
Guidance for Industry

Lupus Nephritis Caused By

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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Clinical/Medical**

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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 lupus nephritis (LN) caused by systemic lupus erythematosus (SLE). Specifically, this guidance addresses the Food and Drug Administration's (FDA's) current thinking regarding study population enrollment and efficacy endpoints for LN trials. 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 developing medical products to treat SLE disease with a focus on kidney manifestations, and finalizes the parts of the draft guidance for industry *Systemic Lupus Erythematosus — Developing Drugs for Treatment* (published March 2005) regarding LN. SLE disease affecting organs other than the kidney will be addressed in separate guidances. If sponsors wish to study other organ-specific forms of disease, they are encouraged to contact the appropriate review division.

Sponsors should become familiar with the guidance for industry, *Systemic Lupus Erythematosus — Developing Medical Products for Treatment* (SLE guidance), for information regarding the

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 medical products for the treatment of LN caused by SLE.

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overall development program and clinical trial designs for general SLE disease.³ The SLE guidance provides general information on clinical trial considerations that may assist sponsors in studying LN, as well as providing specific information on trial design, trial duration, efficacy endpoints, and response criteria in SLE.

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 Trials*. This guidance focuses on specific medical product development and trial design issues that are unique to the study of LN caused by 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

Although LN is the most commonly studied organ-specific manifestation of SLE, there is at present no approved therapy. When long-standing and persistently active, LN causes end-stage renal disease (ESRD) and death. Also, the occurrence of renal flares has been shown to predict progression to doubling of serum creatinine.⁴

Current standard-of-care treatment for LN consists of corticosteroids and immunosuppressives. With such regimens, the prognosis for LN has improved considerably, and the occurrence of renal failure is uncommon.⁵ In addition, treatment that induces remission of active LN has been shown to be associated with a reduced risk of progression to ESRD.^{6,7} However, not all patients respond adequately. Adverse outcomes in patients with LN can arise both from consequences of the disease and adverse effects of these therapies. Therefore, there is an unmet medical need for more effective and less toxic treatments.

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 Ponticelli, C and G Moroni, 1998, Flares in Lupus Nephritis: Incidence, Impact on Renal Survival and Management, *Lupus*, 7;635-638.

⁵ Grootsholten, C, IM Bajema, S Florquin, et al., 2007, Treatment with Cyclophosphamide Delays the Progression of Chronic Lesions More Effectively than does Treatment with Azathioprine plus Methylprednisolone in Patients with Proliferative Lupus Nephritis, *Arthritis & Rheum*, 56:924-37.

⁶ Korbet, SM, EJ Lewis, MM Schwartz, M Reichlin, J Evans, and RD Rohde, 2000, Factors Predictive of Outcome in Severe Lupus Nephritis, *American Journal of Kidney Diseases*, 35(5);1-12.

⁷ Mok, CC, KY Ying, S Tang, Y Leung, KW Lee, WL Ng, RWS Wong, and CS Lau, 2004, Predictors and Outcome of Renal Flares after Successful Cyclophosphamide Treatment for Diffuse Proliferative Lupus Glomerulonephritis, *Arthritis & Rheum*, 50(8);2559-3568.

III. DEVELOPMENT PROGRAM CONSIDERATIONS SPECIFIC TO LUPUS NEPHRITIS

The following sections provide recommendations specific to the development of medical products for the treatment of LN. These recommendations should be considered along with the recommendations provided in the SLE guidance. Even though this guidance focuses on the evidence of effectiveness of medical products for LN, other end organs are also affected by SLE, and disease manifestations in these other organ systems should also be followed clinically during LN trials.

Demonstration that a medical product prevents progression to ESRD in LN clinical trials obviously would be evidence of effectiveness, but it is not likely that this will be shown, given how infrequently ESRD occurs with current standard-of-care treatment. Because both induction of renal remission and reduction in renal flares have been shown to lead to preservation of renal function, they are valid effectiveness endpoints in LN clinical trials.

A. Study Population

Phase 3 clinical trials designed to assess clinical benefit of a medical product for the treatment of LN should enroll patients with established SLE (as defined by the American College of Rheumatology classification criteria), biopsy-proven proliferative glomerulonephritis (World Health Organization (WHO) grades III or IV; or Class III or IV using the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) criteria), or membranous glomerulonephritis (WHO grade V or ISN/RPS Class V). The distribution of the various histologic types of nephritis in a trial should be representative of the overall population of patients with LN, unless an investigational medical product is expected to affect only a particular histologic type. If that is the case, trials should be designed to enrich for that particular subset of the population. When feasible, baseline biopsies also should be assessed for the percent of sclerosed glomeruli, because this endpoint has been suggested to be predictive of long-term outcome.⁸ (See section III.F., Other Endpoints.)

To be eligible for enrollment, a patient should have documentation of a biopsy within the preceding 12 months. In addition, the patient should have documentation of active renal disease at screening, as evidenced by active urinary sediment and proteinuria. An assessment of renal function is not included in the definition of active renal disease for the purposes of enrollment, because patients may present with active LN yet have initially normal renal function. However, renal function should be measured at baseline and during clinical trials to assess any changes in renal function while on therapy. An assessment of renal function should be included in the composite definition of renal response (see section III.D.1., Induction and Maintenance of Renal Remission).

⁸ Grootsholten, C, IM Bajema, et al., 2007, Treatment with Cyclophosphamide Delays the Progression of Chronic Lesions More Effectively than does Treatment with Azathioprine plus Methylprednisolone in Patients with Proliferative Lupus Nephritis, *Arthritis & Rheum*, 56:924-937.

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The following factors used to define active renal disease can be used for enrollment purposes:

1. Urinary protein:creatinine ratio ≥ 0.5

AND

Active urinary sediment as defined by ≥ 1 of the following (in the absence of urinary tract infection):

- > 5 red blood cell (RBC)/high power field (hpf) (or above the reference range for the laboratory)
 - > 5 white blood cell (WBC)/hpf (or above the reference range for the laboratory)
 - Presence of cellular casts (RBC or WBC)
2. Patients with proteinuria alone and without active sediment also can be enrolled if they have a level of proteinuria at baseline that warrants treatment (e.g., ≥ 3.5 grams/day).

Consideration should be given to stratifying LN patients based upon whether or not they received treatment or on the type of treatment received between undergoing a renal biopsy within the past 12 months and the time of enrollment in a trial. Stratification also can be based on presence or degree of baseline renal impairment, although the renal function may not be always correlated with the severity of the diseases. The final clinical outcome of the renal impairment will depend on the histopathology findings such as the acute inflammation or the chronic glomerulosclerosis.

B. Study Duration

Clinical trials should be of sufficient length to assess the durability of therapy benefits, taking into account the chronic nature of LN and its waxing and waning course. In general, a trial should be at least 1 year in duration 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 renal remission, the total duration of follow-up should still be at least 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.

C. Study Design

The preferred design for efficacy trials is a parallel arm, randomized, controlled superiority trial using placebo or active control. At this time, a noninferiority design is not possible because there are no known medical products with an effect size adequately characterized to design a trial. For a description of other possible designs, see the SLE guidance.

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One example of an add-on design that assesses superiority of a new medical product would be a trial of corticosteroids and cyclophosphamide plus placebo compared to corticosteroids and cyclophosphamide plus new medical product. However, demonstration of an efficacy benefit of a new medical product may be difficult in trials in which cyclophosphamide, azathioprine, or mycophenolate mofetil are considered part of the standard-of-care regimen because of the activity of these agents or if the mechanism of action of the standard-of-care drugs and the new medical product are similar.

In principle, a randomized, withdrawal trial also can be considered. In this design, after patients achieve a response, they are randomized either to be withdrawn from the new medical product and continue to receive the active control alone or to continue to receive the new medical product plus active control. The efficacy endpoint would be demonstration of superiority of the treatment arm that received continued use of the new medical product compared to the withdrawal arm.

D. Primary Efficacy Endpoints

Sponsors should consider designing clinical trials for medical products to address the following primary endpoints: *induction of renal remission, maintenance of renal remission, and reduction in renal flares/increase in time to renal flare.*

1. Induction and Maintenance of Renal Remission

The primary composite endpoint in a trial of renal remission should include changes in urinary sediment (i.e., hematuria, pyuria, and cellular casts), proteinuria, and renal function. As noted in section III.A., Study Population, although impairment of renal function is not needed to meet the definition of active renal disease for enrollment purposes, an assessment of renal function is included in the definition of renal response. To demonstrate a complete renal response, all baseline abnormalities in any of these three components should normalize.

Studies have shown that achieving renal remission is associated with a reduced risk of developing renal insufficiency (see section II., Background). However, to assess the safety of new medical products for LN, sponsors should also include an evaluation of the occurrence of ESRD and doubling of serum creatinine in a multiyear trial. Such a trial can be conducted as a postmarketing requirement (see section III.E., Secondary Efficacy Endpoints).

The following is a discussion of the individual components included in the primary composite endpoint of renal remission. A clinical trial should include all three components in the composite endpoint because the individual components are not adequate to assess clinical outcome. However, the components should also be evaluated individually as secondary endpoints (see section III.E., Secondary Efficacy Endpoints).

1. *Urinary sediment.* An assessment of urinary sediment for quantitative changes in cellular casts, hematuria, and pyuria, when measured accurately, is considered a sensitive indicator of the level of LN activity. Local or central laboratories can be used as long as

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the analysis method is shown to be accurate and reproducible. It is desirable to outline standardized methods for collecting and analyzing urine samples in the protocol.

2. *Proteinuria.* Changes in the urine protein/creatinine ratio can serve as an assessment of the extent of proteinuria. Estimates of protein excretion based on timed urine collection also can be used, but it is critical for sponsors to document the completeness of the collection (e.g., based on creatinine excretion) because timed collections have been shown to be frequently incomplete.⁹
3. *Renal function.* In those patients with a decreased creatinine clearance at baseline, failure to normalize renal function in response to therapy may indicate an increased risk of progression to renal failure.¹⁰ Renal function can be assessed based on measured creatinine clearance (24-hour creatinine clearance), estimated creatinine clearance (Cockcroft-Gault formula), estimated glomerular filtration rate (Modification of Diet in Renal Disease (MDRD), MDRD formula), or measured iothalamate clearance, among others.^{11,12} Investigators should design trials to minimize confounding variables (e.g., overdiuresis and use of concomitant medications, such as nonsteroidal anti-inflammatory agents and angiotensin-converting enzyme inhibitors) because they can complicate interpretation of renal function measures, including serum creatinine and creatinine clearance.¹³

Patient response using the composite endpoint should be defined as complete, partial, or no response. To demonstrate a complete renal response, all baseline abnormalities in sediment, protein, and renal function should return to normal. A response should be confirmed by repeat measurement at least 1 month later. The evaluation of efficacy should be based on the comparison of the proportion of patients who achieve complete, partial, or no response across the treatment groups. Statistical analysis of the ranked outcomes of complete, partial, and no response should be performed using an appropriate statistical test.

⁹ Renal Disease Subcommittee of the American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response Criteria, 2006, The American College of Rheumatology Response Criteria for Proliferative and Membranous Renal Disease in Systemic Lupus Erythematosus Clinical Trials, *Arthritis & Rheum*, 54(2):421-432.

¹⁰ Levey, AS, SP Lan, HL Corwin, BS Kasinath, et al., 1992, Progression and Remission of Renal Disease in the Lupus Nephritis Collaborative Study: Results of Treatment with Prednisone and Short-Term Oral Cyclophosphamide, *Ann Int Med*, 116:114-123.

¹¹ Cockcroft, DW and MH Gault, 1976, Prediction of Creatinine Clearance from Serum Creatinine, *Nephron*, 16:31-41.

¹² Levey, AS, JP Bosch, JB Lewis, et al., 1999, A More Accurate Method to Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation, Modification of Diet in Renal Disease Study Group, *Ann Int Med*, 130:461-70.

¹³ Boumpas, DT and JE Balow, 1998, Outcome Criteria for Lupus Nephritis Trials: A Critical Overview, *Lupus*, 7:622-629.

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For example, a complete renal response or a partial renal response can be defined as follows:

Complete Renal Response

Calculated glomerular filtration rate (GFR) is within the normal range

AND

Inactive urinary sediment (< 5 RBCs/hpf and < 5 WBCs/hpf (or within the reference range of the laboratory); and no cellular casts (no RBC or WBC casts)

AND

Urinary protein:creatinine ratio < 0.5

For patients with a normal urinary sediment and GFR at baseline and only the presence of proteinuria (≥ 3.5 grams/day), the urine protein:creatinine ratio should be less than 0.5 to meet the primary endpoint.

Partial Renal Response

Estimated GFR no more than 10% below the baseline value

AND

RBCs/hpf $\geq 50\%$ reduction from baseline and no RBC casts

AND

$\geq 50\%$ improvement in the urine protein:creatinine ratio with one of the following:

– a urine protein:creatinine ratio of < 1.0 , if the baseline ratio was ≤ 3.0

OR

– a urine protein:creatinine ratio of < 3.0 , if the baseline ratio was > 3.0

2. Reduction in Renal Flares/Increase in Time to Renal Flare

An increase in the frequency and severity of flares in LN correlates with a poor outcome.¹⁴ An established definition of flare can be used as the primary endpoint in a trial designed to demonstrate a decreased frequency, or decreased severity, of flares.

¹⁴ Moroni, G, S Quaglini, M Maccario, et al., 1996, Nephritic Flares Are Predictors of Bad Long-Term Renal Outcome in Lupus Nephritis, *Kidney International*, 50:2047-53.

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A success in a clinical trial can be defined as a decrease in the number of flares or as an increase in the time to flare for the new medical product compared to the control group over the course of a 1-year trial. If time to flare is evaluated as the primary endpoint, a critical secondary endpoint should be comparison of flare rates or proportion of patients flare-free at an appropriate time point.

The following definition of *renal flare* consisting of the development of one or more of the following three factors is recommended for use in clinical trials.¹⁵

Increased Proteinuria

A urinary protein:creatinine ratio > 0.5 , provided the 24-hour urine protein contains a total of at least 500 mg of protein.

OR

A reproducible increase in 24-hour urine protein levels to:

$> 1,000$ mg if the baseline value was < 200 mg

OR

$> 2,000$ mg if the baseline value was between 200 and 1,000 mg

OR

More than twice the value at baseline if the baseline value was $> 1,000$ mg

Impaired Renal Function

A reproducible decrease in GFR of $> 20\%$, accompanied by proteinuria ($> 1,000$ mg/24 hours), hematuria (≥ 4 RBCs/hpf or above the reference range for the laboratory), and/or cellular (RBC and WBC) casts

New Hematuria

New, reproducible hematuria (≥ 11 to 20 RBCs/hpf) or a reproducible increase in hematuria by 2 grades compared with baseline, associated with $> 25\%$ dysmorphic RBCs, glomerular in origin, exclusive of menses, accompanied by either an 800 mg increase in 24-hour urinary protein levels or new RBC casts.

If sponsors wish to use an alternative definition of renal flare, then they should provide data to support their definition to the review division in advance of conducting such trials.

¹⁵ Alarcon-Segovia, D, JA Tumlin, RA Furie, et al., 2003, LJP 394 for the Prevention of Renal Flare in Patients with Systemic Lupus Erythematosus, Arthritis & Rheum, 48:442-54.

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E. Secondary Efficacy Endpoints

Urinary sediment, proteinuria, and renal function are components of the composite primary endpoints for various LN trials, but these parameters should also be evaluated individually in all trials as secondary endpoints. The use of the doubling of serum creatinine has been shown to reliably predict long-term renal outcome. Therefore, preservation of renal function can be assessed using either doubling of serum creatinine or progression to ESRD.

- Doubling of serum creatinine is defined as the proportion of patients whose serum creatinine attains a level double that of the baseline value and is confirmed with a second measurement at least 3 weeks later.
- Progression to ESRD is defined as the need for chronic dialysis or renal transplantation.

Other secondary endpoints that should be included in all LN trials include outcomes using a patient global response, and an assessment of overall disease activity (using the British Isles Lupus Assessment Group or other disease activity index).

For LN trials evaluating induction or maintenance of renal remission as the primary endpoint, the duration of response should be included as a secondary endpoint.

In addition to evaluating renal function during a 1-year clinical trial, sponsors also should assess the potential safety risk of the medical product to cause a delayed deterioration in renal function. The assessment of long-term effects on renal outcome generally can be conducted as a postmarketing requirement in the form of a multiyear follow-up trial using the endpoints previously discussed to assess preservation of renal function.

F. Other Endpoints

In addition to the other endpoints discussed in the SLE guidance (i.e., damage and biomarker endpoints), renal histology can be considered as an endpoint for LN trials to confirm renal response. When feasible, renal biopsies should be obtained at the end of a trial evaluating renal response or remission to demonstrate that an improved renal response corresponds to a histologic improvement, including effects on the percent of sclerosed glomeruli. If it is not possible to obtain biopsies on all patients, biopsies should be obtained from a predefined subset of patients. Sponsors may wish to stratify patient enrollment based upon whether or not a post-treatment biopsy will be obtained.