Reviewer’s report

Title: Topical Clobetasol for the Treatment of Toxic Epidermal Necrolysis: Study Protocol for a Phase II Split-Body Randomized Placebo-Controlled Trial

Version: 4  Date: 26 March 2015

Reviewer: Caridad Pontes

Reviewer’s report:

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

Regarding whether the study design will adequately test the hypothesis

1- Blinding: since the assessments are conditioned by the nature of the disease to be mainly subjective assessments of the skin conditions, blinding of study treatment is relevant. However, the fact that corticosteroids produce local vasoconstriction or “blanching” is a well known pharmacodynamic property related to the potency of the compound, and easily perceived by the observed. Actually, blanching has being used for comparison of relative potency of topical corticosteroids and recommended for bioequivalence studies of topical corticosteroids for many years. Thus, despite there is a masking of the organoleptic characteristics of the ointments, the treatment identity will likely be unveiled by the observed blanching effect in the active arm, and thus the study would be probably be conducted under open label conditions.

2- Control: Clobetasol is classified, according to its potency, as a very potent corticosteroid. Also, the product information for clobetasol refers that the compound may be absorbed systemically, specially through diseased skin, and that systemic adverse effects (i.e.: suppression of the adreno-hypophysary axis) may be expected with doses as low as 2g/day. The authors plan to administer doses above this threshold for many days and discuss the acceptability of this dosage form a safety point of view – which is agreed. However, from a efficacy point of view, the potential systemic effects in the contra-lateral control arm derived from the topical administration in the active-treated arm may be leading to relevant confusion in the assessments; the authors discuss this particular briefly in the next to last paragraph, but it is yet a concern regarding the suitability of the study design (i.e: contralateral control).

3- Ethics: since the involvement of children aged 7 or older is foreseen, the specific procedures for consent by representatives and the process for child information and assent should be described. Also, the fact that the disease is severe and often requiring intensive care may condition that some patients may not be able to consent personally until they recover; procedures for consent by representatives and the process for ratification of consent after the subject recovers should also be described.

4– Pediatric patients: The FDA product labeling seems to restrict the use of
clobetasol to children aged 12 and older – since they base their discussion on the treatment safety on the product labeling, the authors should comment on their assessment of risk/benefit for this particular population to be included in the trial.

Regarding whether there are sufficient details provided to allow replication of the work or comparison with related analyses

5- Assessment of the extent of the disease: The assessment of the proportion of the body involved by TEN and the percentage of detached skin are generally described as a percentage of the overall surface body and is a well described variable. However, to use this measures as an efficacy variable for the purpose of the trial, ie: comparing both topical treatments, the authors should describe if they will assess locally in each arm the extent of skin involvement, limited to the percentage of skin involved in each arm. Since TEN starts generally with truncal involvement, and thus they should also describe at entry the percentage of skin involved in the arm. Inclusion criteria should then require bilateral and symmetric involvement of arms, and should require a minimum percentage of skin involved in each arm.

6- Time to reepithelization: the authors plan to assess 90% re-epithelization at several times up to day 15. However, typical acute phase of TEN is 8 to 12 days and time to re-epithelization may last from 2 to 4 weeks. The authors should discuss if the time in follow-up will suffice to their intended assessment.

Regarding whether the planned statistical analysis appropriate

7- Multiplicity: The authors describe a number of secondary contrasts of hypothesis in addition to those of the main study assessment, but there is no description on how they will manage the issues related to multiplicity of analyses for these secondary contrasts.

Regarding whether the writing is acceptable:

8- Redundancy: There is substantial iteration in introduction and discussion; the latter is very extensive and focused on mechanisms of action (i e: paragraphs 1, 2 and 3), rather than on the strenghts and limitations of the study design. Other examples include: redundancy in the description of the methods (ie: last paragraph of introduction and first paragraph of methods, and repetitions within the methods section on the assessments and the details of the treatment – the text can be shortened and made more concise). Inclusion and exclusion criteria are redundant in text and table 2. Description of the skin assessment is redundant in text and table 4. Sections “Clinical studies”, “Primary endpoints” and “secondary endpoints” may be revised in perspective, in order to shorten the manuscript.

9- Subtitles: Section “Statistical analysis of primary and secondary end-points” is not giving details on the analysis of primary end-point.

- Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)
Regarding whether the study design will adequately test the hypothesis

1- Daily skin assessment: There is a mention to avoid wrapping the area close to intravenous access in the antecubital fossa (which may also apply to IV accesses in the forearm or wrist?) which may be non-symmetrical and thus further modify the homogeneity of the treatment and assessments. The authors describe that the assessments will be done daily before treatment and after removing all dressings, but the effect on skin appearance and thus assessments of the previous presence or absence of dressings could be further discussed.

Regarding whether the writing is acceptable:

2- Subtitles: “Clinical studies” may be clearer if referred to “Clinical assessments” or “Clinical measurements”.

3- Clarity: The rationale behind the calculation of exposure and dosing of clobetasol is difficult to follow; an estimate of the amount per surface would be useful to follow the explanation.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare I have no competing interests with the present manuscript.