Author's response to reviews

Title: Efficacy and safety of the human anti-IL-1beta monoclonal antibody canakinumab in rheumatoid arthritis: results of a 12-week, phase II, dose-finding study

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Author's response to reviews: see over

Dear Professor John Isaacs

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We are pleased to hear that our manuscript "Efficacy and safety of the human anti-IL-1beta monoclonal antibody canakinumab in rheumatoid arthritis: results of a 12-week, phase II, dose-finding study" has evoked your interest.

We thank you and the reviewers for your valuable comments and suggestions and offer the following explanations, modifications and corrections.

Reviewer's report

Title: Efficacy and safety of the human anti-IL-1beta monoclonal antibody canakinumab in rheumatoid arthritis: results of a 12-week, phase II, dose-finding study

Version: 1 **Date:** 2 January 2011

Reviewer: Andrew Östör

Reviewer's report:

The authors present important, early trial data regarding a novel biologic agent and is important information which contributes to the field. I do have a number of queries/suggetions:

Major Compulsory Revisions

1. Despite prior dose ranging studies the higher doses of canakinumab in this trail were not as good as the lowest dose. This is very surprising and I feel the authors need to try to explain this finding further.

As suggested by reviewer 1 a discussion section with respect to the outcome of the cohort receiving in addition the i.v. loading dose as compared to the 150 mg dose was included in the manuscript on page 14 :
No dose effect was seen in this study and the canakinumab group receiving the additional loading dose did not provide increase in efficacy. Many hypotheses could be put forward, but none are substantiated with data. One, involves differential up or down regulation of receptors or soluble receptors, including type 2 decoy receptors which modulate the action of IL-1β. Certain combinations of

changes in receptors and modulators could change the sensitivity of the system such that over suppression of IL-1β might be counterproductive. Another factor could have played the sample size which might not have been sufficient to detect a dose effect due to the heterogeneity of the RA disease. The study results indicate that there may be only a subgroup of RA patients where IL-1 is driving the disease pathology and who would therefore benefit from anti IL–1β treatment. This may be another reason which could explain equivocal results in terms of dose-response or superiority over placebo, as although the overall size of the groups may have been comparable to other dose-findings trials in RA, each of the arms may have had a different proportion of patients with RA driven by IL-1, and correspondingly their power may have varied to show treatment effect particularly for an IL-1β therapy. It would be of great importance to identify biomarkers for those patients with good response to predict efficacy.

2. The result that no significant difference between any of the canakinumab dosage groups and the placebo group was observed with regard to the ACR70 response rates at 12 weeks is very disappointing. Does this mean that this drug is not particularly effective for RA, this requires exploration in the discussion (see comment below).
In line with the reviewers comment the outcome that no dose effect has been addressed in the manuscript please see answer to reviewers comment point 1.

3. In the discussion the authors state that the patients were suffering from relatively low disease activity however greater than or equal to 6 swollen and tender joints plus a significantly raised inflammatory response is not low disease activity in my practice. The conclusion that this may have had an impact on response magnitude needs to be readdressed.

This is a valid point made by the reviewer and the authors have therefore deleted this statement from the discussion section.

4. I feel the paper would benefit greatly from one to two paragraphs in the discussion regarding the rationale for blocking IL-1 in RA and the fate of anakinra following its use in RA. Perhaps this is not the ideal target for the majority of RA patients but will be best suited to a subset (especially if biomarkers of response are identified).

In line with the reviewers comments one paragraph discussing outcome of anakinra data in RA has been included and the discussion with respect to the importance of detection of biomarkers for patients with a good response has been expanded (see point 1):
“The biological role of IL-1 beta in the disease pathogenesis of RA is not fully understood. Data from anakinra studies suggest that there might be an relatively inferior biological role of IL–1β as compared to TNF-a in the pathogenesis of RA. In a meta-analysis by the cochrane group including 5 randomized trails involving 2876 patients (781 on placebo , 2065 on anakinra) anakinra has been shown to improve symptoms of pain, function and stiffness over a 6 months period as

compared to placebo [5]. Significant improvements were noted for ACR 20 (38% vs 23%) which were considered clinically meaningful, though modest outcome . ACR 50 was reached by 18 % vs 7% and ACR 70 by 7 % vs 2% of patients for Anakinra dose 50-150 as compared to placebo. The ACR 50 rates achieved in our study within 12 weeks in the canakinumab group 150 mg 4 weekly (26% vs 11% canakinumab vs placebo) compares favorable with this outcome reported for anakinra, however further studies will be needed to confirm results."

Minor Essential Revisions

The conclusion should state specifically the dose which was beneficial (150 mg s/c 4 weekly) as in the abstract conclusion.

The 150 mg s.c q4wk dose has been included in the conclusion as suggested.

Reviewer's report

Title: Efficacy and safety of the human anti-IL-1beta monoclonal antibody canakinumab in rheumatoid arthritis: results of a 12-week, phase II, dose-finding study

Version: 1 **Date:** 22 December 2010

Reviewer: Peter Taylor

Reviewer's report:

This study reports the findings of a double blind, placebo-controlled, parallel group study investigating the effects of a mAb with specificity for IL-1beta in patients with active RA despite methotrexate therapy.

Discretionary revisions

1. The puzzling absence of a dose response is rather reminiscent of early anakinra trial data in RA. In particular, the cohort receiving the intravenous loading dose seems to behave very much like placebo treated patients. Although it is stated that pharmacokinetic data will be published elsewhere, it seems reasonable to ask whether there is a pharmacological explanation for this, for example, an increase in clearance associated with intravenous dosing?

At this point we do not understand why the intravenous loading dose gave no greater response than placebo, and why the lowest dose regimen, 150 mg/kg q4w, was the only one that separated statistically from placebo. Other disease types treated with 10 mg/kg, such as Muckle-Wells, did not experience a lesser response than with lower doses such as 1 mg/kg iv or 150 mg sc. In fact, in the

four patients who received 10 mg/kg, disease symptoms and inflammatory mediators were decreased for up to 200 days (compared with 90 days for 1 mg/kg).
The pharmacokinetics of canakinumab are dose proportional whether administered by the intravenous or the subcutaneous route. The bioavailability is about 70% (clinical pharmacology report at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125319s000_ClinPharmR.pdf.). Therefore, we believe that there is no pharmacokinetic explanation for the outcome.

2. Or alternatively, is there any evidence that a subgroup flare after iv canakinumab and that this drives the relatively low response rate at a cohort level?

We did not detect a higher evidence of flare after 2 weeks than at later timepoints, therefore we would not consider that there is a subgroup that flares after iv injection as an explanation for the lack of dose response seen.

3. Was blood sampling for biomarkers undertaken at a consistent time of day to allow for known diurnal variation in biomarkers such as IL-6?

We thank the reviewer for this important question. The time for blood sampling was not specified in the protocol. We have therefore included this information in the method section and included the following part in the discussion section of the manuscript:
"Biomarker panels were taken at baseline and 1 day post treatment, although the panels were large, our current understanding of the biology of RA and technology of assessment did not allow for a successful identification. This may be due to the fact that overall we may have had too few patients with Il-1β driven RA, or that there would be significant diurnal variation in the biomarker results, and as the biomarker samples had been collected during the study visits without a certain requirement for the time of the day, therefore any possible diurnal variation may have further limited the chances to find a predictive biomarker. However, for clinical practice treating physicians would need a robust biomarker, and one depending e.g. too much on diurnal variation may be limited in its usefulness.

Minor essential revisions

4. P12. The sentence given as follows "In the group receiving canakinumab 300 mg SC q2wk, one patient (1.6%) had an ALT #5 times the ULN and an AST #3 times the ULN, and one patient (1.6%) had an ALT #5 times ULN" the latter part of

the sentence appears to have been repeated in error or is it referring to a second patient with an ALT rise exceeding 5 times ULN?.

It is a second patient with ALT elevation exceeding 5 times ULN. To clarify this further the sentence has been changed to: "another patient (1.6%) had an ALT ≥5 times ULN"

5. The baseline Tender and swollen joint counts are missing from the placebo group reported in Table 1.

We would like to thank the reviewer for this comment. The data has been included in Table 1.

Associate editor's comments

I agree with the referees' reports.
1. The discussion needs to be expanded, particularly with comment on the lack of a dose-response in this study.
The discussion has been expanded (see reviewers comment 1)

2. I also agree that the entry joint counts are not especially low, particularly when based on only a 28 joint count –
This is a valid point made by the reviewer and the authors have therefore deleted this statement from the discussion section

3. Why did the investigators choose to base their ACR outcomes on a 28 joint count - although acceptable this is somewhat unorthodox and may reduce the sensitivity of this outcome measure?
As far as the authors are aware there are no comparative studies providing evidence that the 44 joint count provides more sensitivity of this outcome measure. Further research would be beneficial.

Thanks and regards
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