

# Concept Paper

## Systemic Lupus Erythematosus

**DRAFT**

### 1 I INTRODUCTION

2 Systemic lupus erythematosus (SLE) is a chronic disease characterized by protean manifestations  
3 often demonstrating a waxing-and-waning course. While in the past a diagnosis of SLE often  
4 implied a decreased life span due to internal organ system involvement or to toxic effects of  
5 therapy, recent improvements in care have dramatically enhanced the survival of SLE patients  
6 with the most severe and life-threatening manifestations. Unfortunately, current treatments for  
7 SLE remain inadequate as many patients have incompletely controlled disease, progression to  
8 end stage organ involvement continues, and current therapies carry potential risks of debilitating  
9 side effects. Therefore, it is important to create an environment that will foster the development  
10 of novel therapeutic agents that potentially will be more effective and ideally less toxic.

11 Although many patients with SLE exhibit symptoms that involve the skin and joints, other  
12 symptoms of SLE vary widely between patients. There is no single demonstrated biological  
13 mechanism to explain the varied manifestations of disease. It is challenging to develop indices  
14 of disease response to therapeutic intervention. Disease activity scores allowing a comparison of  
15 disease severity in SLE patients whose disease affects different organ systems have been  
16 developed but may not always perform optimally as response measures in clinical trials. Using a  
17 variety of techniques, several different groups have developed validated indices that have now  
18 been shown to reliably measure disease activity in SLE patients in varied settings. Some of these  
19 indices have been shown to mirror the assessment of experienced clinicians and to sensitively  
20 measure changes in disease activity. One has also been demonstrated to predict the need for  
21 alterations or intensification of therapy; thus, these indices may be able to play an important role  
22 in future clinical trials of novel agents.

23 Although there are indices that measure disease activity in SLE, it is uncertain whether they will  
24 clearly delineate measurable important clinical responses to therapy in all situations. It is not  
25 certain that all agents with therapeutic benefit in SLE would lead to improvement in these  
26 measures. Some treatments may target a biologic mechanism that underpins some lupus  
27 manifestations, or only those related to a single organ system. This guidance addresses claims of  
28 improvement in overall activity of the disease SLE, as well as claims of improvement in organ-  
29 specific manifestations of SLE such as lupus nephritis. It is important that any therapy that  
30 claims to improve disease in one organ system not worsen disease elsewhere. The primary  
31 outcome measure selected for a given trial in SLE, should assess other aspects of the disease  
32 process, as it may be informative about the overall risk-benefit assessment (*see* RISK-BENEFIT  
33 ASSESSMENT). In this situation, the appropriate use of disease activity measures may be very  
34 useful.

35 **I. MEASUREMENT OF LUPUS DISEASE ACTIVITY AND CLINICAL OUTCOMES**

36 **A. Disease activity indices**

37 The clinical measurement of disease activity in SLE involves an assessment of either the  
38 presence or absence of the characteristic signs and symptoms of disease and the results of  
39 laboratory parameters. Recent discussions within the scientifically invested academic and  
40 clinical community of investigators interested in this disease have identified a series of important  
41 measures to be applied as outcomes and, taken together, are probably the critical assessments to  
42 be measured within a clinical trial. These include

43 a measure of disease activity,

44 a measure of disease-induced damage,

45 a measure of therapy induced damage

46 a measure of response as determined by the patient “a patient global response”,

47 a measure of health related quality of life.

48 These should be measured either as co-primary outcomes for response or incorporated into a  
49 response index. Decisions regarding therapy are based on patterns of stable, increasing or  
50 decreasing disease activity. To measure disease activity in studies with groups of patients with  
51 varying manifestations of lupus, indices of disease activity that attempt to correlate these results  
52 with assessments of panels of expert clinicians have been developed. These indices identify  
53 disease manifestations using predefined criteria based on the presence or absence of different  
54 aspects of the disease, or in one measure, on the clinician’s assessment of the need to change  
55 therapy. Studies have attempted to validate these measured indices with regard to: the  
56 concordance of scores with expert opinion; inter-observer variability; correlation between  
57 individual patients’ scores on different indices; correlation between scores and changes in  
58 disease activity; correlation between increases in scores and clinical decisions to increase  
59 therapy.

60 Some of the available instruments have been validated in cohort studies as reflecting change in  
61 disease activity but not in prospective randomized clinical trials: the SLE Disease Activity Index  
62 (SLEDAI); the British Isles Lupus Assessment Group (BILAG); the SLE Activity Measure  
63 (SLAM); the European Consensus Lupus Activity Measure (ECLAM); the Lupus Activity Index  
64 (LAI) and the National Institutes of Health SLE Index Score (SIS) (ref - Strand V, Gladman D,  
65 Isenberg D, Petri M, Smolen J, Tugwell P, Outcome measures to be used in clinical trials in  
66 systemic lupus erythematosus, *J Rheumatol* 1999 Feb;26(2):490-7).

67 The BILAG has also performed appropriately by allowing the clinician to determine whether or  
68 not to increase or decrease therapy based on response. There is disagreement among lupus  
69 investigators about the appropriate weights that should be accorded to individual components of  
70 these scales and how to apply them if at all as responder indices.

71 When applying these disease activity indices to clinical trials, care must be taken to ensure that  
72 these measures accurately assess disease activity. If improvement is noted in one disease  
73 manifestation, it would be important to determine that other disease manifestations do not  
74 significantly worsen. Careful training of investigators is essential to ensure uniform scoring.  
75 Definitions of disease manifestations and levels of disease severity should be clearly specified.  
76 If there is a lack of reproducibility of these measures from clinician to clinician, it may seriously  
77 impair the interpretability of the trial results.

78 It is important to note that there are situations where changes in scores do not accurately reflect a  
79 change in disease activity. Misleading conclusions may result from applying some of the  
80 currently available indices that are transitional instruments, i.e. they score positively with the  
81 new onset of disease manifestations but not with persistent disease. The SLEDAI, for example,  
82 gives a positive score for new onset of CVA, seizure, cranial nerve disorder, rash, alopecia or  
83 mucosal ulcers while continued disease activity in these organ systems does not give a positive  
84 score (Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH and the Committee on  
85 Prognosis Studies in SLE. Derivation of the SLEDAI: A Disease Activity Index for Lupus  
86 Patients. *Arthritis & Rheumatism*, 35:630-640, 1992). This method of scoring would produce an  
87 undesired result in a clinical trial when the SLEDAI score has positive values in the initial visit  
88 for disease in the affected organ systems, and on subsequent visits the SLEDAI score would  
89 decrease, despite persistence of disease. While drawbacks do not preclude the use of an  
90 instrument with these characteristics, indices that produce a straightforward readout of disease  
91 activity are preferred. If a clinical trial indicates a better outcome from a therapeutic agent than  
92 control, the results of the study would be scrutinized carefully to ensure that the apparent benefits  
93 of the study drug are not an artifact of the scoring system. Although the SLEDAI is discussed in  
94 detail, similar concerns exist for a number of the other disease activity indices.

95 In applying disease activity indices to clinical trials of SLE, the interpretation of changes may be  
96 confounded if organ system dysfunction is present and attributable to a concurrent non-SLE  
97 illness, or organ dysfunction occurs and is attributable to therapy given for the disease. It is  
98 unknown how great an impact these concerns will have on the interpretation of clinical trial  
99 results. The results of ongoing and future trials may help assess whether further refinements of  
100 the currently available instruments are required.

101 The clinical course of SLE is characterized in many patients by periods of relatively stable  
102 disease followed by flares of disease activity. A problem with relying on scores to measure  
103 disease activity in trials is that measuring disease activity at fixed time points may miss flares of  
104 disease activity in between the times that measurements are performed. Definitions of flare have  
105 been proposed and applied longitudinally to patient populations. In one study, rates of flare were  
106 measured at an average of 0.6 flares per year [Petri M, Genovese M, Engle E, Hochberg M.  
107 Definition, incidence, and clinical description of flare in SLE. A prospective cohort study. *Arth.*  
108 *Rheum.* 1991; 34:937-44.]. A definition of flare should be shown to validly measure episodes of  
109 increased disease activity and correlate with a clinically determined need for increase in  
110 treatment. Definitions of major flare might include the requirement for initiation of high-dose  
111 glucocorticoid therapy or the institution of change in dose of immunosuppressive therapy, or the  
112 need for hospitalization or the occurrence of death. Important differences in the frequency of  
113 flares may exist based on gender, menopausal status, treatment and other patient characteristics.

114 There has been considerable interest in the development of a responder index to measure  
115 response to therapy on an individual basis. Some proposed definitions of a responder specify a  
116 minimum improvement in a measure of disease activity with no worsening in other aspects of  
117 lupus. A responder index would allow a clinical trial to determine directly what proportion of  
118 patients had a clinically meaningful improvement from therapy. Such a responder index should  
119 be assessed for intra-subject variability, content validity, and sensitivity to change to be fully  
120 validated. Full validation would also include a demonstration of the ability to discriminate  
121 treatment with a known active agent compared to an inactive control in a clinical trial. For  
122 example, a candidate responder index would accurately categorize a patient who experienced  
123 general improvement in many aspects of disease with mild worsening in one. Application of  
124 responder indices in prospective studies will help determine the utility of these measures in  
125 clinical trials.

## 126 **B. Damage**

127 Patients suffering from lupus experience irreversible damage to internal organ systems due  
128 directly to the abnormal biology associated with the active disease. Accumulation of damage  
129 occurs over a period of years while there may be associated therapy-induced damage as well. An  
130 index of damage was proposed and validated as the Systemic Lupus Erythematosus International  
131 Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index.  
132 Validation studies show that high scores on the SLICC/ACR Damage Index are predictive of  
133 increased mortality and damage in the renal and pulmonary components are associated with poor  
134 outcomes [Stoll T, Seifert B, Isenberg, DA. SLICC/ACR damage index is valid, and renal and  
135 pulmonary organ scores are predictors of severe outcome in patients with SLE. Br. J. Rheumatol.  
136 1996; 35: 248-54.]. The prognostic information derived from SLICC/ACR Damage Index scores  
137 suggests they may be useful as stratification variables for clinical trials. The SLICC/ACR  
138 Damage Index measures only changes that have been present for at least 6 months, therefore  
139 only longer term clinical trials could demonstrate reduction in the rate of progression of damage  
140 using this measure. Some of the components of the SLICC/ACR Damage Index are measures of  
141 toxicity related to current treatment modalities. Use of the SLICC/ACR Damage Index as  
142 outcome measures in clinical trials could be complicated if a new therapy were associated with  
143 toxicities not measured by the Damage Index.

## 144 **C. Organ specific indices**

145 Organ specific measures of disease activity provide another approach to the study of therapeutic  
146 efficacy in lupus. This approach recruits a more homogeneous population of patients compared  
147 to the disease activity index approach, although it is recognized that patients will often have  
148 more than one organ system involved. Powering such a study may be problematic. Many  
149 patients with lupus are not given therapy for increase in disease activity, but for disease affecting  
150 specific organs, such as involvement of the CNS, the kidney, the lung, the skin, the joints or  
151 other organs. Responder indices could be applied in clinical trials by determining which organ  
152 system or systems have been most problematic for each enrolled subject, then measuring if  
153 subjects demonstrate improvement in those organ systems using prespecified criteria, such as  
154 components of validated disease activity indices. A responder measure of this type has the  
155 advantage of addressing the particular disease manifestations of most concern for individual  
156 patients. Interpretation of a clinical trial using this type of responder index could be problematic

157 if worsening in other manifestations of lupus counterbalanced improvement in the organ system  
158 being followed.

159 Lupus nephritis has been the most commonly studied organ specific manifestation of lupus. The  
160 presence of glomerulonephritis identifies a subset of lupus patients who may progress to end-  
161 stage renal disease (ESRD) and may have an increased mortality. Patients with severe lupus  
162 nephritis are often treated with high doses of immunosuppressive agents, including  
163 cyclophosphamide and high doses of corticosteroids. The outcome of lupus nephritis has  
164 improved markedly in recent years with 5-year survival rates of 90% or greater and 10-year  
165 survival rates of more than 80% reported (Urowitz MB, Gladman DD. Evolving spectrum of  
166 mortality and morbidity in SLE. *Lupus*. 1999; 8: 253-255). Measurement of renal disease in  
167 SLE in clinical trials requires knowledge of the histologic description delineating the extent of  
168 inflammation or scarring, because the outcome and clinical features vary markedly among the  
169 various WHO categories of lupus nephritis.

170 A variety of outcome measures have been used in clinical trials of lupus nephritis. Mortality is  
171 an important outcome measure, but low mortality rates and necessary long observation times  
172 make mortality a relatively insensitive measure in clinical trials. Measures of renal function are  
173 used as outcome measures, including progression to ESRD, sustained doubling of serum  
174 creatinine, creatinine clearance, iothalamate clearance etc. The protein/creatinine ratio in urine  
175 may serve as an indicator of the need for further assessment of renal function with a study of  
176 creatinine clearance. The use of the doubling of serum creatinine is the most validated of these  
177 measures as it has been shown to reliably predict long-term renal outcomes; however, it is  
178 confounded by its insensitivity. Although less validated and requiring careful collection, the use  
179 of the protein/creatinine ratio followed by estimation of changes in GFR utilizing creatinine or  
180 iothalamate clearance, would be preferable in that, in the acute circumstance, these measures  
181 appear to be more reliable. Confounding variables (Boumpas DT, Balow JE. Outcome criteria  
182 for lupus nephritis trials: a critical overview. *Lupus*. 1998; 7: 622-629) may complicate  
183 interpretation of renal function measures, including serum creatinine, creatinine clearance. The  
184 sponsor should consider a measure that is clinically validated and provide data to support that  
185 choice. Changes in urinalysis may provide important information for the assessment of renal  
186 inflammation in lupus nephritis. The presence of cellular casts and hematuria, when measured  
187 accurately, are considered sensitive indicators of the level of activity of lupus nephritis. Central  
188 laboratories may be unreliable in assessing the presence of casts as they may break up during  
189 transport. Major flares of lupus nephritis, as assessed by urinary sediment, proteinuria and renal  
190 function, are an outcome measure. Patients who experience nephritic flares characterized by a  
191 nephritic sediment and an increase in serum creatinine or decrease in GFR may be at increased  
192 risk of developing a persistent doubling of serum creatinine. Renal remission in response to  
193 therapy has been defined as a return of an elevated creatinine and proteinuria to normal levels  
194 and normalization of nephritic sediment. Patients who fail to normalize an elevated serum  
195 creatinine in response to therapy may have an increased risk of progression to renal failure (  
196 Levey AS, Lan SP, Corwin HL, Kasinath BS, et al. Progression and remission of renal disease in  
197 the Lupus Nephritis Collaborative study: Results of treatment with prednisone and short term  
198 oral cyclophosphamide. *Ann. Int. Med.* 1992; 116: 114-123.). Assessment of proteinuria is  
199 particularly important in patients with membranous glomerulonephritis; however this is a less  
200 common form of lupus nephritis. Increases in proteinuria in patients with other forms of  
201 glomerulonephritis may not translate into unfavorable long-term outcomes.

## 202 **D. Quality of Life/Fatigue**

203 Health-related quality of life measures should be included in all trials of SLE. Instruments that  
204 assess health status and health-related quality of life can measure aspects of SLE and its impact  
205 on patients that are not fully assessed by other outcome measures. Trials demonstrating  
206 improvement in a specific organ or in disease activity should demonstrate no or minimal  
207 worsening in measures of quality of life. Patients with active SLE may have increased disability  
208 as assessed by the Health Assessment Questionnaire (HAQ) or modified Health Assessment  
209 Questionnaire (MHAQ). Health-related quality of life has been assessed in lupus patients using  
210 a number of generic instruments including the HAQ, MHAQ, Arthritis Impact Measurement  
211 Scale (AIMS), the Medical Outcomes Survey Short Form-20 (SF-20) and Short Form-36 (SF-  
212 36). Differences compared to controls have been observed in several domains and subdomains.  
213 Some instruments do not adequately assess fatigue, an important symptom for many lupus  
214 patients. Specific instruments have been studied for assessment of fatigue, (e.g. the Krupp  
215 Fatigue Severity Scale (KFSS)). Health-related quality of life instruments used in clinical trials  
216 of SLE should undergo validation regarding content validity (inclusion of all relevant domains),  
217 construct validity, sensitivity to change and other criteria. The use of these outcomes is a critical  
218 component to understand both the efficacy of an agent as well as its potential adverse events. If  
219 the measure does not improve with a specific therapy, it should not worsen.

## 220 **E. Serologies**

221 Serologic markers play an important role in the assessment of disease activity in SLE, including  
222 assessment of anti-double-stranded DNA, complement levels, and others. Serologic markers are  
223 critical for understanding the pathogenesis of disease. Serologic markers have an imperfect  
224 correlation with disease activity and cannot substitute alone for a direct assessment of clinical  
225 benefit. Serologic marker data should be studied in clinical trials, and in conjunction with  
226 clinical measures may play a role in assessing clinical outcomes and identifying potential clinical  
227 benefit from new therapies. Long-term clinical outcome studies after registration may help to  
228 demonstrate clinical benefit associated with changes in serologic markers (see section V:  
229 Surrogate markers as endpoints).

230

## 231 **III SLE CLAIMS**

232 *There are a number of claims that may be considered for SLE. Organ specific claims or clinical*  
233 *remission/complete clinical response are the most straightforward to define from a purely*  
234 *clinical standpoint. However, additional claims(s) may be considered. A consensus needs to be*  
235 *reached as to whether a claim for “reduction of signs and symptoms of SLE” or a “reduction in*  
236 *the constitutional aspects of SLE” is most appropriate and should be included in this document.*  
237 *A “reduction of signs and symptoms” is meant to designate a change in overall disease status or*  
238 *activity, may be measured conventionally by a disease activity index such as SLEDAI, SLAM,*  
239 *BILAG etc., and may include any and all manifestations of disease. A “reduction in*  
240 *constitutional aspects” as defined here means improvements in the following manifestations:*  
241 *arthritis, rash, fever, fatigue, and serositis, but would not include major organ system*

242 *involvement. Major organ system involvement would be covered by an organ specific claim (and*  
243 *would be studied specifically in each organ). In either instance, a measure of health-related*  
244 *quality of life should be performed. In addition, a question to determine the patient’s assessment*  
245 *of their clinical response should be designed. This “patient global” assessment will allow for an*  
246 *overall determination of the “state of the patient,” which may help infer whether other aspects of*  
247 *the disease have improved or worsened as well identifying possible drug induced adverse events.*  
248 *In addition, the agency is considering a claim that would require a meaningful change in a*  
249 *health-related quality of life measure that has been validated in SLE (e.g. SF-36) in the context*  
250 *of a positive improvement in a question that would reflect the state of the patient (patient global*  
251 *analysis), and a concomitant measure of disease activity that could be one of the presently*  
252 *available disease activity indices or some other measure, and once validated would be*  
253 *appropriately applied. (The committee is asked to specifically discuss and provide feedback to*  
254 *the Agency as to the most clinically meaningful claims and most important, the appropriate use*  
255 *of measures to establish these claims.)*

256 This document proposes the following claims for SLE: (1) Reduction in the constitutional  
257 aspects of the disease; reduction in the signs and symptoms of lupus; (2) indicated for the  
258 treatment of lupus involving a specifically identified organ, for example, lupus nephritis; or (3)  
259 complete clinical response/remission. These proposed claims are discussed in the paragraphs  
260 below.

#### 261 **A. Reduction in constitutional aspects of SLE/ Reduction in Signs & Symptoms of SLE**

262 This claim is intended to reflect the demonstration of a benefit in reducing the signs of disease  
263 activity in SLE as well as in reducing the associated symptoms. As part of this claim, changes in  
264 skin disease, joint involvement, fever, weight loss, and serositis would be considered. SLE is a  
265 disease of long duration, with a waxing and waning course; therefore this claim would ordinarily  
266 be established by a trial of at least 1 year in duration. For products that may elicit the formation  
267 of antibodies, the duration of the clinical trial should be adequate to assess whether antibodies  
268 are formed and if they adversely effect efficacy and safety. Methods to assess the activity of  
269 disease over the duration of the study are preferable to methods that measure disease activity  
270 only at the beginning and end. As part of any trials in support of this claim, measures of damage  
271 and health-related quality of life should be included. A patient global assessment should also be  
272 determined. Acceptable outcome measures to demonstrate a reduction in signs and symptoms of  
273 SLE include:

##### 274 1) A validated disease activity index

275 A disease activity index could be a measure to demonstrate that treatment was associated with a  
276 decrease in overall disease activity during the course of the study. Careful consideration should  
277 be given to the optimal choice of comparator arm (placebo vs. active control, see Trial Design).  
278 For example, the SLEDAI, the SLAM, the BILAG, the ECLAM or other validated index could  
279 be utilized to measure disease activity.

280 *Illustration:* A success in a 1-year trial could be defined as a decrease in the area under the  
281 curve for monthly measurements of SLEDAI scores. It could also demonstrate that changes are  
282 clinically meaningful.

283 2) A validated measure of flare

284 A validated definition of flare could be used in a trial to demonstrate a decreased frequency of, or  
285 decreased severity of, flares. Currently, no measure of flare has been fully validated.

286 *Illustration:* A success could be defined as a decrease in the time-to-flare or as a decrease in  
287 the number of flares over the course of a 1-year trial.

288 **B. Effectiveness in the treatment of a specific organ** (for example lupus nephritis)

289 Trials intended to study clinical benefit for specific organ systems could enroll subjects with  
290 disease affecting a single organ system (e.g. lupus nephritis). Patients enrolled with multiple  
291 organ systems identified as the major clinical concern can be stratified for the different organ  
292 systems for randomization and analysis. The definition of a response should be specified for each  
293 organ system under study.

294 *Illustration:* Trials of patients with disease activity affecting specific organ systems can define  
295 success as an increase in the proportion of responders receiving study drug than in controls.

296 Trials designed to assess efficacy of a product for the treatment of lupus nephritis would be  
297 expected to demonstrate an improved outcome for patients with biopsy-proved severe  
298 glomerulonephritis (WHO grades III or IV), or membranous glomerulonephritis. Short-term  
299 benefits may not reliably predict long-term outcomes, therefore trials of lupus nephritis are  
300 expected to be at least 1-year in duration. The following outcome measures could establish  
301 efficacy in lupus nephritis:

302 1. Incidence of mortality and progression to end-stage renal disease (ESRD)

303 2. Sustained doubling in serum creatinine or other measure that has been validated  
304 including approximations of GFR such as iothalamate clearance or creatinine clearance  
305 studies

306 Doubling of serum creatinine has been shown to be associated with progression to ESRD, so a  
307 decrease in the proportion of subjects meeting this endpoint in the treatment group compared to  
308 controls could be interpreted to define a patient benefit. Lesser degrees of change or changes in  
309 other measures could be considered. Similarly a significant change in GFR, which has clinical  
310 importance, can be considered. Sponsors should provide data to demonstrate that these changes  
311 are associated with benefit or a significant reduction in the rate of progression to ESRD.  
312

313 *Illustration:* A success in a trial using this outcome measure would be defined as a decrease in  
314 the proportion of subjects whose serum creatinine attains a level double that of the baseline value  
315 and remains doubled for at least 6 months. Alternatively, a success in a trial that demonstrates a  
316 sustained change in GFR, such as preventing a fall in GFR of 50%, or demonstrating a rise of  
317 GFR by 50%, can be considered.

318

### 3. A validated surrogate marker for lupus nephritis

319 21 CFR 314, subpart H (Accelerated Approval of New Drugs for Serious or Life Threatening  
320 Illnesses) and 21 CFR 601 subpart E (Accelerated Approval of Biological Products for Serious  
321 or Life Threatening Illnesses), provides for FDA approval of drugs intended to treat serious and  
322 life-threatening diseases. Approval is based on the effect on a surrogate marker, provided  
323 specific criteria are met, and there is a commitment to define the actual clinical benefit of the  
324 agent in studies completed after approval. Demonstration of marked and sustained improvement  
325 in renal function and renal inflammation in a seriously affected population of patients with lupus  
326 glomerulonephritis would qualify for consideration under these regulations, provided that the  
327 measure of improvement was previously demonstrated as associated with improved patient  
328 outcomes. Sponsors are urged to consult with the relevant FDA staff before embarking on a  
329 clinical program based on these regulations.

330 Use of the accelerated approval pathway for a product for lupus nephritis, for example, would  
331 necessitate the timely completion of studies of long-term clinical outcomes post marketing.

332

### 4. Induction of renal remission

333 Active lupus nephritis is associated with evidence of renal inflammation, including cellular casts,  
334 proteinuria, and decreases in renal function. Serious lupus nephritis is frequently treated with  
335 cyclophosphamide and high doses of corticosteroids, agents that are associated with an increased  
336 risk of significant toxicity. A treatment that induces a sustained remission in lupus nephritis  
337 would confer a clinical benefit. Clinical studies of lupus nephritis use varied definitions of renal  
338 remission, but generally specify decreases in hematuria and cellular casts, decreases in  
339 proteinuria, and stabilization or improvement in renal function. A clinical trial intended to  
340 demonstrate induction of renal remission would specify a definition of renal remission that  
341 includes all relevant parameters. Evidence supporting an association with improved clinical  
342 outcome (e.g. decreased likelihood of developing end-stage renal disease or need for dialysis)  
343 should be provided to support the selected definition of renal remission.

344

### 5. A reduction in the number of renal flares

345 A validated definition of flare could be used in a trial to demonstrate a decreased frequency of, or  
346 decreased severity of, flares. Currently, no measure of flare has been fully validated.

347 *Illustration:* A success could be defined as a decrease in the time-to-flare, or as a decrease in the  
348 number of flares over the course on a 1-year trial.

349 Trials to demonstrate effectiveness in the treatment of specific organs should include measures  
350 of damage and health-related quality of life. Ideally these measures should improve in an  
351 important fashion.

352

### **C. Complete clinical response/remission**

353 Complete clinical response/remission claim applies to products that demonstrate the ability to  
354 induce a clinical response, characterized by the complete absence of disease activity for at least 6

355 consecutive months. This response is termed complete clinical response if the subjects continue  
356 to receive lupus-directed therapies. Remission occurs if subjects were receiving no ongoing  
357 therapy for their SLE. A trial in support of the claim of Complete Clinical Response would be at  
358 least 12 months duration and demonstrate an increase in the proportion of subjects in whom a  
359 disease activity measure achieves zero.

360 Claims using the organ specific approach may be either for the treatment of each organ studied  
361 (for example, lupus nephritis), or for the treatment of lupus, depending on the numbers and types  
362 of organs studied. This would also require that there would be no worsening in terms of a patient  
363 global assessment as well as health-related quality of life.

364

## 365 **IV TRIAL DESIGN AND ANALYSIS**

366 Careful consideration should be given to choosing endpoints that will accurately assess the  
367 clinical benefits of the product when designing a trial for SLE. This may involve a focus on one  
368 aspect of disease (e.g. lupus nephritis) over other important aspects. Adequate information  
369 should be collected about other aspects of disease to adequately assess the overall risk-benefit  
370 ratio. Clinical trials in SLE generally are expected to collect information about disease activity;  
371 irreversible damage due to SLE and its treatment; and valid health-related quality of life  
372 measures. Serologic studies may also provide important information about the mechanism of  
373 action of the product under investigation.

### 374 **A. Phase 2 trials**

375 Phase 2 trials are used to better define dose and exposure-related activity and toxicity of products  
376 under development. The safety of concurrent use of a new product with commonly used  
377 concomitant therapies should be established. Many of the outcome measures under  
378 consideration for trials of SLE have not been tested in large-scale randomized trials. Some  
379 outcome measures may prove less sensitive than expected. Unexpected confounding variables  
380 may complicate the interpretation of trials using these endpoints. These are reasons for careful  
381 consideration in phase 2 trials to ensure validation of clinical outcome measures used in  
382 confirmatory phase 3 trials.

### 383 **B. Efficacy trials**

#### 384 1. Disease activity trials

385 The chronic nature of SLE and its waxing-and-waning course requires clinical trials intended to  
386 show a decrease in disease activity and be of sufficient length to assess the durability of benefits.  
387 A trial of 1-year duration is typical. One endpoint that measures the effect on disease activity is  
388 to compare the scores on a disease activity index at the outset and endpoint of the trial in subjects  
389 taking the new product, with those of subjects taking the control regimen. Another measure of  
390 disease activity is to use an area under the curve (AUC) dimension at regular intervals  
391 throughout the trial. This may more accurately measure disease activity during the study than at  
392 a single time point. Trials provide analyses of both landmark and time-weighted averages, to

393 better define measures of efficacy. A trial showing a treatment effect demonstrates a larger  
394 decrease in the disease activity scores in the treatment arm compared to control. Several  
395 confounding factors could complicate the interpretation of such a trial. First, many SLE patients  
396 have frequent low scores on disease activity indices, but experience intermittent flares of disease.  
397 If a new product decreases the frequency and severity of disease flares, but has only a small  
398 effect on background disease activity, this may not be reflected in a clinical trial that measures  
399 disease activity only at the end of the trial. Another confounding factor is the likelihood that  
400 subjects who flare during the trial will be treated with additional medications (e.g.  
401 corticosteroids) potentially reducing their disease activity scores for reasons unrelated to the  
402 study drug.

403 Another measure of decrease in disease activity is to assess the incidence of disease flares during  
404 the course of a clinical trial. This type of trial might use a validated measure of SLE flare as its  
405 primary outcome measure. As not all SLE patients experience flares in a given time frame, the  
406 size and duration of the trial must be adequate to capture a sufficient number of flares in the  
407 treatment and control groups to assess a decrease in the treatment arm. Collection of complete  
408 information on concomitant medications is essential to ensure that a difference in the number of  
409 SLE flares is attributable to the study drug. A trial that shows a treatment effect of study drug  
410 demonstrates a decrease in the number of flares, or in the time to flare, in the treatment group  
411 compared to control.

412 Considerations in determining the appropriate regimen for the control arm of a trial in SLE are  
413 important. No subject should be denied recognized effective treatment for aspects of the disease  
414 that may lead to irreversible harm. A potential design consistent with this principle randomizes  
415 subjects to the addition of placebo or study drug to a generally acceptable standard of care  
416 regimen. This seeks to demonstrate that disease activity is decreased in the treated subjects. A  
417 study could randomize subjects to the receipt of a known active agent or the study drug, then  
418 assess if there is a larger decrease in disease activity in subjects receiving the new product. It  
419 may be appropriate to include early escape provisions for subjects who worsen on study to  
420 ensure that no subject is denied potentially effective therapy.

## 421 2. Lupus nephritis trials

422 Diffuse proliferative (WHO class IV) and severe focal proliferative (WHO class III)  
423 glomerulonephritis in patients with SLE who have measures of inflammatory activity and  
424 damage is associated with increased long-term risk of progression to end-stage renal disease and  
425 high mortality. Severe lupus nephritis is commonly treated with high-dose immunosuppressive  
426 regimens including cyclophosphamide and high-dose corticosteroids. These regimens are based  
427 on non-prospective cohort studies that suggest a decrease in the long-term risk of progression to  
428 end-stage renal disease. There is a need for additional regimens as current treatments may be  
429 highly toxic and not effective in all subjects.

430 Studies that demonstrate improvement in mortality in lupus nephritis could document the  
431 efficacy of a new product. Studies using mortality alone as the primary outcome may be  
432 insensitive indicators of clinical benefit. Recent data shows that mortality is low in the majority  
433 of patients. A study of mortality in lupus nephritis should be of adequate duration to document  
434 benefits.

435 A study demonstrating a decrease in progression to end-stage renal disease would clearly  
436 document efficacy in lupus nephritis. Such a study should be years in duration as progression to  
437 end-stage renal disease occurs slowly. Another possible approach uses a doubling of serum  
438 creatinine as the primary outcome measure, based on studies that indicate a doubling of  
439 creatinine as highly correlated with subsequent progression to end-stage renal disease. As  
440 doubling of serum creatinine is a surrogate marker of clinical benefit, studies using this as an  
441 outcome measure should carefully collect information regarding progression to end-stage renal  
442 disease as well as in follow-up, to directly document the clinical benefits of the new agent.  
443 Validated changes in GFR can also be used as a measure of disease progression. Other possible  
444 measures that would prospectively predict disease progression should be validated.

445 After a diagnosis of lupus nephritis is established, disease activity is assessed by examination of  
446 the urinary sediment and by measures of renal function. Various measures of remission of lupus  
447 nephritis have been used to define patients with a substantial response to treatment, including  
448 measures of renal function, urinary sediment, and proteinuria. Attainment of remission is  
449 defined in terms of laboratory assessments, and patients with renal remission can be expected to  
450 experience a clinical benefit to the extent that they are: a) spared treatment with potentially toxic  
451 agents; and b) spared from ultimate progression to end-stage renal disease. Sponsors proposing  
452 to use attainment of renal remission to demonstrate efficacy of a product for lupus nephritis are  
453 encouraged to discuss their clinical development plans with the responsible review division at  
454 the agency. Proposals for clinical trials using renal remission as an endpoint would be expected  
455 to: a) provide a clear definition for renal remission and data supporting the choice of that  
456 definition; b) provide evidence that attaining a renal remission would be expected to translate  
457 into a clinical benefit to the patient; c) assess the durability of the renal remissions.

458 An increase in the frequency and severity of flares of lupus nephritis is correlated with  
459 worsening outcomes. Efficacy could be established by a reduction in the number of flares during  
460 a specific time period. Proposals for clinical trials using renal flare as an endpoint would be  
461 expected to: a) provide a clear and accepted definition for renal flare, and data supporting the  
462 choice of that definition; b) provide evidence that reducing renal flare incidence, by that  
463 definition of renal flare, would translate into a clinical benefit to the patient; c) assess the  
464 durability of the renal benefit.

465  
466 Consideration should be given to the use of concurrent medications, including ACE inhibitors  
467 and anti-hypertensive agents, levels of blood pressure, and control of diabetes, for studies of  
468 lupus nephritis. If urinalysis is used as a measure of active inflammation, the investigator should  
469 demonstrate reproducibility and validation of the methods used and the results.

### 470 3. Other organ specific claims:

471 Responder measures for each organ system studied can be proposed, or organ specific measures  
472 from a validated disease activity index can be used. A responder measure of this type has the  
473 advantage of addressing the particular disease manifestations of most concern for individual  
474 patients and might provide a more homogeneous population for analysis. Trials can consist of a  
475 single organ or might involve more than one organ, with stratification by organ. Therefore it may  
476 be possible to study several individual organs within a single trial. The advantage of this  
477 approach is the ability to carry out large clinical trials while maintaining the homogeneity of the

478 population studied. Stratification by extent of organ damage at baseline may be advantageous.  
479 Consider restricting baseline glucocorticoid use to reduce the variability seen in studies that may  
480 introduce bias and make interpretation of results more difficult. Clinically important outcomes  
481 should be defined for each organ system and composite endpoints can be considered. In disease  
482 activity trials, multiple time points should be measured and may improve efficiency of the trial.

483 A successful trial may demonstrate a statistically significant number of clinical remissions in the  
484 treated group vs. the control group. Trends for improvement in each organ system can then be  
485 identified. The interpretation of a clinical trial using this approach could be problematic if  
486 improvement in the organ system measured were counterbalanced by worsening in other  
487 manifestations of lupus. If changes in treatment regimens are required, such as an increase in  
488 immunosuppressive agents, the results in the designated organ might be confounded.

489 For organ-specific trials, 3 to 6-month studies may be appropriate for those therapies considered  
490 remittive (induction therapy), with a longer term follow up for safety and durability of response.  
491 Maintenance therapy studies as short as 1 year can be considered.

492  
493 Appropriate outcome measures in organ specific trials include: 1) maintenance, not worsening  
494 of, disease activity in the designated organ; 2) partial response; 3) complete response, still on  
495 medications; 4) complete remission; 5) flares (time to flare and/or numbers of flares); 6) total  
496 corticosteroid dose (defined as dose at the end of study and AUC). If corticosteroid dose is  
497 chosen as the endpoint, use of flexible dosing vs. forced tapering should be addressed. The  
498 potential need for rescue medication should be addressed in the analysis plan.

499  
500 The organ specific measures, in an organ specific approach, call for additional data, including  
501 disease activity indices, damage indices, HRQOL, patient and physician global assessments, and  
502 toxicities.

503  
504 Clinical trials of new therapies, both organ specific and not, may use add-on studies, or head to  
505 head comparisons with standard of care. Corticosteroids plus cyclophosphamide compared to  
506 corticosteroids plus new drug to demonstrate efficacy is an example. However, careful  
507 determination of baseline disease activity at cohort inception should be accomplished.

### 508 509 **C. Safety trials**

510  
511 Studies to demonstrate the improved safety profile of a new drug compared to standard therapy  
512 can also be considered. These trials should be of adequate duration to establish efficacy as well  
513 as a clinically meaningful benefit in terms of safety. Steroid sparing agents should demonstrate  
514 not only that reduction in steroid use is statistically significant, but also that these reductions  
515 translate into an improved safety profile. Powering a trial to demonstrate improved safety may be  
516 problematic in lupus, although studying a collection of adverse events may help in this regard.  
517 Other trial designs can be considered but it is recommended that these be discussed with the  
518 appropriate reviewing division before initiation.

519

520 **V. SURROGATE MARKERS AS ENDPOINTS**

521 Surrogate or early markers of disease activity to assess efficacy in lupus trials can be considered.  
522 Surrogate endpoints should be proposed and validated for the treatment under study. Approval  
523 can be based on this validated surrogate endpoint. If the surrogate is not validated, but appears  
524 to be associated with a clinical benefit, subpart H or E of 21 CFR Part 314.500 can be invoked  
525 with a phase 4 study to demonstrate the clinical benefit required. Trends toward clinical  
526 improvement that are supported by improvement of the surrogate marker will be considered  
527 during the review process. As an example, early approval can be considered if both a measure of  
528 clinical disease activity as well as a surrogate marker improves. Additional efficacy as well as  
529 safety data can then be collected after approval to support the continued marketing of the  
530 product.

531 Surrogate markers may be laboratory studies involving biological markers or pathological  
532 changes identified in the organ under study. For example, a sustained doubling of serum  
533 creatinine has been proposed as a surrogate marker for the clinically important outcomes of end-  
534 stage renal disease (ESRD), and the need for dialysis or renal transplantation. Validated changes  
535 in creatinine clearance or iothalamate clearance can also be considered as surrogates for ESRD.  
536 Other markers might include, but are not limited to, T and/or B cell profiles, as assessed by flow  
537 cytometry, autoantibody subsets, and immune complexes, which are specifically defined,  
538 presence or absence of procoagulants, complement or its products. “Proof of concept” studies  
539 can be useful to support subsequent designs leading to consideration of approval. Sponsors can  
540 consider measuring the effects of a study drug against the effect of true placebo on T and/or B  
541 cell profiles in short term trials to determine a measure of potential efficacy, possible dose, and  
542 treatment duration for subsequent study in pivotal trials for approval.

543 The ability of the surrogate endpoint to predict clinical outcomes will be weighed against the  
544 risks associated with treatment. Sponsors are urged to consult with the relevant FDA staff before  
545 embarking on a clinical program based on surrogate endpoints.

546

547

548 **VI. RISK-BENEFIT ASSESSMENT**

549 Approval is predicated on controlled evidence demonstrating efficacy and an acceptable risk-  
550 benefit assessment. Assessment of risks and benefits includes an appraisal of the effects of the  
551 product on all aspects of the disease process, including disease activity, irreversible damage due  
552 to SLE and its treatment, and quality of life [ref]. The size of the safety database at approval  
553 should be consistent with the recommendations made by the International Conference on  
554 Harmonisation (ICH), but particular attention should be paid to the assessment of known  
555 toxicities, or to suspected pharmacologic effects that might imply delayed toxicities. The  
556 recommended size of the safety database may be lower for orphan indications, as it may be  
557 impossible or impractical to study large numbers of subjects. Although SLE is not an orphan  
558 indication, there may be subsets of patients with specific manifestations of SLE who represent an

559 orphan population indication. Sponsors may wish to discuss these issues with the appropriate  
560 FDA staff early in the development of a new treatment. Sponsors with questions about the  
561 expected size of the safety database should consult with the appropriate review division for  
562 advice. Finally, if there is concern about rare but serious adverse events (e.g., from the  
563 mechanism of action or experience with similar agents), a phase-4 commitment would be  
564 appropriate to enable additional safety information to be gathered post marketing.

565

## 566 VII LUPUS AND PHARMACOKINETICS

### 567 A. General

568 There have been few pharmacokinetic studies done in a prospective manner in the lupus  
569 population. The bulk of the pharmacokinetic experience in these subjects has been anecdotal in  
570 nature. Patient enrollment in pharmacokinetic studies should reflect the population for which  
571 the drug is intended. As women represent the primary population afflicted with lupus,  
572 enrollment in pharmacokinetic studies should incorporate a preponderance of women. Due to  
573 the multi-symptom and body system nature of lupus, subjects enrolled in pharmacokinetic trials  
574 for lupus should have the organ system involvement to obtain organ specific recommendations.

### 575 B. Special Studies

576

577 A characteristic feature of lupus is the associated change in the kidney, both structurally and  
578 functionally. These kidney changes make it difficult to determine whether the standard renal  
579 transplant model is adequate for the assessment of declining renal function in the lupus patient.  
580 It is recommended that separate pharmacokinetic trials be conducted in lupus patients with  
581 varying degrees of proteinuria to assess the impact on drug disposition and binding.

### 582 C. Drug Interactions

583 Drug interaction trials should be conducted with those agents commonly used in the treatment of  
584 lupus. The potential for interactions with hormonal contraceptives should be assessed. These  
585 assessments can include either in vitro or in vivo methodologies or a combination. The reader is  
586 directed to the published FDA guidance's on in vivo and in vitro drug interaction studies.

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591 <sup>1</sup>FDA Guidance Documents

592 ❖ Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In  
593 Vitro (Issued 4/1997) 

594 ❖ In Vivo Drug Metabolism/Drug Interaction Studies - Study Design, Data Analysis, and  
595 Recommendations for Dosing and Labeling (Issued 11/24/1999)

