator (P140 peptide from nuclear ribonucleo-protein U1-70K)</td>
<td>Adults with moderate-to-severe SLE (third line)</td>
<td>SC</td>
<td>Likely to be priced at approximately 10% discount to belimumab</td>
<td>$36,680</td>
<td>2019</td>
</tr>
<tr>
<td>Voclosporin (Orelvo) Aurinia Pharmaceuticals</td>
<td>Immunosuppressive (calcineurin inhibitor)</td>
<td>Add-on to steroids and other immunosuppressive treatments in patients with advanced LN (class III–V)</td>
<td>Oral</td>
<td>Likely to be priced at 10% discount to belimumab</td>
<td>$50,000 to $100,000</td>
<td>2021</td>
</tr>
</tbody>
</table>

BAFF = B-cell activating factor; IFNAR1 = interferon-alpha receptor 1; IV = intravenous; LN = lupus nephritis; mAb = monoclonal antibody; RA = rheumatoid arthritis; SC = subcutaneous; SLE = systemic lupus erythematosus; SoC = standard of care.
body target for lupus autoantibodies. 20 In lupus-prone mice, Lupuzor was found to act as an immunomodulator and not as an immunosuppressant. 21

Clinical efficacy data were provided by a phase 2b trial in which 49 intent-to-treat (ITT) patients with SLE were randomly assigned to receive Lupuzor (200 mcg SC) every four weeks (group 1; n = 49), Lupuzor every two weeks (group 2; n = 51), or placebo (n = 49) in addition to standard of care. 22 In this population, 53% in group 1 (P = 0.048 versus placebo), 45% in group 2 (P = 0.18 versus placebo), and 36% in the placebo group achieved an SRI response at week 12. Slightly more impressive results were obtained from a target ITT group of 136 patients with clinical SLEDAI scores of 6 or greater at baseline. Among these patients, 62% in group 1 (P = 0.016), 48% in group 2 (P = 0.18), and 39% in the placebo group achieved an SRI response at week 12.

In 2013, the FDA granted ImmuPharma a special protocol assessment (SPA) for a planned phase 3 study of Lupuzor. Under the SPA, the study was allowed to include a smaller-than-usual patient population, which reduced the cost of conducting the trial, but it also meant that Lupuzor has to demonstrate a high degree of disease-modifying activity in order to reach statistical significance. The FDA also granted the study a fast-track designation. 6

The 52-week, randomized, double-blind, parallel-group, placebo-controlled trial is evaluating a 200-mcg dose of Lupuzor plus standard of care in an estimated 200 patients with SLE. The primary outcome measure is an assessment of the SRI at week 52. The study began in March 2015 and is scheduled to conclude in March 2018. 23

If Lupuzor is approved by the FDA, analysts expect it to be launched in 2019 in March 2018. 23


18. ClinicalTrials.gov. CHABLIS 7.5: a study of the efficacy and safety of subcutaneous...


