
Guidance for Industry

Systemic Lupus Erythematosus

— Developing Medical

Products for Treatment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

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Guidance for Industry¹

Systemic Lupus Erythematosus — Developing Medical Products for Treatment

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of medical products (i.e., human drugs, therapeutic biological products, and medical devices) for the treatment of systemic lupus erythematosus (SLE). Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding the overall development program and clinical trial designs, and provides specific information on trial design, trial duration, efficacy endpoints, and response criteria. This guidance is intended to serve as a focus for continued discussions among the FDA, medical industry, sponsors, academic community, and the public.² As the science of this indication evolves, this guidance may be revised.

This guidance applies to general information regarding medical product development for the treatment of SLE. Organ-specific forms of disease will be addressed in separate guidances.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical*

¹ This guidance has been prepared by the Systemic Lupus Erythematosus Working Group, which includes representatives from the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Office of Critical Path Programs (OCPP) in the Office of the Commissioner (OC) at the Food and Drug Administration.

² In addition to consulting guidances, sponsors are encouraged to contact the relevant division to discuss specific issues that arise during the development of SLE medical products.

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Trials.³ This guidance focuses on specific medical product development and trial design issues that are unique to the study of SLE.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

SLE is a chronic disease characterized by protean manifestations, often with a waxing and waning course. In the past, a diagnosis of SLE often implied a decreased life span caused by internal organ system involvement or the toxic effects of therapy, but recent improvements in care have dramatically enhanced the survival of SLE patients. Nonetheless, increased mortality remains a major concern and current treatments for SLE remain inadequate.⁴ Many patients have incompletely controlled disease, progression to end-stage organ involvement continues, and the therapies carry risks of debilitating side effects. Therefore, it is important to facilitate the development of medical products that have the potential to be more effective and/or less toxic.

III. DEVELOPMENT PROGRAM

A. General Considerations

1. Early Phase Clinical Development Considerations

Studies to identify an appropriate (safe and effective) dose are an important component of phase 2 development for human drugs and therapeutic biological products used to treat SLE. For additional information on the FDA's current thinking regarding exposure response or dose response, see the ICH guidance for industry *E4 Dose-Response Information to Support Drug Registration* and the guidances for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* and *Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications*.

We recommend that early studies evaluate concurrent use of a new medical product with commonly used standard therapies to obtain preliminary safety information on potential interactions with medical products used in standard-of-care regimens, although at this stage studies will not be powered to fully assess safety endpoints. As discussed in section III.B.8., Primary Efficacy Endpoints, early exploratory clinical studies can be used to gain experience

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Guidances Web page at <http://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

⁴ Ippolito, A and M Petri, 2008, An Update on Mortality in Systemic Lupus Erythematosus, *Clin Exp Rheumatol*, 26(5 Suppl 51):S72-9.

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with a variety of standard clinical outcome measures, which may aid sponsors in determining which endpoints to pursue further in phase 3 trials.

Biomarker assays thought to reflect disease activity also can be helpful in identifying medical products likely to show a clinical benefit and in choosing doses and regimens. See section III.B.10., Other Endpoints, for additional information on the use of biomarkers in SLE clinical studies.

2. Efficacy Considerations

The evidence of effectiveness needed to support approval of medical products for SLE is similar to that for medical products for other indications. For human drugs and therapeutic biological products, at least two adequate and well-controlled trials generally are needed for approval. However, a single study can suffice under some circumstances (see the guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*). A single study can be sufficient, for example, if the medical product is being developed for the treatment of serious acute manifestations and the study shows: (1) robust evidence of efficacy with resolution of the serious acute manifestations; or (2) a decrease in mortality. For medical devices, one confirmatory clinical trial generally is sufficient.

B. Specific Efficacy Trial Considerations

1. Indication

The general indication of *treatment of systemic lupus erythematosus* will be granted for medical products if supported by sufficient evidence of effectiveness. In general, specific efficacy claims (e.g., reduction in disease activity), as discussed in section III.B.8., Primary Efficacy Endpoints, will not be included in the INDICATIONS AND USAGE section of labeling, but can be discussed in the CLINICAL STUDIES section if well-supported. 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. For medical products that demonstrate a reduction in mortality in adequate and well-controlled trials, appropriate additional labeling reflecting that outcome would be included in the INDICATIONS AND USAGE section.

2. Study Design

a. Superiority trials

The preferred design for efficacy trials is a parallel, randomized, controlled superiority trial using placebo or active control. The placebo-controlled trial can compare the test medical product with no treatment, but more commonly adds the test medical product or placebo to standard therapy (add-on trial).

No patient enrolling in an SLE clinical trial should be denied standard therapy if doing so would lead to irreversible harm. To avoid denying patients standard of care, superiority trials of new therapies can use an add-on design, if the medical product is intended as adjunctive treatment, or

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head-to-head comparisons with an alternative standard of care, if the medical product is intended for primary treatment. In a head-to-head comparison, it may be appropriate to include early escape provisions to an alternative standard-of-care regimen for patients who worsen during the study to ensure that no patient is denied potentially effective therapy.

One of the advantages to an add-on trial of this type is that it enables the evaluation of drug effects in the context of commonly used medical products in SLE. An example of an add-on design would be a trial of corticosteroids plus placebo compared to corticosteroids plus the new medical product. The protocol should specify the dose of corticosteroids patients will receive, taking into account the type and severity of the clinical manifestation. The protocol also should include provisions for tapering of corticosteroids during the trial if the manifestations improve.

b. Noninferiority trials

If superiority to a comparator is unlikely (e.g., because the new medical product is pharmacologically similar to a standard-of-care medical product) and an add-on study would be unlikely to succeed (again because the new and standard-of-care medical products are pharmacologically similar), sponsors might want to consider a noninferiority design to evaluate efficacy. However, this design would be difficult to support in this case (see ICH E10). To use a noninferiority design, the effect size of the comparator that will be present in the new study must be identified to define the noninferiority margin.⁵ Currently, there are no known medical products with an effect size adequately characterized to design an adequate noninferiority trial for a new medical product in any SLE setting. A particular problem would also be the inherent variability in outcome and response in different populations. Sponsors considering a noninferiority design should discuss the design with the appropriate review division before trial initiation.

c. Extension trials

If prior evidence suggests clinical activity of the medical product and an acceptable safety profile, sponsors are encouraged to offer patients enrollment into a long-term extension trial to characterize long-term safety. Long-term controlled trial data are preferred over open-label extension safety data because of the difficulty in interpreting adverse event rates in the absence of a concurrent control. Demonstration of long-term benefit would be a critical determination in some settings (e.g., bone marrow transplant).

d. Alternative trial designs

Alternative trial designs, all of which should be designed as superiority trials, include randomized withdrawal, dose-response, and replacement trials. In a replacement trial, patients on a stable standard-of-care regimen should be randomized in a blinded manner to continue that regimen or switch to study treatment. A successful trial would demonstrate better outcomes in the group switched to study treatment. Sponsors should discuss these alternative designs with the review division before initiating these studies.

⁵ See 21 CFR 314.126.

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3. Study Duration

Clinical trials should be of sufficient length to assess the durability of therapy benefits, taking into account the chronic nature of SLE and its waxing and waning course. In general, a trial evaluating the following endpoints should be at least 1 year in duration: reduction in disease activity, complete clinical response or remission, reduction in flare/increase in time to flare, and maintenance of response. The duration should be based on the onset of action of the medical product and incorporate maintenance therapy for a total of at least 1 year to assess for durability of response as well as safety, depending upon the risks of the medical product.

If the investigational medical product is intended for short-term use, such as induction of response, the total duration of follow-up should still be 1 year, but the investigational medical product does not need to be continued beyond the initial treatment period. In this case, patients can be switched to another maintenance therapy for the remainder of the follow-up period.

Studies investigating treatment of serious acute manifestations of SLE (e.g., acute confusional state, acute transverse myelitis, or acute lupus pneumonitis) are considered a special case of induction therapy. Such studies can also be of relatively short duration depending on the nature of the manifestation, the organ system involved, and the expected time for resolution of the serious acute manifestations under investigation. As for any other trial of induction therapy, a subsequent assessment of the durability of response and safety should be based on data of at least 1-year duration.

4. Study Population

Trials should enroll patients with established SLE, as defined by the American College of Rheumatology classification criteria.

The patient population should reflect the patients who would reasonably be considered for the therapy should it be shown to be effective. It is important that the studied population be one that can be generalized to an appropriate population for recommended use, and not made artificially narrow. However, if existing data (e.g., from exploratory studies) suggest that only a specific, limited population can be expected to benefit from the therapy, the inclusion and exclusion criteria can limit enrollment to that subset of patients with a particular range of disease activity or with a particular serious acute manifestation of SLE. However, as discussed in section III.B.1., Indication, the medical product, if approved, would be labeled to indicate this restricted population.

5. Concomitant Medications

It is important to recognize that changes in concomitant medications, whether steroids, immunosuppressive agents, or other therapies (e.g., angiotensin converting enzyme inhibitors, antihypertensive agents, and agents to control diabetes), can influence outcomes and confound the effect of treatment. Treating physicians should respond to patient needs appropriately, but an attempt should be made in the protocol to define the baseline therapy that is acceptable and

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provide guidance on how therapy should be adjusted. Sponsors should collect complete information on use of concomitant medications during trials.

It is important that investigators consider restricting baseline glucocorticoid use (e.g., stable dose or limit the range of doses) to reduce the variability of dosing that may make interpretation of results more difficult. The protocol should specify if glucocorticoid dose changes are allowed during the trial or if patients should be discontinued if they require an increased glucocorticoid dosage.

Potential eligible patients should not be deliberately tapered off their concomitant medications to induce a flare in disease activity for purposes of meeting enrollment criteria in a trial.

We also recommend defining the use of rescue medications and specifying how patients needing such treatment will be treated and analyzed.

6. Stratification

If the effects of treatment are expected to differ substantially in patients with severely active disease as compared to moderately or mildly active disease, it may be desirable to stratify at randomization.

The Systemic Lupus Erythematosus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index was developed, and found to be well-defined and reliable, for measuring organ damage. It may be particularly useful as a means of stratifying patients at trial entry because increased damage has been shown to correlate with a worse prognostic outcome.⁶

If it is expected that particular demographic groups may respond differently to therapy, sponsors also can consider stratification based on a demographic variable.

7. Pediatric Populations

To help standardize the conduct and reporting of pediatric SLE clinical trials and enhance identification of new medical products, the Pediatric Rheumatology International Trials Organization, in collaboration with the Pediatric Rheumatology Collaborative Study Group and with the support of the European Union and the National Institutes of Health, has developed a core set of five domains for the evaluation of response to therapy. These domains include the following:

1. A disease activity index (DAI) (e.g., European Consensus Lupus Activity Measure (ECLAM), Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), Systemic Lupus Erythematosus Activity Measure (SLAM), British Isles Lupus Assessment Group (BILAG), or other DAI deemed appropriate for clinical trials)

⁶ Stoll, T, B Seifert, and DA Isenberg, 1996, SLICC/ACR Damage Index Is Valid, and Renal and Pulmonary Organ Scores Are Predictors of Severe Outcome in Patients with SLE, *Br. J. Rheumatol*, 35:248-54.

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2. Renal function (24-hour proteinuria)
3. Parent's global
4. Physician's global
5. Health status (Child Health Questionnaire physical summary score)

Evaluation of response in these five domains can be considered for exploratory use in pediatric SLE trials. Future research will help to establish the degree of change in these domains that represents a clinically important benefit to establish efficacy in clinical trials. Sponsors should discuss the design of pediatric SLE trials with the review division before beginning such trials.

8. *Primary Efficacy Endpoints*

Sponsors should consider designing clinical trials for medical products to address one or more of the following primary endpoints, as discussed in detail below.

a. Reduction in disease activity

The primary endpoint for a trial evaluating reduction in signs and symptoms of SLE disease activity can be determined using a DAI that has documented evidence of validity, reliability, and ability to detect change in the targeted clinical trial setting. Disease activity scores allow inclusion of patients whose disease affects different organ systems by providing an overall severity score.

Disease activity should be measured at the beginning and end of the trial as well as over the course of the trial. To meet the primary endpoint of the trial, the change in DAI between the outset and the end of the trial should show a statistically significant difference between the treatment groups. It is also important to determine that an improvement in DAI score is not accompanied by a worsening of other disease manifestations. (See also section III.B.14., Risk-Benefit Considerations.)

Several indices exist that mirror the assessment of experienced clinicians and are sensitive to changes in disease activity. The BILAG is the preferred index to study reduction in disease activity in clinical trials. The BILAG scores patients based on the need for therapy; therefore, the clinical interpretation of a change in score is apparent.

Other DAIs include the SLEDAI and Safety of Estrogen in Lupus Erythematosus National Assessment Trial (SELENA)-SLEDAI, the SLAM, and the ECLAM. Updated versions of the BILAG, SLAM, and SLEDAI have been released (BILAG2004, SELENA-SLEDAI/SLEDAI 2K, and SLAM-R). These indices have been shown to be valid in some treatment settings based on the concordance of scores with expert opinion, acceptable interobserver variability among trained evaluators, correlation between individual patient scores on different indices, and correlation between increases in scores and clinical decisions to increase therapy. They also have been shown in cohort studies to be sensitive to changes in disease activity, and can be used

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in clinical trials if the instrument measurement properties are adequate for the specific clinical trial setting.⁷

It is important to ensure that the selected DAIs accurately assess disease activity over time. Some DAIs allot points for a new disease manifestation and no points for a stable manifestation. Thus, a disease manifestation that is present at screening and that is stable during the trial can contribute points to the baseline score but no points to subsequent scores leading to an artifactual reduction in the overall disease activity score. The DAIs should also address disease manifestations not caused by SLE and how they will be scored (e.g., hematuria and/or pyuria caused by a urinary tract infection versus lupus nephritis).

If using the BILAG in a 1-year SLE trial, sponsors should conduct an assessment of disease activity at both 6 months and 12 months, as well as at other time points (e.g., monthly) to assess the time course of response. 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.

In patients with active disease at baseline (defined as one or more BILAG A or two or more BILAG B scores), the primary efficacy analysis using a clinically meaningful benefit can be based on the outcome of major clinical response (MCR) or partial clinical response (PCR), showing a greater frequency in drug-treated patients than in control-treated patients.

An example of the definition of MCR or PCR is presented here. In the example of PCR, flare is defined as the presence of one or more new BILAG A scores or two or more new BILAG B scores. BILAG C scores do not affect the definition of flare, since, by definition, they are not judged to be serious enough to require treatment.

An adjudication committee should be employed to determine which patients meet the predefined outcome. The following factors can be used to define MCR and PCR:

Major Clinical Response

A patient with BILAG C scores or better at 6 months with no new BILAG A or BILAG B scores **AND** maintenance of response with no new BILAG A or B scores between 6 and 12 months.

Partial Clinical Response

A patient with BILAG C scores or better at 6 months with no new BILAG A or BILAG B scores and maintenance of response without a flare for 4 months.

⁷ Strand, V, D Gladman, D Isenberg, M Petri, J Smolen, and P Tugwell, 1999, Outcome Measures to Be Used in Clinical Trials in Systemic Lupus Erythematosus, *J Rheumatol*, 26(2):490-7.

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OR

A patient with a maximum of 1 BILAG B score or better at 6 months **AND** maintenance of response without a flare out to 1 year.

OR

A patient with very high disease activity (as defined below) who achieves a maximum of 2 BILAG B scores at 6 months **AND** maintenance of this response without developing a flare out to 1 year. *Very high disease activity* is defined as the presence of one of the following conditions:

- ≥ 2 BILAG A scores (regardless of the number of BILAG B scores)
- OR**
- 1 BILAG A score and ≥ 2 BILAG B scores
- OR**
- ≥ 4 BILAG B scores (with no BILAG A scores)

A trial of a new medical product's ability to induce response in patients with active disease can also be conducted using a DAI, such as BILAG. In this case, the primary endpoint would be an increase in the proportion of patients with a category C score or better at the end of induction (e.g., 3 or 6 months). Response should be confirmed by repeat measurement at least 1 month later. It is also important that a new medical product not only demonstrate early activity, but also not worsen long-term outcome. Therefore, the maintenance of response also should be assessed as a secondary endpoint at 1 year.

Some treatments may target a biologic mechanism that leads to only certain disease manifestations, or to only disease manifestations related to a single organ system. In these situations, it would usually be preferable to use an organ-specific measure of disease activity as the primary endpoint as opposed to an overall disease activity measure.

The interpretation of a clinical trial using the organ-specific approach can be problematic, however, if improvement in the organ system selected is counterbalanced by worsening manifestations of disease occurring in other organ systems. In addition, results from organ-specific trials may be confounded if changes in treatment regimens are made, such as an increase in immunosuppressive agents (see section III.B.5., Concomitant Medications). Therefore, organ-specific trials should also assess overall disease activity as a secondary endpoint, because the safety information should be taken into consideration in determining the overall risk-benefit assessment of the medical product.

b. Complete clinical response or remission

The primary endpoint for a trial evaluating complete clinical response or remission is defined by the complete absence of disease activity, using a DAI (as described above). The term *response* is used if the patients continue to receive SLE-directed therapies, whereas *remission* is used if patients do not continue to receive ongoing therapy for SLE.

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The evaluation of efficacy should be based on the proportion of patients who achieve a BILAG level D score, or zero if using the SLEDAI, in all organ systems for at least 6 consecutive months.

c. Reduction in flare/increase in time to flare

The primary endpoint for a trial evaluating flares can be a reduction in flares or an increase in the time to flare for the new medical product compared to the control group. If time to flare is evaluated as the primary endpoint, the trial should be at least 1 year in duration to evaluate whether the flares are suppressed or only delayed in occurrence. A critical secondary endpoint should be comparison of flare rates or proportion of patients flare-free at an appropriate time point.

A trial assessing flares should randomize patients with quiescent disease (e.g., BILAG C score or better in all organ systems) and assess flares in the group receiving the new medical product compared to the control group.

The definition of flare should be specified in the protocol and should reflect an episode of increased disease activity that correlates with the need for an increase in or change in treatment on clinical grounds. All possible flares should be adjudicated by a data monitoring board that is blinded to treatment.

An index used to measure flare should measure disease activity over a month's period, rather than at fixed time points, in order not to miss any intercurrent flares and to allow full characterization of activity of the medical product over the course of the trial. Acceptable flare indices for clinical trials include the BILAG and SELENA-SLEDAI flare indexes. For example, the BILAG identifies flares as A for severe flare and B for mild to moderate flare. A worsening from an E, D, or C to two or more B scores or one or more A score in any body or organ system during the 1-year trial period can be used to define the occurrence of flare. Time to flare should be the number of days since randomization to occurrence of flare based on BILAG A or B scores.

A trial evaluating maintenance of response can also be considered for a new medical product once active disease (i.e., flares) is in remission (defined as BILAG C or better). Such trials can be a continuation of an induction trial of the new medical product. Patients with active disease who achieve quiescence following induction with a new medical product can be further randomized to switch to placebo or continue the new medical product for the duration of the trial. Alternatively, the induction regimen can consist of a standard-of-care regimen whereby patients are randomized to continue standard of care or are switched to the new medical product for maintenance. The primary endpoint for a trial evaluating maintenance of response can be met by demonstrating an increase (compared to standard of care) in the proportion of patients maintaining a BILAG C score or better at 1 year. If the endpoint is assessed at 6 months, then clinical benefit should also be assessed at 1 year as a secondary endpoint.

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d. Reduction in concomitant steroids

Reducing corticosteroid use is an important goal in treatment of patients with SLE if it occurs in the context of a treatment that effectively controls disease activity. 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.

In an add-on trial to test the steroid-sparing potential of a new medical product, patients should be enrolled during a flare and randomized to the addition of the new medical product or placebo to induction doses of corticosteroids. In both study arms, when patients achieve quiescent disease, the corticosteroid dose should be tapered to a maintenance dose that is not usually associated with major toxicities while still maintaining quiescence. The induction steroid dosage and duration of induction therapy and taper schedule should be based on the severity of disease activity in the dominant organ system involved.⁸

The evaluation of efficacy should be based on the proportion of patients in treatment and control groups that achieve a reduction in steroid dose to less than or equal to 10 mg per day of prednisone or equivalent, with quiescent disease and no flares (see definition above) for at least 3 consecutive months during a 1-year clinical trial. For a result to be clinically meaningful, the patient population should be on moderate to high doses of steroids at baseline. Trials should also assess the occurrence of clinically significant steroid toxicities.

e. Treatment of serious acute manifestations

Treatment of serious acute manifestations of SLE can be considered a special case of induction therapy for treatment of SLE emergencies (e.g., acute confusional state, acute transverse myelitis, or acute lupus pneumonitis). The primary endpoints for a trial evaluating treatment of serious acute manifestations should reflect the proportion of patients with improvement after administration of a new medical product or placebo. The improvement should be measured as a lower score in the organ system score on a DAI of the involved organ(s), such that there is no longer a threat to that organ.

As stated in section III.B.3., Study Duration, studies investigating treatment of serious acute manifestations of SLE are considered a special case of induction therapy. Therefore, therapy with the investigational medical product can be of relatively short duration depending on the nature of the manifestation. It is understood that in many cases maintenance therapy will involve a different regimen than the study drug used for induction. Assessment of the durability of response and safety should be obtained after the patient is switched to maintenance therapy for a total of at least 1-year duration.

Trials investigating treatments for serious acute manifestations of SLE can include the following secondary endpoints: time to resolution of the acute manifestation, mortality, need for re-treatment, use of corticosteroids, and overall disease activity as measured by a DAI, such as the SLEDAI or BILAG.

⁸ 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 & Rheum*, 50:3427.

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Study designs investigating therapies for serious acute manifestations of SLE should be discussed with the review division before beginning trials.

9. Patient-Reported Outcomes

We recognize that improvements in clinical outcome measures (e.g., lab tests, clinical evaluation) in patients with SLE may not always translate to improvements in how patients feel or function. Therefore, we encourage the use of patient-reported outcome (PRO) instruments to measure all relevant and important SLE symptoms and patient-perceived abilities to function and perform daily activities. PRO instrument development should be based upon qualitative research conducted in the target patient population to ensure the content validity of the measure.

Most experts agree that fatigue is an important symptom in SLE. However, experts and patients define fatigue differently. Measurement of fatigue in SLE should include the following: (1) a clear definition of fatigue as it relates to patients with SLE; (2) a clear conceptual framework describing fatigue in SLE including physical and mental components, as appropriate; and (3) methods for measuring fatigue symptoms and effect in the presence of comorbid factors (e.g., depression and medication effects). We have not identified an existing PRO instrument optimal for measurement of fatigue symptom complex in patients with SLE to support labeling claims. Therefore, an exploratory endpoint measure consisting of the use of an existing fatigue measure as well as an open-ended item that asks patients to identify their symptoms could be useful in the development of future instruments for measuring fatigue in SLE.

PRO instruments should be used as key secondary endpoints in all SLE trials. PRO instruments that are intended as key trial endpoints should be demonstrated to be well-defined and reliable in the SLE trial population. We encourage development of new PRO instruments where appropriate. Additional information on how the FDA reviews PRO instruments used to support medical product labeling can be found in the guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.

10. Other Endpoints

Endpoints other than those discussed above for consideration in particular SLE trials are discussed here.

a. Damage

An assessment of damage caused by manifestations of SLE disease should be considered for inclusion in SLE trials of at least 1-year duration.

Use of the SLICC/ACR Damage Index measures irreversible organ system damage caused by SLE disease that has been present for at least 6 months. The SLICC/ACR Damage Index assesses damage that accrues over time in the renal, pulmonary, cardiovascular, and other organ systems. It can be used in clinical trials to measure the rate of progression of damage caused by

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the disease, or its treatment, but is not sensitive to change unless the time interval for observation is at least 1 year in duration.

An assessment of damage during a trial also can be complicated if a new therapy is associated with toxicities not measured by the Damage Index (e.g., in organs not associated with SLE disease). Therefore, we recommend discussing use of the SLICC/ACR Damage Index or other instrument to assess damage with the review division before beginning trials.

b. Biomarkers

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In some cases, biomarkers can assist in the development and evaluation of therapies for SLE by supporting a hypothesized mechanism of action or by suggesting an appropriate dose or duration of action.

Surrogate endpoints are a subset of biomarkers that are expected to predict clinical benefit (or harm or lack of benefit) and are intended to substitute for a clinical endpoint.⁹ Currently, none of the known biomarkers (e.g., anti-dsDNA levels, complement levels) in SLE has been validated as a surrogate endpoint, and therefore no biomarker can substitute for a direct assessment of clinical benefit in clinical trials.

In some cases, biomarkers are used to define risk or identify potential responders to a treatment. Sponsors should consult the appropriate FDA center to determine whether a biomarker used to select patients or monitor response in clinical trials can be used in prescribing the medical product if it is approved (e.g., for selection of patients or for monitoring safety or effectiveness).¹⁰

11. Study Procedures and Timing of Assessments

In SLE trials using reduction in disease activity as an endpoint, it is important that the protocol specify procedures to ensure that the scoring of the DAI specifically reflects SLE-related organ dysfunction. The interpretation of score changes can be confounded if organ system dysfunction caused by a disease or condition other than SLE is present or organ dysfunction caused by the treatment occurs. Investigators should be appropriately trained to ensure uniform scoring, as variability can decrease study power. In some cases, it may be helpful to have an adjudication committee confirm assessment based on DAIs (e.g., flares or quiescence of disease).

12. Statistical Considerations

The particular statistical analysis used can differ depending on the endpoints and outcomes of interest. To assess a reduction in disease activity or flare, induction of response, treatment of

⁹ Biomarkers Definitions Working Group, 2001, Biomarkers and Surrogate Endpoints: Preferred Definitions and Conceptual Framework, Clin Pharm Therap, 69(3):89-95.

¹⁰ Contact CBER or CDRH's Office of In Vitro Diagnostic Devices Evaluation and Safety.

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serious acute manifestations, or maintenance of response, the statistical test usually should evaluate the difference between the treatment and control groups in the proportion of patients meeting a predefined outcome, although measures of continuous variety also can be useful. These outcomes can be summarized as binary or ordinal for the purpose of the primary analysis. Although outcomes at the end of the trial are usually the primary focus, outcomes also should be evaluated at multiple times during the trial. To assess the time to flare in patients with quiescent disease, the statistical test usually would evaluate the difference in the time-to-event curves using an appropriate test. This analysis also should be supported by an analysis comparing the proportion of flare-free patients at the end of the trial. Analysis considerations of primary endpoints for organ-specific disease should be similar to those for SLE.

In addition to the primary assessments of disease activity, other aspects of the disease process may be important in fully elucidating the effect of the treatment on patients. The overall probability of a false positive finding for a completely ineffective treatment should be controlled by prespecifying a single primary analysis or several analyses with appropriate adjustment for multiplicity. Secondary analyses also should be adjusted to avoid error and the protocol should describe the plan for controlling such errors.

We recommend prespecifying in the protocol statistical approaches (e.g., regarding dropouts or missing data) (see ICH E9).

13. Accelerated Approval Considerations for Human Drugs and Therapeutic Biological Products (Subpart H and Subpart E)

For serious or life-threatening conditions, a new human drug (21 CFR part 314, subpart H) or therapeutic biological product (21 CFR part 601, subpart E) can be approved on the basis of adequate and well-controlled clinical trials that establish that the human drug or therapeutic biological product has an effect on a “surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit” (21 CFR 314.510 and 21 CFR 601.40). Full approval would be contingent on required postmarketing clinical trials to verify the clinical benefit.

No surrogate marker has been reliably shown to predict clinical benefit in patients with SLE and there has been no Subpart H or Subpart E approval of medical products for SLE. Sponsors should be very cautious about selecting a potential surrogate marker intended to support accelerated approval until there is confidence regarding its predictive value.

14. Risk-Benefit Considerations

Assessment of risks and benefits involves an appraisal of the effect of the medical product on all aspects of the disease process, including disease activity, irreversible damage caused by the disease or its treatment, and health-related quality of life.¹¹ The primary efficacy analysis should show a statistically significant result and the measured clinical effect of the medical product should be clinically meaningful. Toxicities related to the pharmacologic effects of the medical

¹¹ Strand, V, D Gladman, D Isenberg, et al., 1999, Outcome Measures to Be Used in Clinical Trials in Systemic Lupus Erythematosus, *J Rheumatol*, 26:490-7.

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product (e.g., immunosuppression) also should be considered as part of this overall risk-benefit assessment of the medical product.

It is important that the size of the safety database for human drugs and therapeutic biological products at approval be consistent with the recommendations made in the ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions*. Particular attention should be paid to the assessment of known toxicities, or to pharmacologic and biological effects that might be suspected to imply delayed toxicities. It is important to consider these toxicities in formulating the clinical development program. This information may influence the size of the safety database.

A smaller safety database may be appropriate to support approval of medical products designed to treat aspects of SLE that represent orphan indications or for the treatment of serious acute manifestations, because it may be impossible or impractical to study a large number of patients with these conditions.¹² Sponsors may wish to discuss these issues with the appropriate review division early in the development of a new treatment.

Finally, if there is concern about rare but serious adverse events (e.g., from the mechanism of action or experience with similar human drugs and therapeutic biological products), a postmarketing study or clinical trial may be needed to gather additional safety information.

¹² For information regarding orphan indications, see the following Web site:
<http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/ucm135122.htm>.