Author’s response to reviews

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

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Author’s response to reviews:

5/9/18

Dear Dr. Chu,

Thank you for the response for the review of our manuscript (BRHM-D-18-00020). The authors would like to thank the reviewers for the thorough, thoughtful comments and very helpful suggestions. We have addressed the concerns in the revised manuscript and have responded to
the comments below. Our responses are typed in the space following the original comment marked as “response”. We look forward to hearing from you in due time regarding our revised submission and to respond to any further questions you may have.

Sincerely,

Andrew Long, PhD

Editor Comments:

What statistics methods were used for Figures 2, 3, and 4? These should provide in the methods section.

Response:  Figure 2 was analyzed with a Dunnett’s multiple comparison test. This is indicated in the Methods sections under Statistics heading and in the body of Figure 2b.

No statistics data were provided for Figure 3 and Figure 4.

Response:  Figures 3 and 4 are composite graphs of data from different experiments and analyses. The authors utilized these graphs to illustrate the relative differences of either upadacitinib or tofacitinib between several in vivo endpoints. As such, statistical analysis would be inappropriate as the data is derived from separate experiments reading out distinct endpoints.

Reviewer reports:

Tue Wenzel Kragstrup (Reviewer 1)

Major concerns:

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

Response:  Changes were made as suggested in the abstract, introduction, and discussion. Tofactinib is referred to as the first Jak inhibitor approved for RA.
2. Please mention and discuss potential disadvantages with not inhibiting JAK2 and 3 and TYK2.

Response: A section was added to the discussion to address the balance of inhibition of other JAK isoforms at efficacious concentrations (page 20).

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

Response: Language was added to the discussion section referring to other Jak inhibitor in clinical development for RA (page 16).

Minor concerns:

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

Response: Language was changed to include additional biologic generic names.

2. Minor grammatical mistakes in the main manuscript. Please proof read

Response: Grammatical errors were identified and corrected throughout.

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.

Response: Section was rephrased to more clearly explain the comparisons between tofacitinib and upadacitinib (page 18-19).

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.

Response: The “In vivo” heading was changed to “Upadacitinib spares reticulocyte deployment and NK cell count depletion relative to efficacy” in line with other section headings (page 13). The last section describing results from HC whole blood was separated out into a separate
section with heading with the title of “Upadacitinib spares common gamma chain signaling relative to IL-6 signaling in healthy volunteers” (page 15)

Wen Feng Tan (Reviewer 2):

1. Compared with AIA model, collagen-induced arthritis (CIA) are more identical to human RA. Therefore, it seems more appropriate to expand relevant research in CIA model.

Response: Studies were also performed in the rat CIA model, with comparable results to those seen in the AIA model. Language was added to the results section indicating this (page 13).

2. Figure 2 studied the effect of upadacitinib on bone erosion in AIA. The author only showed the changes of bone volume as assessed by micro CT after upadacitinib treatment. The bone volume only represents the bone mass rather than bone erosion. Did author evaluate AIA histologically?

Response: Histological endpoints were also assessed in AIA studies. Language was added to the results section indicating the results, with reference to data not shown (page 13).

3. Figure 3-4 showed the more safety of upadacitinib on reticulocytes and NK cells naive rats, as compared with tofacitinib. Did author test the drug concentration in these animals? whether could the drug levels in serum affect the safety?

Response: Figure 3 is an exposure-effect analysis where the drug concentrations are plotted on the X axes in Figure 3 as free AUC 0-12 (ng*hr/mL) compared to the effect on the parameter indicated. Figure 3 is used to represent the exposure required to achieve the effect (efficacy, NK cell inhibition, reticulocyte inhibition) comparing upadacitinib and tofacitinib. Figure 4, on the other hand, is the comparison of the effect in the preclinical model (% Inhibition of Paw Swelling) relative to the effect on the measured selectivity parameter (% Inhibition of Reticulocytes or % Inhibition of NK Cell Number).