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Challenges in the Development of Drugs for Systemic Lupus Erythematosus: A Regulatory Perspective

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Abstract

Systemic lupus erythematosus (SLE) is a debilitating disease that affects at least 5 million people worldwide. Currently, there are limited approved treatment options for patients with SLE, and a great need remains for therapies to achieve important treatment goals such as reductions in flares, prevention of organ damage, clinical low disease activity or remission. The purpose of this article is to review the current health authority guidance for the development of drugs to treat SLE and discuss some of the challenges in the development of drugs for SLE from a regulatory perspective. Given the substantial number of failed late-stage clinical trials in this indication despite the inclusion of large numbers of subjects, reviewing the regulatory guidance and complexities surrounding the development of drugs for the treatment of SLE is crucial to understand the complexities of the disease itself and the challenges and limitations to conducting successful trials evaluating the impact of treatment of new agents in SLE. As only one new drug (belimumab, trade name BENLYSTA®) with a novel mechanism of action has been approved over the last six decades, the prescribing information for belimumab will be reviewed in the context of the guidance.

Keywords: Systemic lupus erythematosus, lupus, FDA, EMA, regulatory guidance, clinical development

Abbreviations: ACR, American College of Rheumatology; ACTH, adrenocorticotropic hormone; ANA, anti-nuclear antibodies; anti-dsDNA, anti-double-stranded DNA; APS, antiphospholipid syndrome; AZA, azathioprine; BICLA, BILAG-based Composite Lupus Assessment; BILAG, British Isles Lupus Assessment Group; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; CLE, cutaneous lupus erythematosus; CNS, central nervous system; DMARDs, disease-modifying antirheumatic drugs; DORIS, Definitions of Remission In SLE; ECLAM, European Consensus Lupus Activity Measurements; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-fatigue; FDA, U.S. Food and Drug Administration; HAQ, Health Assessment Questionnaire; HIV, human immunodeficiency virus; IV, intravenous; LLDAS, Lupus Low Disease Activity State; LN, lupus nephritis; LupusQoL, Lupus Quality of Life; MCR, major clinical response; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; PCR, partial clinical response; PGA, Physician Global Assessment; PML, progressive multifocal leukoencephalopathy; PRO, patient reported outcome; SC, subcutaneous; SELENA-SLEDAI, Safety of Estrogens in Lupus National Assessment- SLE Disease Activity Index; SF-36, Short-Form-36; SLAM-R, Systemic Lupus Activity Measure-Revised; SLE, systemic involvement; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; SLEDAI-2K, SLEDAI-2000; SLICC, Systemic Lupus International Collaborating Clinics; SLICC/SDI, Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; SmPC, Summary of Product Characteristics; SRI, Systemic Lupus Erythematosus Responder Index; US, United States; USPI, U.S. Prescribing Information

1. Background

1.1. Disease

The estimated annual incidence of SLE varies from 1.8 to 7.6 cases per 100,000, with a worldwide prevalence ranging from 14 to 172 cases per 100,000 people (0.015-1.5% of the population worldwide). The disease occurs up to 15 times more frequently in women than in men, with the highest prevalence in women of childbearing age (over 90% are women with a peak age range from 30-70 years), and occurs more commonly in those of African, Hispanic, or eastern Asian descent [75]. Those with childhood onset SLE generally display more systemic manifestations such as nephritis, neuro-psychiatric disease, and cytopenias [2].

Lupus is a complex, chronic, immune-mediated inflammatory disorder of unknown etiology, in which the immune system attacks the body's cells and tissues, resulting in in-

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flammation and tissue damage that can harm the heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system [44]. As a result, lupus can affect almost any or all organ systems with a multitude of manifestations, including systemic involvement (SLE), cutaneous lupus erythematosus (CLE), lupus nephritis (LN), involvement of the central nervous system (CNS), with associated antiphospholipid syndrome (APS), and frequent overlapping presentations with allied diseases. In addition, there is often overlap among these manifestations. For example, CLE can be a feature of SLE or occur on its own, and LN is considered a diagnostic criterion for SLE [93]. The course of disease in lupus is characterized by periods of relative quiescence (either due to the waxing and waning nature of the disease or effective pharmacological management) interrupted by disease flares. Roughly less than 10% who are diagnosed with SLE will demonstrate a spontaneous remission without treatment [108, 84, 95]. The long-term outcome for patients with lupus depends on a variety of factors, including whether they have organ involvement, the presence of certain laboratory measures (such as autoantibodies like antiphospholipid antibodies or depressed complement levels), frequency of flares, race, sex, age of onset, side effects due to treatments such as glucocorticoids, access to health care, adherence to treatment, education, and comorbidities [31]. At 10 years, approximately 50% of patients have organ damage, with most damage accrual in the renal, CNS, and cardiovascular systems [45]. Two-thirds of patients report complete or partial disability, with prominent fatigue and cognitive dysfunction. Early mortality is two times higher in patients with SLE and six times higher in patients with LN compared with the general population [104, 7]. Between 2000 and 2015, SLE was the leading cause of death in women between ages 15 and 24 in the United States, ranking higher than diabetes, HIV infection, chronic lower respiratory disease, nephritis, pneumonitis, and liver disease [111].

1.2. Diagnosis

Due to the overall complexity of variable organ system involvement in various combinations, coupled with a chronic relapsing-remitting course, proper diagnosis and classification of SLE can be challenging [56]. The time from onset of symptoms to diagnosis is on average 3.5 years [3], due in part to the initial stages of SLE, when there may be an inadequate number of symptoms to make a definitive diagnosis, or patients who present with uncommon features [8]. Since several other conditions can mimic lupus, distinguishing SLE from other conditions can be difficult [13]. This is reflected by the fact that most cases are often ultimately diagnosed at secondary and tertiary centers with experience in the disease [4, 30]. Some of the primary complaints of newly diagnosed lupus patients are arthralgia (62%) and cutaneous symptoms (new photosensitivity; 20%), followed by persistent fever, and malaise [108, 93]. Patients with mild disease typically have skin rashes and joint pain and require less aggressive treatment. With more severe disease, patients may experience a variety of serious conditions depending on the organ systems involved, including lupus nephritis with potential renal failure, endocarditis or myocarditis, pneumonitis, maternal and/or fetal complications during pregnancy, stroke, neurological complications, vasculitis, and cytopenias with associated risks of bleeding or infection. About half of the patients diagnosed with SLE present organ-threatening disease, but it can take several years to diagnose patients who do not present organ involvement. In SLE, the production of destructive auto-reactive antibodies, such as anti-nuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA) antibodies, anti-Smith antibodies, anti-phospholipid, and anti-Cq1 antibodies by dysregulated B lymphocytes is common [74], and the use of serology for these autoantibodies is incorporated into the diagnosis of SLE; however, the sensitivity and specificity of serologic testing varies widely [73].

The American College of Rheumatology (ACR) proposed initial diagnostic criteria for SLE in 1971. These criteria were initially intended to classify the disease and became widely adopted for clinical use. These ACR criteria were revised in 1982 [87], which improved specificity [71] and sensitivity [43]. The criteria were again revised in 1997 to incorporate the presence of anti-phospholipid antibodies in SLE [32]. By comparison, the Systemic Lupus International Collaborating Clinics (SLICC) group revised and validated the ACR SLE classification criteria to improve clinical relevance, meet stringent methodology requirements, and incorporate new knowledge regarding autoantibodies and low complement in SLE [72]. The ACR revised classification criteria for SLE require four or more of the eleven clinical and immunological criteria to be present at some time-point during the course of the disease, and as such, tends to identify more severe disease of longer duration. The SLICC classification consists of seventeen criteria, and for the SLE classification requires: 1) fulfilment of at least four criteria with at least one clinical criterion and one immunologic criterion; or 2) lupus nephritis as the sole clinical criterion in the presence of ANA or anti-dsDNA [72, 112]. The presence of lupus nephritis in isolation was also added as a criterion to classify a patient as exhibiting systemic disease. These criteria were shown to have higher sensitivity but less specificity than the ACR revised criteria. More recently, a collaborative effort by the European League Against Rheumatism (EULAR) and the ACR to develop new classification criteria for SLE, particularly early disease, is underway [88, 37].

1.3. Treatments

Similar to rheumatoid arthritis, treatment for SLE is moving toward a "treat to target" approach with the goals of control of disease activity and remission, prevention of disease flares, minimization of disease activity or treatment-related comorbidity (e.g., corticosteroid adverse effects), overall improvements in the quality of life, and Lupus Low Disease Activity State (LLDAS) [54, 26]. As discussed later, unlike RA, there is a lack of globally accepted definitions of several of these goals (e.g., remission) for the purposes of registrational labeling claims.

Only a few of the drugs used to treat SLE have received specific health authority approval for use in the disease, and many disease-modifying antirheumatic drugs (DMARDs) and biologics are used off-label to treat SLE [93]. Patients with mild SLE have mainly skin rashes and joint pain and require less aggressive treatment regimens that include nonsteroidal

anti-inflammatory drugs (NSAIDs), antimalarials (e.g., hydroxychloroquine, chloroquine, or quinacrine and compounded formulations thereof), and low-dose corticosteroids. In 1948, the FDA approved aspirin as the first drug to treat lupus. Later, corticosteroids, such as prednisone, which suppress the immune system and reduce inflammation were also approved to treat adult SLE. In 1952, Acthar, an adrenocorticotropic hormone (ACTH) analogue was approved by the FDA for use as an injection during an exacerbation or as maintenance therapy in selected cases of SLE. In 1955, the FDA approved the antimalarial drug Plaquenil (hydroxychloroquine sulfate), which was shown to relieve some lupus symptoms such as fatigue, rashes, joint pain, and mouth sores.

For those patients with more severe disease, immunosuppressive agents, such as methotrexate (MTX), azathioprine (AZA), cyclophosphamide, cyclosporine, and mycophenolate mofetil, high-dose corticosteroids, and biologic B-cell cytotoxic agents or modulators (e.g., belimumab) are used [18, 105, 108, 57, 93, 103]. These more aggressive therapies for SLE are generally cytotoxic and are associated with notable safety risks, as well as poor tolerability, when used over a prolonged period of time. In 2011, BENLYSTA® (belimumab), a human IgG1λ monoclonal antibody specific for soluble human B lymphocyte stimulator protein (BLyS, also referred to as BAFF and TNFSF13B), was the only new drug mechanism approved in the past 60 years for the treatment of adult patients with active, autoantibody-positive SLE who are receiving standard therapy (e.g., corticosteroids, antimalarial agents, immunosuppressive agents, NSAIDs). It is administered either by IV infusion at 10 mg/kg at two-week intervals for the first three doses and at four-week intervals thereafter, or as a subcutaneous injection in the abdomen or thigh of 200 mg once weekly [21, 99, 100]. In combination with standard of care, belimumab demonstrated approximately a 14% greater improvement, as measured by a four-point improvement in the Systemic Lupus Erythematosus Responder Index (SRI-4), compared with placebo, and overall good safety and tolerability in SLE [41, 11]. While it was reported in some studies to exhibit limited efficacy in black/African-American patients [16, 99], it further lists mortality, serious infections, progressive multifocal leukoencephalopathy (PML), hypersensitivity reactions, including anaphylaxis, and depression listed as warnings and precautions [99], many of which have been noted with use in combination therapy. Belimumab is not presently recommended for use in combination with cyclosporine or other biologics; however, based upon data showing that levels of BAFF increase after treatment with rituximab (a monoclonal antibody that binds CD20 on B cells), the use of belimumab following rituximab induction treatment is being explored in SLE [60]. While initial data from this combination have been promising, further studies are needed [42]. Thus, while belimumab represents an improvement in efficacy over standard of care, particularly in those patients who are positive for antibodies to dsDNA and have lower complement, a significant number of patients fail to experience a detectable positive response to belimumab [48], and therefore, a large unmet need for new alternative treatments with greater efficacy in SLE, without incurring a high safety risk, remains.

2. Regulatory Guidance

The U.S. Food and Drug Administration (FDA) issued the guidance document for industry, "Systemic Lupus Erythematosus - Developing Drugs for Treatment" in 2010 [96], and the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued the "Guideline on Clinical Investigation of Medicinal Products for the Treatment of Systemic Lupus Erythematosus and Lupus Nephritis" in 2015 [22].

As previously discussed, there has been only one drug (belimumab; BENLYSTA®) approved to treat SLE in the last 60 years. Where appropriate, this review will refer to the product labeling for BENLYSTA® (U.S. Prescribing Information [USPI], [99]) and EMA (SmPC, [21]) to highlight how this product's approved labeling relates to these guidance documents. It is important that the chronology of the guidance documents issue dates with respect to the approval date of belimumab be taken into consideration. BENLYSTA® was approved for IV administration by the FDA and the European Commission in 2011, and, subsequently, for subcutaneous administration in 2017. The FDA guidance document was issued in 2010, prior to the initial approval of BENLYSTA®, whereas the EMA guidance was issued in 2015, after the initial approval of BENLYSTA®.

2.1. Scope

Overall, the EMA and FDA guidance documents are generally consistent in scope and recommendations with respect to patient selection/diagnostic criteria, efficacy assessments, trials designs, safety assessments, and recommendations for pediatric subjects with SLE. The one notable exception is that the EMA guidance includes information specifically regarding LN, which is absent in the FDA guidance. The FDA guidance for SLE does state that the scope is specifically limited to SLE and that organ-specific forms of the disease would be addressed in separate guidance documents. The FDA had released a separate companion guidance document on lupus nephritis titled, "Guidance for Industry, Lupus Nephritis Caused By Systemic Lupus Erythematosus - Developing Medical Products for Treatment, June 2010" [98]; however, this guidance was subsequently withdrawn in June 2012 by the FDA citing that, "*This guidance is being withdrawn because it does not reflect FDA's current thinking on the development of medical products for the treatment of lupus nephritis.*" [98]. However, despite withdrawal of the FDA LN guidance, there are recent Phase 2 studies in LN conducted in the U.S. (e.g. [63, 65]) that have used the EMA guidelines for study endpoints (e.g., complete renal response as a primary outcome). In the absence of any currently published FDA guidance or precedence in the U.S. for registration trials in LN, it seems reasonable that sponsors follow the EMA recommendations.

Other clinical manifestations of lupus such as those involving the CNS, APS, and CLE are specifically not included in

the scope of either guidance. In the EMA guidance, this is explained as either a difficulty in making a diagnosis and/or the absence of validated efficacy assessment tools (CNS lupus and secondary antiphospholipid syndrome), or limited regulatory experience with a subset (CLE). While studies in these subsets of SLE are not specifically addressed by any current guidance, they reflect a population with a high unmet medical need. Both guidance documents provide for the possibility of working with sponsors to define and agree on clinically meaningful endpoints to demonstrate efficacy in subpopulations of patients with these manifestations of SLE, provided the data support use in such a subpopulation. As stated in the FDA guidance, "*If the medical product is studied only in a subset of the general SLE population, then the restricted population in which the medical product was studied would be reflected in labeling*", in line with the appropriate labeling guidance. In addition, if the SLE population studied in a clinical program did not include or intentionally excluded those with certain manifestations of SLE, and extrapolation of efficacy to a broad SLE population with such manifestations could not be justified, then this would most likely be reflected in product labeling. as indicated in the SmPC and USPI for BENLYSTA®, which indicate that belimumab has not been studied in individuals with lupus with severe active renal and severe active CNS involvement, and is therefore not recommended for use in these populations.

As with other disease-specific guidance, both EMA and FDA documents address aspects relevant to general drug development (e.g., pharmacokinetics, dose response, drug-drug interactions, statistical considerations, standard monitoring of safety, etc.). As these topics are not unique to drug development for SLE, they will not be discussed.

2.2. Study Population

2.2.1. Patient Demographics

As mentioned, patients with SLE demonstrate a high degree of inter- and intra-individual heterogeneity in their disease manifestations that can fluctuate over time in relation to organ system involvement, severity, and symptoms. This heterogeneity can present challenges in enrolling an appropriate population to demonstrate efficacy and safety. In addition, many patients with lupus have comorbidities or overlapping disorders (e.g., fibromyalgia [110]), which can present confounding issues when assessing endpoints such as joint pain and fatigue. While both guidance documents recommend studying a, "*broad spectrum of patients*" (EMA) with SLE, "*that can be generalized to an appropriate population for recommended use, and not made artificially narrow*" (FDA), they do make provision for studying more selective subgroups of patients. The FDA guidance states that if data, "*suggest that only a specific, limited population can be expected to benefit from the therapy*", the inclusion and exclusion criteria should reflect this. This may be potentially reflected in stratifying and/or enrolling patients based upon a biomarker, such as those currently being employed for some trials (e.g. [64]). This flexibility is echoed in the EMA guidance, which recommends enrolling a "*broad spectrum of patients unless a specific subset or subsets of SLE patients is planned to be targeted (e.g. renal lupus)*" [22].

Given that SLE occurs more commonly in those of African, Hispanic, or eastern Asian descent, it is important to ensure inclusion of sufficient patients of these demographic groups. This was highlighted by the finding that exploratory subgroup analyses of the response rate in black/African-American patients indicated that the efficacy of belimumab 10 mg/kg, as measured by SRI-4, was numerically lower than placebo plus standard (36% for belimumab vs. 44% for placebo) (BENLYSTA® USPI, [99]). In the FDA's Summary Review for Application Number 125370 for BENLYSTA®, it was noted that a, "*post-hoc analysis of racial subgroups suggests that there may be a reversal in the direction of treatment effect in patients of African American or African heritage compared to other races*" [100]. While both labels indicate that no definitive conclusions can be drawn from this subgroup analysis due to the small number (n=148) of black/African-American patients enrolled in the belimumab clinical trials (BENLYSTA® USPI, [99]; [21, 47, 10]), this resulted in a conservative labeling position in the United States with regard to the limited data, resulting in inclusion of language in the USPI indicating that, "*Caution should be used when considering treatment with BENLYSTA® in black/African-American patients*" and a FDA post-marketing commitment [100] requiring the sponsor to conduct a clinical trial of belimumab specifically in black patients with SLE [59]. This emphasizes the importance of including a sufficiently broad enough patient demographic in clinical trials, especially if there is a known higher prevalence/incidence in a gender or ethnic group. Thus, the absence of adequate data to allow evaluation of a drug in relevant subpopulations may result in restrictive labeling statements similar to belimumab, which could potentially result in either appropriate or inappropriate restriction of the drug to a particular population. Interestingly, while there is similar language in the SmPC stating a lack of data for black/African American patients to draw meaningful conclusions, the SmPC does not contain any corresponding text restricting use in this population.

2.2.2. Diagnostic Entry Criteria

There are no internationally validated diagnostic criteria for SLE [56]. However, both the FDA and EMA guidance documents indicate trials should enroll patients with established SLE based upon the ACR or SLICC criteria. The ACR criteria have undergone several updates to reflect both the changing understanding of the disease and the validity of the criteria in use. The two guidance documents recognize these criteria as being generally accepted by the medical community and suitable as use for diagnosis for inclusion into clinical studies. In contrast to the FDA guidance, the EMA guidance specifically mentions both the ACR and SLICC criteria. This difference is most likely due to the dates the guidance documents were issued, since the SLICC criteria [72] were not published at the time the FDA guidance was issued [96], as opposed to the EMA guidance, which was released later [22].

Unless internationally validated diagnostic criteria are developed that deviate substantially from the current ACR/SLICC criteria, the SLE diagnostic criteria for inclusion in clinical studies set forth in both guidance documents are written broadly

enough to support use of the current criteria and appear flexible enough to accommodate updates to these criteria by the SLE medical community.

2.2.3. Disease Severity

Trials should enroll patients with established SLE, as defined by the American College of Rheumatology classification criteria that would, "*reasonably be considered for the therapy*" [96], with severe enough active SLE such that a therapeutic improvement can be demonstrated and is representative of disease in the general SLE population. Although the EMA guidance recommends a Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) >6 at baseline, other measurements of disease activity (e.g. SLEDAI-2000, SLEDAI-2K; British Isles Lupus Assessment Group, BILAG) have been validated and used by the SLE medical community in clinical studies to ensure that populations with clinically meaningful disease activity are included in trials [77, 14, 53]. Typically, the population is also required to be autoantibody positive (e.g., anti-dsDNA or antinuclear antibodies). This may be a result of the first Phase 3 study of belimumab, in which 28% of the population was autoantibody negative at baseline, did not meet its primary endpoint [99], and necessitates further studies. A recent survey of studies on Clinicaltrials.gov indicates most of the interventional studies are recruiting individuals with this active established disease, as indicated in the guidance (i.e., SLEDAI >6, autoantibody positive, etc.), who are receiving standard of care that is reasonable to ensure that there is a demonstrable and clinically meaningful improvement by the outcome measure.

2.2.4. Concomitant Medications and standard of care

Almost all current SLE clinical trial designs are add-on trials that incorporate a background of "*standard of care*" medication into the treatment arms. This is due to the lack of a single "*gold standard*" agent that, when administered alone, would demonstrate similar efficacy to standard of care. However, since there is no global definition for standard of care, this can pose a challenge when conducting a clinical trial globally, for background medications such as glucocorticoids or mycophenolate mofetil have the potential to confound efficacy results if not carefully controlled. This principle is reflected in both guidance documents, which indicate the need for study protocols to standardize baseline concomitant medication use and define how medication adjustments are to be made, if needed, and how these changes will impact analyses of the data. The product labeling for BENLYSTA® does not specifically define standard of care therapy, only stating it is to be used in patients with active disease as, "*add-on therapy*" [21] or in those, "*receiving standard therapy*" (USPI, [99]).

2.3. Clinical Trial Design

While both guidance documents discuss several options for clinical trial designs (e.g., superiority, noninferiority, alternative designs such as randomized withdrawal), both of them indicate that the recommended design is a parallel, randomized, controlled, superiority study in which a compound is tested against placebo, with all study participants receiving background standard of care treatment (add-on design). In addition, the EMA guidance states that the preferred design is a superiority trial against an active comparator or placebo.

The guidances mention the possibility of including an active comparator arm in the study, which, as stated in the EMA guidance would, "*allow putting results into perspective*". Although the FDA guidance was written prior to the approval of BENLYSTA®, it indicated that at the time there were no approved drugs available, "*with an effect size adequately characterized to design an adequate noninferiority trial for a new medical product in any SLE setting*". The EMA guidance, which was written post-approval of BENLYSTA®, does indicate that a non-inferiority study could only be accepted, "*provided that the selected comparator could be justified on the basis of well-established efficacy, and an appropriately justified non-inferiority margin could be predefined*". Both documents recommend consultation with the health authority prior to initiating this type of study. Given the evolving landscape, the increase in the number of studies being conducted with agents having new mechanisms of action in lupus, the importance of comparator data and proper delineation of concomitant therapy should be considered when designing a development program intended for registration. This will help inform not only health authorities but also prescribers.

Due to the "waxing and waning course" of SLE, both guidance documents are aligned in recommending a 1-year duration for a clinical trial in SLE to demonstrate efficacy in several endpoints such as organ damage, "*reduction in disease activity, complete clinical response or remission, reduction in flare/increase in time to flare, and maintenance of response*" [98]. This addresses a concern that short-term improvement in certain domains of efficacy measurements could mask worsening in other domains over the long term. It is noted that several Phase 2 studies (e.g. [109, 66]) used a 24-week primary endpoint to demonstrate early proof-of-concept in SLE prior to advancing to longer duration Phase 3 studies. The FDA guidance does state that shorter time points can be considered provided there is justification, such as a compound's "onset of action" indicating that, "*The timing of the primary efficacy analysis, at either 6 or 12 months, depends upon the time it takes for the new medical product to achieve optimal activity. If 12 months is chosen as the primary endpoint, BILAG should show a statistically significant improvement at 12 months that has been sustained at a minimum for 2 months. Alternatively, if the primary endpoint is set at 6 months, clinical benefit should be assessed at 12 months as a secondary endpoint*". The EMA guidance similarly states that, "*The time point chosen for the evaluation of the effect on disease activity will depend on the time it takes the study drug to achieve an optimal effect, on the severity of the disease and whether it is intended for acute or chronic use*". The EMA guidance also mentions other aspects of trial design, such as randomized withdrawal, which could be incorporated to provide information on long-term persistence of efficacy once short-term efficacy is established.

Although the EMA and FDA guidance documents are consistent in recommending a one-year length for a SLE trial, both

have a somewhat different perspective regarding the use of induction and maintenance treatment modalities for SLE. The EMA guidance considers SLE more as a chronic disease requiring maintenance, in contrast to the acute flares in LN. The EMA guidance indicates that "*Studies conducted in patients with lupus nephritis should be aimed for control of renal activity*". Since the EMA guidance also includes information on LN, it highlights that, "*induction and maintenance therapy are not considered as separate treatment modalities of SLE treatment in clinical practice - this is in contrast to lupus nephritis where treatment of acute flares is separated from chronic maintenance treatment*", and, "*Contrary to SLE, a clear distinction between induction and maintenance is generally accepted for lupus nephritis*". For LN, induction and maintenance are generally accepted for the treatment with a recommended three- to six-month period for assessing induction or partial response, and a longer follow-up, i.e., one year, to assess maintenance of response. The FDA guidance makes provision, "*for short term use, such as induction of response*", provided that long-term follow-up be incorporated even if the agent is not administered beyond the initial treatment period, allowing for patients to be, "*switched to another maintenance therapy for the remainder of the follow-up period*". For example, the SYNBIoSe study [60] in SLE includes two agents directed against two separate B cell-related targets in an induction/maintenance-type design. It is examining the use of an initial intravenous treatment with 1000 mg rituximab (an anti-CD20 mAb) on Days 0 and 14, followed by belimumab (anti-BLyS mAb) at 10 mg/kg on Days 28, 42, and 56, and every four weeks through 72 weeks, with a primary efficacy assessment of a sustained reduction of pathogenic autoantibodies, in particular anti-dsDNA autoantibodies, at 24 weeks after the start of treatment. The considerations for a development program, and subsequent labeling, for agents used in combination for SLE, would likely be very different from a program developing a single agent for chronic treatment.

In addition, the FDA discusses studying short-term use to treat, "*serious acute disease manifestations of SLE*" such as acute lupus pneumonitis, acute confusional state, and acute transverse myelitis. These are considered, "*a special case of induction therapy*", where the investigational product is used for a short period of time to achieve a response, followed by maintenance therapy with that compound or another treatment. The recommended secondary endpoints such as, "*mortality, time to resolution of the acute manifestation, need for retreatment, use of corticosteroids*", reflect the seriousness and acute nature of these conditions. Similarly, a registration program for such agents would again be likely to differ from agents used for chronic treatment and would require consultation with health authorities.

2.3.1. Endpoints

Both guidance documents are very similar with respect to the endpoints for clinical trials in SLE. The endpoints discussed are reduction in disease activity, remission, prevention of or reduction in time to disease flares, reduction in concomitant glucocorticoid use, prevention of damage, treatment of serious acute manifestations, patient-reported outcomes (PROs), and biomarkers. The endpoints in a study should consider an agents mechanism of action and pharmacokinetic/pharmacodynamic properties, as the study could be designed to test the type of effect the drug is likely to have (e.g., induction versus maintenance of response, impact on disease flares, impact on acute symptoms, impact on organ damage, etc.).

2.3.2. Reduction in Disease Activity

There are several tools to assess either global SLE disease activity (e.g. SLEDAI; SLEDAI-2K; Safety of Estrogens in Lupus National Assessment-SLE Disease Activity Index, SELENA-SLEDAI; European Conensus Lupus Activity Measurements, ECLAM; Systemic Lupus Activity Measure-Revised, SLAM-R; BILAG index, including variants of this tool) or organ specific disease activity (e.g. Cutaneous Lupus Erythematosus Disease Area and Severity Index, CLASI; and each of the BILAG domains) (reviewed in [89, 53]). However, due to the various strengths and weaknesses of each of these instruments, composite indices such as the SRI (reviewed in [46]) or BILAG-based Composite Lupus Assessment (BICLA) have been developed and validated through use in clinical trials (reviewed in [89, 91]). The SRI was developed as a composite tool derived from three different internationally-validated indices, SELENA-SLE Disease Activity Index (SELENA-SLEDAI), Physician Global Assessment (PGA), and the 2004 BILAG [27, 46].

As the SRI was developed around the time the FDA guidance was released in 2010 [27], it is not included in the FDA guidance. In contrast, the EMA guidance issued in 2015 specifically mentions the use of the SRI and BICLA as composite responder measures. For recent studies, SRI-4 composite response ($\geq$ 4-point reduction in SLEDAI-2K and no worsening of BILAG and PGA) is most commonly used as a primary endpoint by the SLE community, based upon the validation of this tool from clinical trials, primarily with belimumab [29, 28]. It is possible that as newer therapies show greater gains in efficacy, the use of SRI-4 as a discriminatory endpoint for all clinical trials may change (e.g., SRI-5, etc.). Attempts have been made to balance the specificity of change by increasing the level of reduction in score, with the effect in many cases of improved discrimination with depression of response rates/suitability for subjects with lower disease activities. Several studies now include other SRI breakpoints (e.g., SRI-5, SRI-6) as endpoints [40]. Attempts are also in place to show achievement of a low disease activity state versus relative reduction (LLDAS), and appear to have met with some success [55, 23].

Even though both guidance documents consider SLE to be a chronic disease with a varying disease course and recommend assessment of the primary endpoint at 1-year, unless the mechanism of action or pharmacodynamics indicate otherwise, both documents indicate the importance of assessing disease activity at multiple times (i.e., 6-months and 12-months) to assess the time course of response, demonstrate consistency of response over time, and that, "*improvement in a disease activity index score is not accompanied by a worsening of other disease manifestations*" [98]. This is critical for composite index scores where improvement in one component can potentially

mask worsening in another. The FDA guidance goes further in delineating measurement of the primary efficacy analysis on the outcome of a, "*major clinical response (MCR)*" or "*partial clinical response (PCR)*", which would be determined by a predefined outcome. While many clinical trials currently employ SRI or BICLA composites in part to address aspects of the guidance documents, newer endpoints like LLDAS or modeled endpoints may be more suitable to address disease in broader populations [26, 94, 115].

2.3.3. Remission

The overall remission rate in patients with SLE remains low (5-10%) [108, 84, 49, 114, 95]. While the current "treat-to-target" recommendations have identified remission as a goal of therapy [78, 94], there is no universally accepted definition for remission [106]. As such, remission presents a high bar for any new agent to demonstrate, and would differentiate it from current therapies. Both the FDA and EMA guidance make the clear distinction between response and remission, defining remission as the absence of clinical disease without the need to continue receiving ongoing therapy for SLE, although the EMA guidance makes provision for remission in patients receiving glucocorticoids to be either steroid-free, "*or at least to achieve a low-steroid dose to maintain remission*". The FDA guidance goes further to specify patients would need to be disease-free using a validated assessment tool, "*for at least 6 consecutive months*", to demonstrate remission. More recently, measures of remission such as Definitions Of Remission In SLE (DORIS) [106] and LLDAS [26, 94, 115] are gaining interest within the lupus medical community and may satisfy this aspect of the guidance in the future, although they would require validation in randomized clinical trials.

2.3.4. Disease Flares

There is no universally recognized definition of flare by the SLE community [35, 90]. Diagnosis of disease flares is further complicated by the fact that other conditions such as infections, can mimic aspects of SLE disease flares [70]. Both guidance documents indicate that flares should be characterized as clinically significant increases in disease activity in one or more organ systems that would require increases or changes in treatment, and that the definition of disease flare should be predetermined and specified in the study protocol. The FDA guidance further indicates that possible flares should be adjudicated by a blinded data monitoring board. Both documents list SELENA-SLEDAI and BILAG as acceptable indices for the assessment of flares. Studies with belimumab employed the SELENA-SLEDAI Flare Index [90].

Viable endpoints could include the impact of treatment on the number or severity of disease flares, as well as increase in the time to flare. The FDA guidance specifies that if the time to flare is evaluated as a primary endpoint, then, "*the trial should be at least 1 year in duration*", to distinguish between reduction in flare number or delay in occurrence. It goes on to further indicate that, "*critical secondary endpoint should be a comparison of the flare rates or proportion of patients that are flare-free at an appropriate time point*". The EMA guidance considers prevention of flares as a primary (time to a new flare) or key secondary (rate of flares over appropriate time points) endpoint, and is also a rationale for recommending a one-year study duration, stating that, "*A study duration of at least 1 year is usually needed to demonstrate the effect on flares*".

2.3.5. Reduction of Glucocorticoids

Due to the well-known toxicities associated with long-term usage of glucocorticoids, particularly moderate to high doses [81, 76], reduction of steroid use is a key goal in the treatment of patients with SLE, as indicated in both the EMA and FDA guidance documents. Both suggest similar ways to evaluate the ability to taper glucocorticoids in patients whose disease is currently controlled by a stable dose of moderate or high doses of steroids (e.g., >30 to >100 mg prednisone equivalent a day [12]. The dose of glucocorticoids can be gradually reduced by a clinically meaningful amount to ≤7.5-10.0 mg/day, or discontinued while maintaining quiescent disease without any flares for at least three months during a one-year study. The FDA guidance also indicates that reduction of steroid use must occur in the context of a treatment that effectively controls disease activity, stating, "*Therefore, for a medical product to be labeled as reducing corticosteroid usage, it should also demonstrate another clinical benefit, such as reduction in disease activity as the primary endpoint*". Reduction of steroid use in the absence of overall treatment efficacy is not sufficient on its own. Interestingly, a meta-analysis of 28 Phase 3 studies in SLE or LN indicated that belimumab, tabalumab, and epratuzumab had a greater steroid-sparing effect compared with placebo, although only belimumab met its primary endpoint [69]. The FDA guidance further indicates ways to study reduction of induction doses of glucocorticoids during a disease flare [1], although this entails enrolling patients during a disease flare. As already discussed, the lack of a globally defined/acceptable clinical tapering regimen remains a challenge for clinical trials. The results of the Biomarkers of Lupus Disease (BOLD) Study suggest that there may be approaches that would allow for the safe withdrawal of background treatments if participants who experience disease flares are designated as nonresponders and placed back on standard therapy [51].

2.3.6. Long-term damage due to SLE

Over the course of the disease, the chronic, immune-mediated inflammation in SLE can lead to irreversible and permanent scarring damage in a multitude of organ systems in some patients (reviewed in [24]). Both guidance documents recommend considering the assessment of damage caused by SLE, and mention the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/SDI) as a means of assessing damage. They also stipulate that due to the length of time needed to determine the impact of a treatment on damage and the length of time needed to demonstrate a change in the SLICC/SDI, trials should be at least one year in length. Additionally, they both indicate that organ damage due to a drug's toxicities can present confounding issues when using the SLICC/SDI (e.g., damage occurring

in organs not measured by the SLICC/SDI), and that the assessment of damage should be discussed with the health authority prior to starting the trial. The EMA guidance makes the point that since a SLE population can be highly variable with regard to baseline damage, stratifying patients according to baseline damage can be of value, "*as the evaluation of damage accrual will be clearer in those with low baseline damage*".

2.3.7. Patient-reported Outcomes

While both guidance documents recognize the importance of patient-reported outcomes (PROs), particularly fatigue, there is some divergence between the two guidance documents with respect to the acceptance of measurements to assess PROs. While the FDA guidance emphasizes the inclusion of PROs as a key secondary endpoint in SLE trials, it states that they, "*have not yet identified an existing PRO instrument optimal for the measurement of fatigue symptom complex in patients with SLE to support labeling claims*", but support the development of such tools. Similarly, the EMA guidance highlights the importance of assessing changes in health-related quality of life in SLE, and mentions the Short-Form-36 (SF-36) and the fatigue severity scale (FSS) as examples of instruments that could be used to assess fatigue, although, "*other alternatives might be used provided they are validated and generally accepted*". For example, the Lupus Impact Tracker is a 10-item PRO designed to measure the impact of SLE or its treatment on the daily lives of patients [38] that has been shown to be responsive to several outcomes (e.g., PGA, SLEDAI, SRI, etc. [17]), and has been validated in studies in multiple countries across the globe [38, 83, 5]. This divergence in guidance regarding PROs is reflected in the product labeling for BENLYSTA®, which includes claims of improvement in fatigue using the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale in the EMA label (SmPC) that are absent in the USPI. Such regional differences in labeling for PROs are not unique to the SLE indication.

In addition to the FACIT-fatigue and Health Assessment Questionnaire (HAQ), several SLE specific Quality of Life measurements (LupusQoL, LupusPRO, L-QoL and SLEQOL) have been developed (reviewed in [50, 36]). However, the interpretation of the results of PROs has often been difficult for several reasons. Since many trials fail to meet their primary and/or secondary endpoints, it is not possible to evaluate the PROs, especially since the results of PROs do not consistently track with results in clinical endpoints [28, 50]. Additional validation of these tools for SLE (e.g., consistency/tracking with measurements of clinical endpoints) would be beneficial in supporting labeling claims based upon these PRO assessments, particularly in the U.S. For example, there are no systematically studied and established SLE-specific minimal clinically important difference (MCID) values for the various assessment tools such as SF-36 and the variety of fatigue scales being used in SLE clinical trials. In addition, due to the lack of agents for SLE, the role that PROs will play in determining issues such as market access and reimbursement are not yet clear; however, based upon patient needs [82] and as highlighted in the guidance documents, the impact of agents on PROs is likely to play an important role in future treatments for SLE.

2.3.8. Biomarkers

Serum biomarkers such as anti-nuclear, anti-dsDNA, and anti-Smith antibodies have long been used clinically in SLE for the purposes of diagnosis, classification, study entry criteria, and endpoint measurements; however, there still is a lack of clarity as to the clinical significance of changes in the presence, composition, or titers of these antibodies with respect to efficacy [58, 85]. The peripheral blood monocytes of many SLE patients have a characteristic interferon signature often ascribed to being mediated by type I interferon signaling (reviewed in [9, 20]). This interferon signature has also been observed to occur more frequently in families with lupus and may be a risk factor for development of SLE. Consequently, several compounds targeting components of the type I interferon pathway (e.g., anifrolumab, sifalimumab, and rontalizumab) are either in development or have been in development for SLE [25]. More recently, some of these studies have incorporated the use of the type I interferon signature as means of enrolling or stratifying patients (ClinicalTrials.gov Identifier: NCT03435601; [79]).

While selective enrollment or stratification of the study population based upon a biomarker may increase the probability of success for a compound whose mechanism of action impacts that biomarker, it may potentially lead to a more restrictive labeling for a compound, as indicated in both guidance documents, unless a compelling argument can be made that the results in the selected subpopulation are extrapolatable to a broader group. To date, no biomarkers for assessing efficacy have been identified and validated.

Both guidance documents acknowledge the exploratory nature and lack of validation of biomarkers in SLE for use as surrogate endpoints, but remain open to their inclusion in studies. The EMA guidance advises that biomarkers be an, "*integral part of the drug development programme*", and the FDA guidance advises consultation with the Agency, "*to determine whether a biomarker used to select patients or monitor response in clinical trials can be used in prescribing the medical product if approved*".

Despite the lack of understanding with respect to their clinical significance or validation as surrogate efficacy endpoints, many clinical studies include an assessment of the impact of treatment on autoreactive antibodies as secondary or exploratory endpoints. In the case of BENLYSTA®, such information is reflected in the product indication labeling and pharmacodynamic section of the label (USPI, SmPC). The first Phase 3 trial for BENLYSTA® failed to show any difference between active treatment and placebo in the overall trial population, which was 28% autoantibody negative at baseline. Exploratory analysis showed that belimumab demonstrated efficacy in the subgroup of patients who were autoantibody positive. These results informed the design of the following two trials, which showed the efficacy of belimumab in those who had positive autoantibody test results at screening, and led to the subsequent labeling of belimumab limiting its use to only those SLE patients who are autoantibody-positive.

Other biomarkers such as the type I interferon signature are being explored for use as a means of patient selection or stratification in clinical trials (ClinicalTrials.gov Identifier: NCT03435601; [79]). A greater understanding of the molecular pathways that play key roles in disease process in SLE will facilitate the identification and validation of biomarkers for use in patient selection/stratification, assessing efficacy in key subgroups, and safety monitoring in clinical trials.

Biomarkers have potential utility in selection of participants in clinical trials or predicting those subjects most likely to benefit from treatment or at risk of adverse reaction. If a biomarker is to be employed as a companion diagnostic tool, a sponsor will need to consult with health authorities to incorporate this into the development program for the therapeutic agent in a manner that would allow for contemporaneous marketing authorizations for both the agent and the associated companion diagnostic.

3. Discussion and Conclusions

3.1. Compounds in Development

A variety of new therapeutic agents are currently in development and have been evaluated over the years for the treatment of lupus; however, to date, very few have succeeded in late stage clinical testing, or demonstrated notable clinical efficacy and safety beyond those medications currently considered standard of care for patients with this disease (reviewed in [92, 47]). For example, tabalumab, an anti-BLyS mAb against the same target as belimumab, was discontinued after two Phase 3 trials failed to demonstrate efficacy [34, 50]. Although the development of other molecules targeting the interferon alpha pathway (sifalimumab and rontalizumab) has been discontinued, anifrolumab is currently the most advanced [61, 62]. Recent results from the first Phase 3 study of anifrolumab (TULIP 1; [61]) were disappointing, with the trial failing to meet its primary endpoint of a reduction of disease activity as measured by the SLE Responder Index [6]. Other recent failures in Phase 3 include epratuzumab (anti-CD22 mAb; [15]) and tabalumab (anti-BAFF mAb; [80]), highlighting the difficulties in drug development in this area. Recent results from a Phase 2 study of ustekinumab, an anti-IL-12/23 mAb in SLE appear promising [106], and a Phase 3 study is underway [67].

3.2. Current Challenges and the Future

There are multiple challenges currently facing the development of drugs to treat SLE. These challenges are articulated in the guidance documents and come from the nature of the disease itself, such as a high degree of inter- and intra-individual variability in disease manifestations resulting in a study population with a good deal of heterogeneity being enrolled; multiple instruments with various limitations in assessing disease and clinical endpoints; need for validated tools for use in SLE to assess patient-reported outcomes (e.g., fatigue); a lack of predictive biomarkers or surrogate endpoints; and confounding by background therapy, particularly glucocorticoids. These factors combined present challenges for those who diagnose and treat patients with SLE, as well as those who regulate the approval of drugs for SLE.

What is needed is a better understanding of the disease itself, both at a molecular level and from a clinical perspective [52]. For example, identification of key biomarkers could help identify patients who would be more likely to respond to a drug based upon its mechanisms of action, and those more likely to develop disease flares or experience damage to a particular organ system. New validated PROs could provide additional utility in assessing the impact of a drug on improving disease manifestations such as fatigue and other aspects, which have a substantial negative impact on a patients quality of life [113].

Not all drugs used to treat SLE are approved globally, and for those that are approved there can be differences in dosing and labeling. As such, a global definition of standard of care from the clinical community would help to standardize entry criteria for clinical trials and allow for a better understanding of clinical trials results across studies [39]. Identification of a safe and effective "gold standard" approved and accepted globally would allow for comparator studies in which new drugs could be tested and results placed in context to determine if new treatments are truly improvements, which would help inform market access in this indication. It is hoped that new drugs will become available despite the long history of failures in this indication [19]. Given the number of trials in SLE [92], it is critical that learnings from failed trials be applied to help future studies succeed [33]. For example, trials focused on subsets of patients afflicted with a specific aspect of lupus such as LN, CLE, CNS lupus, lupus arthritis, may help address the challenge of participant heterogeneity associated with trials in a broader SLE population. Health authority guidance on innovative trial designs such as master protocols (e.g., basket and umbrella designs) [102] or adaptive design trials [101], may also provide alternate approaches to rapidly evaluate more compounds and increase the success rate of clinical trials in this indication. In addition, there is the Accelerating Medicines Partnership (AMP), which brings together the resources of the National Institutes of Health (NIH) and industry to improve our understanding of disease pathways in rheumatoid arthritis and lupus – as well as Alzheimer's disease, type 2 diabetes, and Parkinson's disease – to facilitate better selection of drug targets for treatment; however, to date, this partnership has focused primary on rheumatoid arthritis and has not yielded sufficient results to have a meaningful impact on regulatory guidance for SLE.

While the development of drugs for SLE remains challenging, the currently available regulatory guidance documents provide a solid framework with sufficient flexibility to accommodate sponsors developing drugs to treat this important disease. Although too much flexibility can create ambiguity and not provide enough guidance, and while more specific and proscriptive guidance in the areas of reduction of signs and symptoms, reduction in concomitant medications, prevention and treatment of flares, and maintenance of low disease activity, treatment failure rules and other analyses would be useful for designing clinical studies, such guidance will need to be based upon data from clinical trials and the lupus community. In addition, improvements to address issues concerning assays (e.g., serology

testing), a global definition of standard of care, and identification of a "gold standard" medication for use as an active comparator would all facilitate development of agents to treat SLE. While discussions with health authorities throughout the development of any drug are always recommended, given the issues associated with SLE, these types of interactions are even more critical in dealing with the complexities faced by both, clinicians and regulators, in the development of drugs to treat SLE, as well as a rapidly evolving understanding of the biology underlying the disease itself.

4. Declaration of Conflicting Interest

All authors are employees of Janssen Pharmaceuticals Research and Development, LLC.

5. Article Information

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6. References

[1] Ad Hoc Working Group on Steroid-Sparing Criteria in Lupus. (2004). Criteria for steroid-sparing ability of interventions in systemic lupus erythematosus: report of a consensus meeting. *Arthritis & Rheumatology, 50*(11), 3427-3431. doi: 10.1002/art.20599

[2] Aggarwal, A., & Srivastava, P. (2015). Childhood onset systemic lupus erythematosus: how is it different from adult SLE? *International Journal of Rheumatic Diseases, 18*(2), 182-191. doi: 10.1111/1756-185X.12419

[3] Al Sawah, S., Daly, R. P., Foster, S., Naegeli, A., Benjamin, K., Doll, H., . . . Alarcón, G. (2015). Understanding Delay in Diagnosis, Access to Care, and Satisfaction with Care in Lupus: Findings from a Cross-Sectional Online Survey in the United States. *Annals of the Rheumatic Diseases, 74*(Suppl 2), 812.3-812. doi: 10.1136/annrheumdis-2015-eular.1159

[4] Aljohani, R., Gladman, D. D., Su, J., & Urowitz, M. B. (2017). Comparison of systemic lupus erythematosus (SLE) patients managed early after diagnosis in specialty versus community care clinics. *Clinical Rheumatology, 36*(8), 1773-1778. doi: 10.1007/s10067-017-3713-7

[5] Antony, A., Kandane-Rathnayake, R. K., Ko, T., Boulos, D., Hoi, A. Y., Jolly, M., & Morand, E. F. (2017). Validation of the Lupus Impact Tracker in an Australian patient cohort. *Lupus, 26*(1), 98-105. doi: 10.1177/0961203316664593

[6] AstraZeneca. (2018, August 31). Update on TULIP 1 Phase III trial for anifrolumab in systemic lupus erythematosus. Retrieved September 11, 2018 from https://www.astrazeneca.com/media-centre/press-releases/2018/update-on-tulip-1-phase-iii-trial-for-anifrolumab-in-systemic-lupus-erythematosus-31082018.html

[7] Bernatsky, S., Boivin, J. F., Joseph, L., Manzi, S., Ginzler, E., Gladman, D. D., . . . Ramsey-Goldman, R. (2006). Mortality in systemic lupus erythematosus. *Arthritis & Rheumatology, 54*, 2550-2557. doi: 10.1002/art.21955

[8] Bertsias, G. K., Pamfil, C., Fanouriakis, A., & Boumpas, D. T. (2013). Diagnostic criteria for systemic lupus erythematosus: has the time come? *Nature Reviews Rheumatology, 9*(11), 687-694. doi: 10.1038/nrrheum.2013.103

[9] Bezalel, S., Guri, K. M., Elbirt, D., Asher, I., & Sthoeger, Z. M. (2014). Type I interferon signature in systemic lupus erythematosus. *Israel Medical Association Journal, 16*(4), 246-249.

[10] Blair, H. A., & Duggan, S. T. (2018). Belimumab: A Review in Systemic Lupus Erythematosus. *Drugs, 78*(3), 355-366. doi: 10.1007/s40265-018-0872-z

[11] Borba, H. H., Funke, A., Wiens, A., Utiyama, S. R., Perlin, C. M., & Pontarolo, R. (2016). Update on Biologic Therapies for Systemic Lupus Erythematosus. *Current Rheumatology Reports, 18*(7), 44. doi: 10.1007/s11926-016-0589-5

[12] Buttgereit, F., da Silva, J. A., Boers, M., Burmester, G. R., Cutolo, M., Jacobs, J., . . . Bijlsma, J. W. (2002). Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. *Annals of the Rheumatic Diseases, 61*(8), 718-722. doi: 10.1136/ard.61.8.718

[13] Calixto, O. J., Franco, J. S., & Anaya, J. M. (2014). Lupus mimickers. *Autoimmunity Reviews, 13*, 865-872. doi: 10.1016/j.autrev.2014.05.002

[14] Castrejón, I., Tani, C., Jolly, M., Huang, A., & Mosca, M. (2014). Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care. *Clinical and Experimental Rheumatology, 32*(5 Suppl 85), S-85-95.

[15] Clowse, M. E., Wallace, D. J., Furie, R. A., Petri, M. A., Pike, M. C., Leszczyński, P., . . . EMBODY Investigator Group. (2017). Efficacy and Safety of Epratuzumab in Moderately to Severely Active Systemic Lupus Erythematosus: Results From Two Phase III Randomized, Double-Blind, Placebo-Controlled Trials. *Arthritis & Rheumatology, 69*(2), 362-375. doi: 10.1002/art.39856

[16] D'Cruz, D., Maksimowicz-McKinnon, K., Oates, J., Santiago, M. B., Bass, D., Burriss, S., . . . Ji, B. (2019). Efficacy and safety of belimumab in patients of black race with systemic lupus erythematosus: results from the EMBRACE study. *Lupus Science & Medicine, 6*, A149.2-A150. doi: 10.1136/lupus-2019-lsm.200

[17] Devilliers, H., Bonithon-Kopp, C., & Jolly, M. (2017). The lupus impact tracker is responsive to changes in clinical activity measured by the systemic lupus erythematosus responder index. *Lupus, 26*(4), 396-402. doi: 10.1177/0961203316667494

[18] Doria, A., Gatto, M., Zen, M., Iaccarino, L., & Punzi, L. (2014). Optimizing outcome in SLE: treating-to-target and definition of treatment goals. *Autoimmunity Reviews, 13*(7), 770-777. doi: 10.1016/j.autrev.2014.01.055

[19] Doria, A., Cervera, R., Gatto, M., Chehab, G., & Schneider, M. (2017). The new targeted therapy in systemic lupus erythematosus: Is the glass half-full or half-empty? *Autoimmunity Reviews, 16*(11), 1119-1124. doi: 10.1016/j.autrev.2017.09.006

[20] El-Sherbiny, Y. M., Psarras, A., Yusof, M. Y. M., Hensor, E. M. A., Tooze, R., Doody, G., . . . Vital, E. M. (2018). A novel two-score system for interferon status segregates autoimmune diseases and correlates with clinical features. *Scientific Reports, 8*(1), 5793. doi: 10.1038/s41598-018-24198-1

[21] European Medicines Agency. (n.d.) Summary of Product Characteristics. Accessed July 1, 2019 from http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002015/WC500110150.pdf

[22] European Medicines Agency. (2015, February 26). Guideline on clinical investigation of medicinal products for the treatment of systemic lupus erythematosus and lupus nephritis. EMA/CHMP/51230/2013.

[23] Fanouriakis, A., Adamichou, C., Koutsoviti, S., Panopoulos, S., Staveri, C., Klagou, A., . . . Boumpas, D. T. (2018). Low disease activity-irrespective of serologic status at baseline-associated with reduction of corticosteroid dose and number of flares in patients with systemic lupus erythematosus treated with belimumab: A real-life observational study. *Seminars in Arthritis and Rheumatism, 48*(3), 467-474. doi: 10.1016/j.semarthrit.2018.02.014

[24] Feld, J., & Isenberg, D. (2014). Why and how should we measure disease activity and damage in lupus? *La Presse Médicale, 43*(6 Pt 2), e151-156. doi: 10.1016/j.lpm.2014.03.002

[25] Felten, R., Dervovic, E., Chasset, F., Gottenberg, J. E., Sibilia, J., Scher, F., & Arnaud, L. (2018). The 2018 pipeline of targeted therapies under clinical development for Systemic Lupus Erythematosus: a systematic review of trials. *Autoimmunity Reviews, 17*(8), 781-790. doi: 10.1016/j.autrev.2018.02.011

[26] Franklyn, K., Lau, C. S., Navarra, S. V., Louthrenoo, W., Lateef, A., Hamijoyo, L., . . . Asia-Pacific Lupus Collaboration. (2016). Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). *Annals of the Rheumatic Diseases, 75*(9), 1615-1621. doi: 10.1136/annrheumdis-2015-207726

[27] Furie, R. A., Petri, M. A., Wallace, D. J., Ginzler, E. M., Merrill, J. T., Stohl, W., . . . Freimuth, W. W. (2009). Novel evidence-based systemic lupus erythematosus responder index. *Arthritis & Rheumatology, 61*, 11431151. doi: 10.1002/art.24698

[28] Furie, R., Khamashta, M., Merrill, J. T., Werth, V. P., Kalunian, K.,

Brohawn, P., . . . CD1013 Study Investigators. (2017). Anifrolumab, an antiinterferon-α receptor monoclonal antibody, in moderate-to-severe systemic lupus erythematosus. *Arthritis & Rheumatology, 69*, 376-386. doi: 10.1002/art.39962

[29] Furie, R., Wang, L., Illei, G., & Drappa, J. (2018). Systemic Lupus Erythematosus (SLE) Responder Index response is associated with global benefit for patients with SLE. *Lupus, 27*(6), 955-962. doi: 10.1177/0961203318758506

[30] Gergianaki, I., & Bertsias, G. (2018). Systemic Lupus Erythematosus in Primary Care: An Update and Practical Messages for the General Practitioner. *Frontiers in Medicine, 5*, 161. doi: 10.3389/fmed.2018.00161

[31] Gordon, C. (2002). Longterm complications of systemic lupus erythematosus. *Rheumatology, 41*(10), 1095-1100.

[32] Hochberg, M. C. (1997). Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis & Rheumatology, 40*(9), 1725.

[33] Hruskova, Z., & Tesar, V. (2018). Lessons learned from the failure of several recent trials with biologic treatment in systemic lupus erythematosus. *Expert Opinion on Biological Therapy, 18*(9), 989-996. doi:10.1080/14712598.2018.1504918

[34] Isenberg, D. A., Petri, M., Kalunian, K., Tanaka, Y., Urowitz, M. B., Hoffman, R. W., . . . Wallace, D. J. (2016). Efficacy and safety of subcutaneous tabalumab in patients with systemic lupus erythematosus: results from ILLUMINATE-1, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. *Annals of the Rheumatic Diseases, 75*(2), 323-331. doi: 10.1136/annrheumdis-2015-207653

[35] Isenberg, D., Sturgess, J., Allen, E., Aranow, C., Askanase, A., Sang-Cheol, B., . . . Gordon, C. (2018). Study of Flare Assessment in Systemic Lupus Erythematosus Based on Paper Patients. *Arthritis Care & Research, 70*(1), 98-103. doi: 10.1002/acr.23252

[36] Izadi, Z., Gandrup, J., Katz, P. P., & Yazdany, J. (2018). Correction: Patient-reported outcome measures for use in clinical trials of SLE: a review. *Lupus Science & Medicine, 5*, e000279. doi: 10.1136/lupus-2018-000279corr1

[37] Johnson, S. R., Khanna, D., Daikh, D., Cervera, R., Costedoat-Chalumeau, N., Gladman, D. D., . . . Aringer, M. (2018). Use of Consensus Methodology to Determine Candidate Items for Systemic Lupus Erythematosus Classification Criteria. *Journal of Rheumatology, 46*(6). doi: 10.3899/jrheum.180478

[38] Jolly, M., Kosinski, M., Garris, C. P., & Oglesby, A. K. (2016). Prospective Validation of the Lupus Impact Tracker: A Patient-Completed Tool for Clinical Practice to Evaluate the Impact of Systemic Lupus Erythematosus. *Arthritis & Rheumatology, 68*(6), 1422-1431. doi: 10.1002/art.39601

[39] Kalunian, K. C., Kim, M., Xie, X., Baskaran, A., Daly, R. P., & Merrill, J. T. (2016). Impact of standard of care treatments and disease variables on outcomes in systemic lupus erythematosus trials: analysis from the Lupus Foundation of America Collective Data Analysis Initiative. *European Journal of Rheumatology, 3*(1), 13-19. doi:10.5152/eurjrheum.2015.0048

[40] Kalunian, K. C., Urowitz, M. B., Isenberg, D., Merrill, J. T., Petri, M., Furie, R. A., . . . Linnik, M. D. (2018). Clinical trial parameters that influence outcomes in lupus trials that use the systemic lupus erythematosus responder index. *Rheumatology, 57*(1), 125-133. doi: 10.1093/rheumatology/kex368

[41] Kleinmann, J. F., Tubach, F., Le Guern, V., Mathian, A., Richez, C., Saadoun, D., . . . Gottenberg, J. E. (2017). International and multidisciplinary expert recommendations for the use of biologics in systemic lupus erythematosus. *Autoimmunity Reviews, 16*(6), 650-657. doi: 10.1016/j.autrev.2017.04.011

[42] Kraaij, T., Kamerling, S. W. A., de Rooij, E. N. M., van Daele, P. L. A., Bredewold, O. W., Bakker, J. A., . . . Teng, Y. K. O. (2018). The NET-effect of combining rituximab with belimumab in severe systemic lupus erythematosus. *Journal of Autoimmunity, 91*, 45-54. doi: 10.1016/j.jaut.2018.03.003

[43] Levin, R. E., Weinstein, A., Peterson, M., Testa, M. A., & Rothfield, N. F. (1984). A comparison of the sensitivity of the 1971 and 1982 American Rheumatism Association criteria for the classification of systemic lupus erythematosus. *Arthritis & Rheumatology, 27*, 530-538.

[44] Lisnevskaia, L., Murphy, G., & Isenberg, D. (2014). Systemic lupus erythematosus. *Lancet, 384*(9957), 1878-1888. doi: 10.1016/S0140-6736(14)60128-8

[45] Lopez, R., Davidson, J. E., Beeby, M. D., Egger, P. J., & Isenberg, D. A. (2012). Lupus disease activity and the risk of subsequent organ damage and mortality in a large lupus cohort. *Rheumatology, 51*(3), 491-498. doi: 10.1093/rheumatology/ker368

[46] Luijten, K. M., Tekstra, J., Bijlsma, J. W., & Bijl, M. (2012). The Systemic Lupus Erythematosus Responder Index (SRI); a new SLE disease activity assessment. *Autoimmunity Reviews, 11*(5), 326-329. doi: 10.1016/j.autrev.2011.06.011

[47] Mahieu, M. A., Strand, V., Simon, L. S., Lipsky, P. E., & Ramsey-Goldman, R. (2016). A critical review of clinical trials in systemic lupus erythematosus. *Lupus, 25*(10), 1122-1140. doi: 10.1177/0961203316652492

[48] Marcondes, F., & Scheinberg, M. (2018). Belimumab in the treatment of systemic lupus erythematous: An evidence based review of its place in therapy. *Autoimmunity Reviews, 17*(2), 103-107. doi: 10.1016/j.autrev.2017.11.013

[49] Medina-Quiñones, C. V., Ramos-Merino, L., Ruiz-Sada, P., & Isenberg, D. (2016). Analysis of Complete Remission in Systemic Lupus Erythematosus Patients Over a 32-Year Period. *Arthritis Care & Research, 68*(7), 981-987. doi: 10.1002/acr.22774

[50] Merrill, J. T., van Vollenhoven, R. F., Buyon, J. P., Furie, R. A., Stohl, W., Morgan-Cox, M., . . . Dörner, T. (2016). Efficacy and safety of subcutaneous tabalumab, a monoclonal antibody to B-cell activating factor, in patients with systemic lupus erythematosus: results from ILLUMINATE-2, a 52-week, phase III, multicentre, randomised, double-blind, placebo-controlled study. *Annals of the Rheumatic Diseases, 75*(2), 332-340. doi: 10.1136/annrheumdis-2015-207654

[51] Merrill, J. T., Immermann, F., Whitley, M., Zhou, T., Hill, A., O'Toole, M., . . . Sridharan, S. (2017). The Biomarkers of Lupus Disease Study: A Bold Approach May Mitigate Interference of Background Immunosuppressants in Clinical Trials. *Arthritis & Rheumatology, 69*(6), 1257-1266. doi: 10.1002/art.40086

[52] Merrill, J. T., Manzi, S., Aranow, C., Askenase, A., Bruce, I., Chakravarty, E., . . . Werth, V. P. (2018) Correction: Lupus community panel proposals for optimising clinical trials: 2018. *Lupus Science & Medicine, 5*(1), e000258. doi: 10.1136/lupus-2018-000258corr1

[53] Mikdashi, J., & Nived, O. (2015). Measuring disease activity in adults with systemic lupus erythematosus: the challenges of administrative burden and responsiveness to patient concerns in clinical research. *Arthritis Research & Therapy, 17*, 183. doi: 10.1186/s13075-015-0702-6

[54] Mok, C. C. (2016). Treat-to-target in systemic lupus erythematosus: are we there yet? *Expert Review of Clinical Pharmacology, 9*(5), 675-680. doi: 10.1586/17512433.2016.1146589

[55] Morand, E. F., Trasieva, T., Berglind, A., Illei, G. G., & Tummala, R. (2018). Lupus Low Disease Activity State (LLDAS) attainment discriminates responders in a systemic lupus erythematosus trial: post-hoc analysis of the Phase IIb MUSE trial of anifrolumab. *Annals of the Rheumatic Diseases, 77*(5), 706-713. doi: 10.1136/annrheumdis-2017-212504

[56] Mosca, M., Costenbader, K. H., Johnson, S. R., Lorenzoni, V., Sebastiani, G. D., Hoyer, B. F., . . . Touma, Z. (2018). How Do Patients with Newly Diagnosed Systemic Lupus Erythematosus Present? A Multicenter Cohort of Early Systemic Lupus Erythematosus to Inform the Development of New Classification Criteria. *Arthritis & Rheumatology, 71*(1). doi: 10.1002/art.40674

[57] Muangchan, C., van Vollenhoven, R. F., Bernatsky, S. R., Smith, C. D., Hudson, M., Inanç, M., . . . Pope, J. E. (2015). Treatment Algorithms in Systemic Lupus Erythematosus. *Arthritis Care & Research, 67*(9), 1237-1245. doi: 10.1002/acr.22589

[58] Mummert, E., Fritzler, M. J., Sjöwall, C., Bentow, C., & Mahler, M. (2018). The clinical utility of anti-double-stranded DNA antibodies and the challenges of their determination. *Journal of Immunological Methods, 459*, 11-19. doi: 10.1016/j.jim.2018.05.014

[59] National Library of Medicine. (2012). Efficacy and Safety of Belimumab in Black Race Patients With Systemic Lupus Erythematosus (SLE) (EMBRACE). Retrieved from https://clinicaltrials.gov/ct2/show/NCT01632241?cond=NCT01632241&rank=1

[60] National Library of Medicine. (2014). Synergetic B-cell Immodulation in SLE (SYNBIoSe). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02284984?term=NCT02284984&rank=1

[61] National Library of Medicine. (2015). Efficacy and Safety of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Ery-

thematosus. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02446899?term=NCT02446899&rank=1

[62] National Library of Medicine. (2015). Efficacy and Safety of Two Doses of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02446912?term=NCT02446912&rank=1

[63] National Library of Medicine. (2015). Safety and Efficacy of Two Doses of Anifrolumab Compared to Placebo in Adult Subjects With Active Proliferative Lupus Nephritis (TULIP-LN1). Retrieved from https://clinicaltrials.gov/ct2/show/NCT02547922?term=NCT02547922&rank=1

[64] National Library of Medicine. (2016). A Study to Characterize the Pharmacokinetics, Pharmacodynamics, and Safety of Anifrolumab in Adult Type I Interferon Test High Systemic Lupus Erythematosus Subject With Active Skin Manifestations. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02962960?term=NCT02962960&rank=1

[65] National Library of Medicine. (2016). Dose Finding, Efficacy and Safety of BI 655064 in Patients With Active Lupus Nephritis. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02770170?term=NCT02770170&rank=1

[66] National Library of Medicine. (2018). A Phase 2a, Efficacy and Safety Study of Ustekinumab in Systemic Lupus Erythematosus. Retrieved from https://clinicaltrials.gov/ct2/show/NCT02349061?term=NCT02349061&rank=1

[67] National Library of Medicine. (2018). A Study of Ustekinumab in Participants With Active Systemic Lupus Erythematosus. Retrieved from https://clinicaltrials.gov/ct2/show/NCT03517722?term=NCT03517722&rank=1

[68] Navarra, S. V., Guzmán, R. M., Gallacher, A. E., Hall, S., Levy, R. A., Jimenez, R. E., . . . BLISS-52 Study Group. (2011). Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet, 377*(9767), 721-731. doi: 10.1016/S0140-6736(10)61354-2

[69] Oon, S., Huq, M., Godfrey, T., & Nikpour, M. (2018). Systematic review, and meta-analysis of steroid-sparing effect, of biologic agents in randomized, placebo-controlled phase 3 trials for systemic lupus erythematosus. *Seminars in Arthritis & Rheumatology, 48*(2), 221-239. doi: 10.1016/j.semarthrit.2018.01.001

[70] Ospina, F. E., Echeverri, A., Zambrano, D., Suso, J. P., Martínez-Blanco, J., Cañas, C. A., & Tobón, G. J. (2017). Distinguishing infections vs flares in patients with systemic lupus erythematosus. *Rheumatology, 56*(suppl. 1), i46-i54. doi: 10.1093/rheumatology/kew340

[71] Passas, C. M., Wong, R. L., Peterson, M., Testa, M. A., & Rothfield, N. F. (1985). A comparison of the specificity of the 1971 and 1982 American Rheumatism Association criteria for the classification of systemic lupus erythematosus. *Arthritis & Rheumatology, 28*, 620-623.

[72] Petri, M., Orbai, A. M., Alarcón, G. S., Gordon, C., Merrill, J. T., Fortin, P. R., . . . Magder, L. S. (2012). Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis & Rheumatology, 64*(8), 2677-2686. doi: 10.1002/art.34473

[73] Pisetsky, D. S., Spencer, D. M., Lipsky, P. E., & Rovin, B. H. (2018). Assay variation in the detection of antinuclear antibodies in the sera of patients with established SLE. *Annals of the Rheumatic Diseases, 77*(6), 911-913. doi: 10.1136/annrheumdis-2017-212599

[74] Ramsey-Goldman, R., Li, J., Dervieux, T., & Alexander, R. V. (2017). Cell-bound complement activation products in SLE. *Lupus Science & Medicine, 4*(1),e000236. doi: 10.1136/lupus-2017-000236

[75] Rees, F., Doherty, M., Grainge, M. J., Lanyon, P., & Zhang, W. (2017). The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. *Rheumatology, 56*(11), 1945-1961. doi: 10.1093/rheumatology/kex260

[76] Rice, J. B., White, A. G., Scarpati, L. M., Wan, G., & Nelson, W. W. (2017). Long-term Systemic Corticosteroid Exposure: A Systematic Literature Review. *Clinical Therapeutics, 39*(11), 2216-2229. doi: 10.1016/j.clinthera.2017.09.011

[77] Romero-Diaz, J., Isenberg, D., & Ramsey-Goldman R. (2011). Measures of adult systemic lupus erythematosus: updated version of British Isles Lupus Assessment Group (BILAG 2004), European Consensus Lupus Activity Measurements (ECLAM), Systemic Lupus Activity Measure, Revised (SLAM-R), Systemic Lupus Activity Questionnaire for Population Studies (SLAQ), Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). *Arthritis Care & Research, 63*(S11), S37-46. doi: 10.1002/acr.20572

[78] Romo-Tena, J., la Garza, R. R., Bartnicki-Navarrete, I., Alcocer-Varela, J., & Gómez-Martin, D. (2018). Factors associated with remission in patients with systemic lupus erythematosus: new insights into a desirable state. *Clinical Rheumatology, 37*(11), 3033-3042. doi: 10.1007/s10067-018-4226-8

[79] Rose, T., Grützkau, A., Klotsche, J., Enghard, P., Flechsig, A., Keller, J., . . . Biesen, R. (2017). Are interferon-related biomarkers advantageous for monitoring disease activity in systemic lupus erythematosus? A longitudinal benchmark study. *Rheumatology, 56*(9), 1618-1626. doi: 10.1093/rheumatology/kex220

[80] Rovin, B. H., Dooley, M. A., Radhakrishnan, J., Ginzler, E. M., Forrester, T. D., & Anderson, P. W. (2016). The impact of tabalumab on the kidney in systemic lupus erythematosus: results from two phase 3 randomized, clinical trials. *Lupus, 25*(14), 1597-1601. doi: 10.1177/0961203316650734

[81] Sarnes, E., Crofford, L., Watson, M., Dennis, G., Kan, H., & Bass, D. (2011). Incidence and US costs of corticosteroid-associated adverse events: a systematic literature review. *Clinical Therapeutics, 33*(10), 1413-1432. doi: 10.1016/j.clinthera.2011.09.009

[82] Schmeding, A., & Schneider, M. (2013). Fatigue, health-related quality of life and other patient-reported outcomes in systemic lupus erythematosus. *Best Practice & Research Clinical Rheumatology, 27*(3), 363-375. doi: 10.1016/j.berh.2013.07.009

[83] Schneider, M., Mosca, M., Pego-Reigosa, J. M., Gunnarsson, I., Maurel, F., Garofano, A., . . . Devilliers, H. (2017). Cross-cultural validation of Lupus Impact Tracker in five European clinical practice settings. *Rheumatology, 56*(5), 818-828. doi: 10.1093/rheumatology/kew492

[84] Steiman, A. J., Urowitz, M. B., Ibañez, D., Papneja, A., & Gladman, D. D. (2014). Prolonged clinical remission in patients with systemic lupus erythematosus. *Journal of Rheumatology, 41*(9), 1808-1816. doi: 10.3899/jrheum.131137

[85] Swaak, T., & Smeenk, R. (1987). Clinical significance of antibodies to double stranded DNA (dsDNA) for systemic lupus erythematosus (SLE). *Clinical Rheumatology, 6*(Suppl 1), 56-73.

[86] Swaak, A. J.,van den Brink, H. G., Smeenk, R. J., Manger, K., Kalden, J. R., Tosi, S., . . . Smolen, J. S. (2001). Systemic lupus erythematosus. Disease outcome in patients with a disease duration of at least 10 years: second evaluation. *Lupus, 10*(1), 51-58. doi: 10.1191/096120301666282314

[87] Tan, E. M., Cohen, A. S., Fries, J. F., Masi, A. T., McShane, D. J., Rothfield, N. F., . . . Winchester, R. J. (1982). The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis & Rheumatology, 25*(11), 1271-1277.

[88] Tedeschi, S. K., Johnson, S. R., Boumpas, D. T., Daikh, D., Dörner, T., Diamond, B., . . . Costenbader, K. H. (2019). Multicriteria decision analysis process to develop new classification criteria for systemic lupus erythematosus. *Annals of the Rheumatic Diseases, 78*(5), 634-640. doi: 10.1136/annrheumdis-2018-214685

[89] Thanou, A., & Merrill, J. T. (2013). Top 10 things to know about lupus activity measures. *Current Rheumatology Reports, 15*, 334. doi: 10.1007/s11926-013-0334-2

[90] Thanou, A., Chakravarty, E., James, J. A., & Merrill, J. T. (2014). How should lupus flares be measured? Deconstruction of the Safety of Estrogen in Lupus Erythematosus National Assessment Systemic Lupus Erythematosus Disease Activity Index flare index. *Rheumatology, 53*(12), 2175-2181. doi: 10.1093/rheumatology/keu153

[91] Thanou, A., Chakravarty, E., James, J. A., & Merrill, J. T. (2014). Which outcome measures in SLE clinical trials best reflect medical judgment? *Lupus Science & Medicine, 1*(1), e000005. doi: 10.1136/lupus-2013-000005

[92] Thanou, A., & Merrill, J. T. (2018). New Trials in Lupus and where Are we Going? *Current Rheumatology Reports, 20*(6), 34. doi: 10.1007/s11926-018-0745-1

[93] Thong, B. & Olsen, N. J. (2017). Systemic lupus erythematosus diagnosis and management. *Rheumatology, 56*(Suppl 1), i3-i13. doi: 10.1093/rheumatology/kew401

[94] Tsang-A-Sjoe, M. W., Bultink, I. E., Heslinga, M., & Voskuyl, A. E. (2017). Both prolonged remission and Lupus Low Disease Activity State are associated with reduced damage accrual in systemic lupus erythematosus. *Rheumatology, 56*(1), 121-128. doi: 10.1093/rheumatology/kew377

[95] Tselios, K., Gladman, D. D., Touma, Z., Su, J., Anderson, N., & Urowitz, M. B. (2018). Clinical remission and low disease activity have comparable outcomes over 10 years in systemic lupus erythematosus. *Arthritis Care & Research, 71*(6). doi: 10.1002/acr.23720

[96] U.S. Food and Drug Administration. (2010). Guidance Document: Systemic Lupus Erythematosus - Developing Drugs for Treatment. Retrieved from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072063.pdf

[97] U.S. Food and Drug Administration. (2011). Summary Review of Regulatory Action for Benlysta (belimumab). Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125370Orig1s000SumR.pdf

[98] U.S. Food and Drug Administration. (2012). Guidance for Industry on Lupus Nephritis Caused by Systemic Lupus Erythematosus - Developing Medical Products for Treatment; Withdrawal of Guidance. Retrieved from https://www.pharmamedtechbi.com/~/media/Images/Publications/Archive/The%20Pink%20Sheet/72/026/00720260005/0621_ln_guidance.pdf (Retraction issued June 22, 2010, withdrawn June 27, 2012. Retrieved from https://www.regulations.gov/document?D=FDA-2010-D-0249-0003)

[99] U.S. Food and Drug Administration (2017). Highlights of Prescribing Information for Benlysta. Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761043lbl.pdf

[100] U.S. Food and Drug Administration. (2017). Supplement Approval Letter for Benlysta (belimumab). Retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125370Orig1s000SumR.pdf

[101] U.S. Food and Drug Administration. (2018). Adaptive Designs for Clinical Trials of Drugs and Biologics: Guidance for Industry. Retrieved from https://www.fda.gov/media/78495/download

[102] U.S Food and Drug Administration. (2018). Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics – Guidance for Industry. Retrieved from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/master-protocols-efficient-clinical-trial-design-strategies-expedite-development-oncology-drugs-and

[103] Ugarte, A., Danza, A., & Ruiz-Irastorza, G. (2018). Glucocorticoids and antimalarials in systemic lupus erythematosus: an update and future directions. *Current Opinion in Rheumatology, 30*(5), 482-489. doi: 10.1097/BOR.0000000000000527

[104] Urowitz, M. B., Gladman, D. D., Abu-Shakra, M., & Farewell, V. (1997). Mortality studies in systemic lupus erythematosus. Results from a single center. III. Improved survival over 24 years. *Journal of Rheumatology, 24*, 1061-1065.

[105] van Vollenhoven, R. F., Mosca, M., Bertsias, G., Isenberg, D., Kuhn, A., Lerstrøm, K., . . . Schneider, M. (2014). Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Annals of the Rheumatic Diseases, 73*, 958-967. doi: 10.1136/annrheumdis-2013-205139

[106] van Vollenhoven, R., Voskuyl, A., Bertsias, G., Aranow, C., Aringer, M., Arnaud, L., . . . Ward, M. (2017). A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). *Annals of the Rheumatic Diseases, 76*(3), 554-561. doi: 10.1136/annrheumdis-2016-209519

[107] van Vollenhoven, R. F., Hahn, B. H., Tsokos, G. C., Wagner, C. L., Lipsky, P., Touma, Z., . . . Rose, S. (2018). Efficacy and safety of ustekinumab, an IL-12 and IL-23 inhibitor, in patients with active systemic lupus erythematosus: results of a multicentre, double-blind, phase 2, randomised, controlled study. *Lancet, 392*(10155), 1330-1339. doi: 10.1016/S0140-6736(18)32167-6

[108] Wallace, D. J. (2014). *Lupus: The essential clinician's guide*. New York, NY: Oxford University Press, Inc.

[109] Wallace, D. J., Furie, R. A., Tanaka, Y., Kalunian, K. C., Mosca, M., Petri, M. A., . . . Hoffman, R. W. (2018). Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet, 392*(10143), 222-231. doi: 10.1016/S0140-6736(18)31363-1

[110] Wolfe, F., Petri, M., Alarcón, G. S., Goldman, J., Chakravarty, E. F., Katz, R. S., & Karlson, E. W. (2009). Fibromyalgia, systemic lupus erythematosus (SLE), and evaluation of SLE activity. *Journal of Rheumatology, 36*(1), 82-88. doi: 10.3899/jrheum.080212

[111] Yen, E. Y., & Singh, R. R. (2018). Brief Report: Lupus – An unrecognized leading cause of death in young females: A population-based study using nationwide death certificates, 20002015. *Arthritis & Rheumatology, 70*(8), 1251-1255. doi: 10.1002/art.40512

[112] Yu, C., Gershwin, M. E., & Chang, C. (2014). Diagnostic criteria for systemic lupus erythematosus: a critical review. *Journal of Autoimmunity, 48-49*, 10-13. doi: 10.1016/j.jaut.2014.01.004

[113] Yuen, H. K., & Cunningham, M. A. (2014). Optimal management of fatigue in patients with systemic lupus erythematosus: a systematic review. *Therapeutics and Clinical Risk Management, 10*, 775-786. doi: 10.2147/TCRM.S56063

[114] Zen, M., Gatto, M., Nalotto, L., Larosa, M., Iaccarino, L., & Doria, A. (2017). The Management of Systemic Lupus Erythematosus (SLE) Patients in Remission. *Israel Medical Association Journal, 19*(7), 454-458.

[115] Zen, M., Iaccarino, L., Gatto, M., Saccon, F., Larosa, M., Ghirardello, A., . . . Doria, A. (2018). Lupus low disease activity state is associated with a decrease in damage progression in Caucasian patients with SLE, but overlaps with remission. *Annals of the Rheumatic Diseases, 77*(1), 104-110. doi: 10.1136/annrheumdis-2017-211613