Reviewer's report

Title: Biomarkers can predict potential clinical responders to DIMS0150 a Toll-Like Receptor 9 agonist in ulcerative colitis patients

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Reviewer: Abdul Elkadri

Reviewer's report:

Interesting manuscript with data on a treatment using a TLR9 agonist. It appears that there is a "re-sensitization" to steroids, or that the steroid responsiveness is established. After reading the manuscript, I am very interested in the upcoming clinical trial.

Major compulsory revisions:

- It is unclear throughout the manuscript what the number of patients included in a particular portion of the study is. From the abstract, 9 steroid refractory patients is stated, but then in results, 34 patients is stated. The abstract has to be re-written to either clarify the fact that there are different portions of the study with each containing different numbers of patients, or the number of patients should be not included in the abstract as it confuses the reader. Throughout the paper, this difference in number hinders the ability to conclude that patients were analyzed in the same way with no selection bias or dropout bias in who was left in a particular portion or experiment.

- In the results, the panel of 34 markers stated to be steroid response genes are given (Table 3). Only IL-6, CD163, TSP-1 and IL-1RII are then used. No mention of what the other 31 markers were found to do is given. I would think it was done and the data could be given in some way in Table 3.

- The first statement of how many patients actually responded and the details were given only in the discussion and not in the results. There should be a paragraph discussing Table 4 and Figure 3 during the results and there should be a clarification of what endpoints were used to evaluate clinical response, or at least a discussion of that point.

- In the methods, no discussion is given to whether patients were on concomitant steroids or not. From the results given in Table 4, 33% of the patients had a response to placebo (saline rectally). I would assume that some of these patients had steroids as well, but no statement is given to this effect. Could the manuscript and analysis not benefit from the exclusion of patients not on steroids? In the introduction, the fact that the lack of steroid resistance or exposure in the larger phase 2 study with three doses used did not find any efficacy is stated as a logical lead up to the current study. Inclusion of these patients is slightly counter-intuitive as currently written.

- From the introduction in the abstract, the statement is given: "steroid refractory subjects". During the introduction, this is defined as steroid dependency with
return of symptoms below 10 mg/day, and resistance as no response with at least 0.75 mg/kg. Some patients were no on steroids at all. 20/22 in treatment, and 11/12. Plus the dose cutoff listed on page 7 line 12 was 5 mg/day. I'm unclear why patients were included when they didn't meet the steroid cutoff level.

-There is no clarification of what other medications were used, including cyclosporine, anti-TNF and ASA.

-Figure 7: It would benefit the graph if the experiment with DIMS0150 and negative Dex was given as well. This was given in Figure 5.

-Figure 6 has circled points which are not defined. These are all points where the pattern of distribution was not followed.

-Page 14, first paragraph: Stated that only those patients that had a clinical response following DIMS0150 treatment experienced sustained clinical response or remission and that it was mucosal healing. No evidence is given to back this up. This should be re-written or removed as it's an interesting conclusion, just not one that follows from the given evidence.

-Page 15, Line 2 and 3: Sentence with “the use of IL-6 circumvents the need for patients to undergo what are otherwise uncomfortable procedures...” should be reworded. The word procedure may be misinterpreted as endoscopic procedure.

-Page 15: Discussion in second paragraph states that there are four markers looked at: IL-6, CD163, TSP-1, IL-1RII. In third paragraph, “Both biomarkers” is unclear as to which biomarkers being referred to. I’d assume IL-6 and CD163, but this paragraph should be re-written.

-A ROC curve was discussed, but only the calculations were given in Table 5. Wouldn't an actual ROC curve help visualize the author's point?

-Table 6 is confusing to me and I'm not sure it clarifies the point being made without clinical data to accompany it. A table summarizing the positive predictive value, negative predictive value etc would probably help. Also, wouldn't it make sense to collapse the number of categories being looked at rather than saying Steroid response, enhancing, and then steroid response AND enhancing with such a small number of patients included in the study? Also, any further comment on N07 and R05? They appear to contradict the model being put forth.

Minor essential revisions:

-Page 21, line 17: An easily drawn instead of easy to draw conclusion.

-Page 7, line 11: First mention of ITT abbreviation, but no definition of what it means. Intention to treat? It shows up in the footnote of Table 4.

-Table 6: n.d=? not done?

Discretionary revisions:

-There may be a benefit from defining the disease activity index a bit more. What components of the DAI were used? Is it the partial Mayo score?

-Page 18, line 8, spelling of prednisolon is European? spelling. Should revise or define the spelling in the body of the manuscript.
Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:

I declare that I have no competing interests