

Composite Response

A. From a lupus MD/scientist:

“Congratulations on excellent document” suggestion: Title “Developing Interventions”—Biologics not always considered “drugs”.

B. From a company:

Overall: “Well written and timely, adequately addresses most of the issues that face industry in the development of new agents for lupus”.

I. Major Comments:

Section IV, A: SLE Claims, Reduction in Disease Activity of SLE

The requirement to confirm positive results with 2 disease activity indices (DAI) if a DAI other than BILAG is used appears unwarranted. The other DAIs described in the guidance document have been shown to be sensitive to changes in disease activity and therefore an additional hurdle of confirmation by a second DAI, if these are used, seems unjustified.

If such confirmation by a second DAI is deemed required, it raises a number of issues that would need to be addressed including:

- Would the second DAI need to be a co-primary endpoint?
- Would it be acceptable for the second DAI to be a secondary endpoint?
- Would trends in the second DAI be sufficient confirmation?
- Would adjustment for multiple comparisons (and hence increase in sample size) be required when evaluating 2 DAIs?

Section VI: Surrogate Markers as Endpoints

In this section it is stated that early markers of disease activity can be considered for assessment of efficacy in lupus trials (being particularly useful in Phase 2 studies). Later in the section it states that accelerated approval may be considered using non-validated surrogate markers that are reasonably likely to predict clinical benefit. We would suggest that FDA discuss in the guidance their position on the use of shorter-term evaluation of a clinical benefit endpoint (e.g., improvement in disease activity at 6 months) for accelerated approval, with continued follow-up (e.g., 1 year) of the endpoint in the same trial for confirmation of response durability for full approval. This approach is akin to that routinely used in HIV drug development where HIV viral load at 24 weeks is used for accelerated approval, and 48 week data are provided for confirmation of clinical benefit and full approval.

2. Minor Comments:

Section IV, A: SLE Claims, Reduction in Disease Activity of SLE.

In this section (lines 272-274) it is indicated that evaluation of damage (presumably using the SLICC/ACR Damage Index) be included in any trials to support this claim. In order to use this instrument, exclusion of the evaluations that are not clinically indicated is suggested. For instance, to evaluate some elements, radiological studies would be required and these would be scored only if they were ordered by the investigator. To proceed with this index, the fact that, in clinical practice, studies will only be ordered as clinically indicated should be clarified.

Section IV, B, 4: SLE Claims, Effectiveness in the Treatment of a Specific Organ System Manifestation, Induction of Renal Remission

In lines 385 – 388 it is recommended that follow-up renal biopsies in a subset of patients be obtained in studies using renal remission as an outcome measure.

Although we agree that such data would be valuable, given the concerns regarding patients with inactive urinary sediment possibly progressing to renal failure, practically speaking it will be very difficult to enforce compliance with repeat biopsy unless it is clinically indicated.

C. From an MD/Scientist/Rheumatologist:

Congratulations on this excellent document. Following are suggestions which I would regard as improvements:

1. Title: Developing INTERVENTIONS instead of Drugs: Biologics not always considered drugs.
2. Line 50: No single biological mechanism..... Is a little harsh. Can't think of a manifestation that is not initiated by autoantibodies/immune complexes.
3. line 51 Disease activity scores allow a comparison of disease severity – yes and no. They are not designed for that purpose. I think the comment should be referenced if you are going to retain it (it becomes important later in the document as well), and you should allow for a proposal that combines certain features as a measure of severity – such as DAI, SCLICC and number of ACR criteria present. This is particularly pertinent since you suggest later that patients be stratified by SLICC scores. Weighting of different manifestations of activity becomes important in using DAI for severity, and there is some discomfort with the weighting in certain of the DAIs: 8 points for “lupus headache” for example in SLEDAI and SELENA-SLEDAI.
4. Line 142: Continuing on the same theme as the preceding point, I am a bit uncomfortable stratifying patients at entry by SLICC scores, since so much of SLICC depends on treatment and/or age-influenced outcomes rather than active SLE. If this were done, should one consider only the damages that are likely to be from SLE?
5. Line 165 raises two problems. The first is that WHO VI is not mentioned and should be as correlating with poor outcome. The second, more important, is the apparent blessing that this paragraph and some later give to using WHO classifications and not the newer guidelines published by ASN and everyone else who has anything to do with renal pathology. It seems to me this question should be addressed in the document. Will the FDA require the now outdated WHO classifications, or the new ones, or either one? I favor accepting either one for the current document; we can go to the new ones in the next document after we have an idea of how they perform. You can save yourselves a lot of phone calls if you state here which – or both- you will accept.
6. Line 279. You use the word “both” followed by 3 choices. Delete it.
7. Line 425: “An increased in the frequencyof flares in LN is correlate with worse outcomes..” needs a reference. I can't think of one but there may be several in the renal Rx data. It's such a key point for this whole paragraph that it needs to be solid.
8. Line 516 – We come again to the problem of assessing disease severity. “levels of disease severity be clearly specified”. Would you like to suggest how by

example or suggestion of use of composite measures for general disease and organ-specific function assays for organ-specific? A combo??? I don't think we have a really good measure for disease severity per se and thus a composite may be required, except for organ-specific trials.

9. Lines 625-628 I found confusing. Would it be clearer to state "...standardization of the use of concomitant medications including ACE inhibitors to minimize proteinuria, anti-hypertensives to attain a target blood pressure, and hypoglycemic therapies to attain a target HbA1C? Or do you have in mind limitation to certain drugs in these categories, or certain doses – or stratification by use of drugs in these classes. ? I think to standardize could require use vs non-use during a trial, or targets achieved or not achieved at various points in a trial, or stratification for use of any proteinuria-lowering, anti-hypertensive, anti-diabetes, anti-osteoporosis, preventive antibiotic regimen, etc.
10. Line 647. To make this section current, I recommend this line read "to the extent that cyclophosphamide, mycophenolate mofetil or azathioprine may be effective..." Along this line I reviewed my infusion orders for the past 6 months and found that I have not ordered i.v. cytoxan for SLE a single time in that period. Very different from a year or two ago.
11. Line 659: A blinded extension study is an interesting concept. Do you mean that individuals would continue on placebo for a few years after a study ends? Please clarify. I doubt any IRB would ever permit that, but perhaps IRBs will never participate in postmarketing studies. The newly proposed safety agency of the FDA might not permit it either – should that come to pass.
12. Line 673 – In the title to this I recommend "Surrogate markers or Combinations of Surrogate Markers as Endpoints". You do get to a discussion of combinations late in the paragraph, and I think it would be better upfront. I remain skeptical that we will ever find one surrogate marker for all SLE patients that defines activity. I think the money is in combos – and in anti-DNA plus complement -.
13. Line 697: I recommend you begin the sentence: Changes in creatinine clearance.. with "Sustained changes in creatinine clearance..". This would be consistent with the earlier recommendations.

D. From a lay person—family with lupus nephritis:

Pg 8: ll 324-328 – contradicts pg 7, ll 301-304

Pg 15: 4. extension trials/5. trial duration – too general

E. From an MD/Industry Consultant:

Not a lot of specifics. Not very helpful from a sponsor viewpoint.

