Reviewer’s report

Title: In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494)

Version: 0 Date: 22 Mar 2018

Reviewer: Tue Kragstrup

Reviewer's report:

In this manuscript Parmentier et al describes the in vitro and in vivo effects of the JAK inhibitor upadacitinib. The manuscript is in general well written, the experiments are performed with relevant controls and data interpreted reasonably.

The research question is clear and the study seems important.

Different effects of upadacitinib were tested. 1) in vitro assays including biochemical assessments, engineered cell lines, and cytokine stimulation, 2) In vivo effect in a rat adjuvant induced arthritis model and activity on reticulocyte deployment and circulating NK cells, and 3) ex vivo stimulation with JAK-dependent cytokines in treated healthy volunteers.

Here are my suggestions for the authors:

Major concerns:

1. Tofacitinib is in the manuscript often described as the only approved JAK inhibitor. This is not correct. Please rephrase.

2. Please mention and discuss potential disadvantages with not inhibiting JAK2 and 3 and TYK2.

3. Please mention other JAK1 selective JAK inhibitors in clinical development in the discussion.

Minor concerns:

1. Abstract: Mentioning tocilizumab and no other biologic generic names seems misplaced.

2. Minor grammatical mistakes in the main manuscript. Please proof read.
3. It is difficult to fully understand the results and discussion about potency of upadacitinib. E.g. page 18: "whereas the inhibition of NK cell counts was 5-fold less sensitive than disease activity after upadacitinib administration". Please carefully go through these sections and rephrase.

4. The Results section "In vivo" should have a heading in line with the other section headings (more descriptive). Preferentially the last section describing results from HC whole blood should have its own section heading.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

**Declaration of competing interests**
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?
3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal