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LETTER

Authors' Response to Letter to the Editor Regarding Comparative Efficacy of JAK Inhibitors for Moderate-to-Severe Rheumatoid Arthritis: A Network Meta-Analysis

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Dear Editor,

We thank Dr. Fakhouri et al. for their comments on our study. The comments note possible heterogeneity resulting from differences in study designs and patient characteristics among the trials included in our network meta-analysis (NMA), which are limitations common to all meta-analyses. In particular, Dr. Fakhouri raised concerns relating to cross-trial differences in prior exposure to biologic disease-modifying antirheumatic drugs (bDMARDs), number of prior conventional synthetic disease-modifying antirheumatic drug (csDMARD) failures, background dose of methotrexate (MTX), and placebo arm response rates among all the trials included in the network. In this response letter, we will discuss the approaches taken to mitigate and estimate the heterogeneity of trials included in the NMA and introduce supportive evidence to address the concerns raised by Dr. Fakhouri.

To minimize confounding differences between the trial populations in our NMA, the studies included in the NMA were required to meet the pre-defined selection criteria to be eligible for inclusion in the analysis. Specifically, the studies were required to be phase III randomized controlled trials evaluating Janus kinase (JAK) inhibitors among patients who had an inadequate response or were intolerant to at least one csDMARD (csDMARD-IR). In addition, patients were eligible for inclusion if the patient population was naïve to bDMARDs or if no more than 20% of patients in the trial had prior exposure to bDMARDs. These inclusion criteria were selected on the basis of prior publications, health technology assessment reports, and clinical input to reduce the heterogeneity between trials [1–3].

Additionally, a random-effects model was implemented to account for the potential between-trial heterogeneity in treatment contrasts and ensure proper statistical inference under such heterogeneity. The tau heterogeneity parameter, which is the precision parameter of the distribution of the underlying true effects across studies and quantifies the between-trial

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heterogeneity, was summarized from our model results. The posterior median estimate for tau in our random-effects model for American College of Rheumatology (ACR) outcomes is 200.1 for the 12-week network and 61.7 for the 24-week network. While the posterior medians for tau suggest heterogeneous treatment contrasts across studies, such heterogeneity was taken into account in the estimation of the model through the use of the random-effects model.

In regards to the first concern about the inclusion of studies enrolling patients with prior bDMARD exposure, the majority of trials of JAK inhibitors included a small proportion of patients (at most 20%) with prior exposure to bDMARDs. These trials have been widely used in prior indirect comparison studies or health technology assessments among the csDMARD-IR patient population [1–4]. Prior studies have specifically evaluated the impact of including trials with a small proportion of patients with prior bDMARD exposure and found negligible impact on meta-analysis results [1,3,5].

The second concern notes the difference between trials related to the number of prior csDMARD failures experienced by patients at baseline. We agree that the included trials vary in terms of number of prior csDMARD failures. However, we do not believe these differences will have significant impact on response to treatment especially as Kremer et al. note that "the response to baricitinib was similar across levels of disease duration and the number of prior csDMARDs used, suggesting that baricitinib is an equally effective treatment option for patients regardless of their previous treatment experience" [6].

Dr. Fakhouri also noted the potential for bias resulting from including trials with Asian patients, arguing that these patients may be exposed to lower doses of concurrent MTX treatment. To address these concerns, we ran two sensitivity analyses to control for the geographic regions in which the trials took place. First, we excluded trials that were conducted exclusively in Asian countries. This resulted in the exclusion of SELECT-SUNRISE, a phase III randomized controlled trial of upadacitinib conducted in Japan. Placebo-controlled data in SELECT-SUNRISE were available only at 12 weeks because of the trial design [7]. As such, the reported 24-week network is unchanged with the exclusion of SELECT-SUNRISE. The 12-week ACR results for the sensitivity analysis excluding SELECT-SUNRISE are reported in Table 1. Only minor differences in median ACR response rates are observed in the 12-week network, with the efficacy rankings of treatments remaining consistent across ACR20/50/70 and surface under the cumulative ranking curve (SUCRA) outcomes.

An additional sensitivity analysis excluding both SELECT-SUNRISE and RA-BALANCE was run to further provide supportive evidence. RA-BALANCE was a global phase III randomized controlled trial of baricitinib conducted in China, Argentina, and Brazil. ACR results for the sensitivity analysis excluding SELECT-SUNRISE and RA-BALANCE are reported in Table 2. Similarly, this sensitivity analysis resulted in minor numerical differences in the median ACR response rates while the efficacy ranking of treatments in both networks again remained unchanged.

As such, the incremental benefit of including evidence generated from these trials outweighs the potential for bias resulting from the geographic region in which the trials took place.

Finally, our model used an anchor-based approach which subtracts the placebo arm response from the response of the active treatment arm on a probit scale to inform comparisons between active treatments across different trials. To further address concerns regarding the impact of cross-trial differences in reference arm response, we conducted a sensitivity analysis adjusting for reference arm response as a trial-level covariate [8]. The results of the reference arm response-adjusted model are presented in Table 3. Once again, minor numerical differences are observed in the median ACR response rates for both 12-week and 24-week results. In the 24-week network, the efficacy rankings of baricitinib 2 mg + csDMARD and tofacitinib

Table 1 ACR outcomes and SUCRA scores at week 12 in the csDMARD-IR RA population excluding SELECT-SUNRISE

Treatment	Median ACR20% (95% CrI)[a]	Median ACR50% (95% CrI)[a]	Median ACR70% (95% CrI)[a]	SUCRA[b]
Week 12 network[c]				
csDMARD	35.7 (28.7, 43.2)	13.8 (9.9, 18.6)	4.2 (2.7, 6.4)	0.001
JAK combination therapies[d]				
Upadacitinib 15 mg + csDMARD	69.6 (58.9, 78.4)	41.6 (30.8, 52.5)	19.9 (12.8, 28.4)	0.844
Tofacitinib 5 mg + csDMARD	66.6 (56.1, 76.1)	38.4 (28.4, 49.4)	17.7 (11.4, 25.9)	0.663
Baricitinib 2 mg + csDMARD	65.1 (51.9, 76.8)	36.9 (25.0, 50.3)	16.6 (9.5, 26.6)	0.563
Baricitinib 4 mg + csDMARD	64.8 (54.6, 74.0)	36.6 (27.1, 46.8)	16.4 (10.7, 23.8)	0.528
JAK monotherapy therapies[d]				
Upadacitinib 15 mg	66.6 (52.3, 78.7)	38.3 (25.2, 52.8)	17.6 (9.7, 28.7)	0.642
Tofacitinib 5 mg	58.0 (42.6, 72.5)	30.1 (18.1, 45.1)	12.4 (6.1, 22.5)	0.258

ACR American College of Rheumatology, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *csDMARD-IR* inadequate response to csDMARD, *CrI* credible interval, *JAK* Janus kinase, *RA* rheumatoid arthritis, *SUCRA* surface under the cumulative ranking curve

[a] Medians and credible intervals for ACR outcomes were estimated using a random-effects multinomial model. The distribution of means and credible intervals were sampled using Monte Carlo methods (150,000 posterior simulations per treatment after 50,000 burn-in, thinning parameter of 10, and 3 chains)

[b] SUCRA was calculated to assess the overall ranking of each treatment based on ACR20 outcomes. Higher SUCRA values (closer to 1) represent more favorable rankings

[c] As a result of differences in trial design, ACR outcomes were used in the 12-week network if reported between 12 and 14 weeks

[d] JAK combination therapies and monotherapy treatments were analyzed together in the same network for 12-week ACR outcomes

5 mg + csDMARD switch between 3rd and 4th among the JAK combination therapies. Upadacitinib 15 mg + csDMARD remains ranked numerically highest across ACR20/50/70 and SUCRA outcomes in both the 12-week and 24-week networks.

We also calculated the deviance information criterion (DIC) for the reference arm response-adjusted model and compared the DIC with that of the reported model, shown in Table 4. DIC is often considered a measure of model fit, with lower values of DIC suggesting better fit [9]. The DIC for both models were similar, but slightly favor the non-reference arm response-adjusted model reported in the manuscript.

All analyses referenced in this article are based on previously conducted studies and do not contain any studies with human participants or animals performed by any of the authors. No institutional board review was required.

We appreciate the feedback provided by Dr. Fakhouri and the opportunity to further discuss the potential limitations of our study. We

Table 2 ACR outcomes and SUCRA scores at week 12/24 in the csDMARD-IR RA population excluding SELECT-SUNRISE and RA-BALANCE

Treatment	Median ACR20% (95% CrI)[a]	Median ACR50% (95% CrI)[a]	Median ACR70% (95% CrI)[a]	SUCRA[b]
Week 12 network[c]				
csDMARD	36.2 (29.1, 43.8)	14.1 (10.1, 19.0)	4.4 (2.8, 6.6)	0.004
JAK combination therapies[d]				
Upadacitinib 15 mg + csDMARD	69.9 (57.8, 79.5)	42.1 (29.9, 54.1)	20.3 (12.4, 29.9)	0.827
Tofacitinib 5 mg + csDMARD	67.1 (55.7, 77.3)	39.0 (28.1, 51.1)	18.2 (11.3, 27.5)	0.669
Baricitinib 2 mg + csDMARD	65.4 (50.0, 78.5)	37.2 (23.5, 52.6)	17.0 (8.8, 28.7)	0.563
Baricitinib 4 mg + csDMARD	64.8 (52.2, 75.6)	36.6 (25.2, 48.9)	16.6 (9.7, 25.6)	0.514
JAK monotherapy therapies[d]				
Upadacitinib 15 mg	67.0 (50.7, 80.5)	38.9 (24.0, 55.5)	18.1 (9.1, 31.2)	0.642
Tofacitinib 5 mg	58.6 (40.6, 75.3)	30.7 (16.8, 48.6)	12.9 (5.6, 25.4)	0.282
Week 24 network[c]				
csDMARD	35.0 (28.1, 42.6)	18.9 (14.0, 24.8)	7.7 (5.2, 11.1)	0.016
JAK combination therapies				
Upadacitinib 15 mg + csDMARD	69.8 (41.5, 89.2)	50.9 (23.9, 77.1)	30.1 (10.5, 57.9)	0.830
Baricitinib 4 mg + csDMARD	65.3 (43.6, 81.9)	46.0 (25.6, 66.1)	25.9 (11.5, 45.0)	0.676
Tofacitinib 5 mg + csDMARD	62.1 (44.3, 77.8)	42.5 (26.1, 60.6)	23.2 (11.8, 39.2)	0.520
Baricitinib 2 mg + csDMARD	60.4 (32.8, 82.7)	40.8 (17.3, 67.3)	21.9 (6.9, 46.2)	0.458

ACR American College of Rheumatology, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *csDMARD-IR* inadequate response to csDMARD, *CrI* credible interval, *JAK* Janus kinase, *RA* rheumatoid arthritis, *SUCRA* surface under the cumulative ranking curve

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[b] SUCRA was calculated to assess the overall ranking of each treatment based on ACR20 outcomes. Higher SUCRA values (closer to 1) represent more favorable rankings

[c] As a result of differences in trial design, ACR outcomes were used in the 12-week network if reported between 12 and 14 weeks and used in the 24-week network if reported between 24 and 26 weeks

[d] JAK combination therapies and monotherapy treatments were analyzed together in the same network for 12-week ACR outcomes

believe the discussions and additional results reported in this letter support the robustness of the findings in the reported NMA. Ultimately, continued research involving head-to-head randomized trials will be ideal to evaluate comparative efficacy among JAK inhibitors. In the absence of such data, we believe our network meta-analysis provides timely and

Table 3 Reference arm response-adjusted ACR outcomes and SUCRA scores at week 12/24 in the csDMARD-IR RA population

Treatment	Median ACR20% (95% CrI)[a]	Median ACR50% (95% CrI)[a]	Median ACR70% (95% CrI)[a]	SUCRA[b]
Week 12 network[c]				
csDMARD	35.9 (28.9, 43.4)	13.9 (10.0, 18.8)	4.3 (2.7, 6.4)	0.008
JAK combination therapies[d]				
Upadacitinib 15 mg + csDMARD	71.5 (57.6, 82.2)	43.8 (29.7, 57.9)	21.4 (12.1, 33.1)	0.848
Tofacitinib 5 mg + csDMARD	66.4 (49.4, 85.6)	38.3 (23.0, 63.2)	17.5 (8.4, 38.2)	0.657
Baricitinib 2 mg + csDMARD	65.3 (48.0, 79.8)	37.1 (22.0, 54.5)	16.7 (7.9, 29.9)	0.549
Baricitinib 4 mg + csDMARD	64.8 (50.7, 76.6)	36.5 (24.0, 50.1)	16.3 (8.9, 26.3)	0.510
JAK monotherapy therapies[d]				
Upadacitinib 15 mg	66.8 (45.7, 81.9)	38.6 (20.3, 57.4)	17.7 (7.1, 32.6)	0.606
Tofacitinib 5 mg	58.3 (34.9, 82.2)	30.4 (13.3, 58.0)	12.5 (4.0, 33.1)	0.322
Week 24 network[d]				
csDMARD	34.8 (27.9, 42.4)	18.5 (13.7, 24.3)	7.4 (5.0, 10.7)	0.025
JAK combination therapies				
Upadacitinib 15 mg + csDMARD	71.1 (45.3, 88.4)	52.0 (26.7, 75.4)	30.9 (12.1, 55.6)	0.868
Baricitinib 4 mg + csDMARD	66.2 (47.2, 80.5)	46.4 (28.2, 63.8)	26.2 (13.1, 42.2)	0.691
Tofacitinib 5 mg + csDMARD	55.2 (25.4, 85.6)	35.3 (12.1, 71.1)	17.8 (4.3, 50.5)	0.386
Baricitinib 2 mg + csDMARD	62.4 (37.0, 83.0)	42.4 (20.1, 67.2)	23.0 (8.3, 45.9)	0.530

ACR American College of Rheumatology, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *csDMARD-IR* inadequate response to csDMARD, *CrI* credible interval, *JAK* Janus kinase, *RA* rheumatoid arthritis, *SUCRA* surface under the cumulative ranking curve

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[b] SUCRA was calculated to assess the overall ranking of each treatment based on ACR20 outcomes. Higher SUCRA values (closer to 1) represent more favorable rankings

[c] As a result of differences in trial design, ACR outcomes were used in the 12-week network if reported between 12 and 14 weeks and used in the 24-week network if reported between 24 and 26 weeks

[d] JAK combination therapies and monotherapy treatments were analyzed together in the same network for 12-week ACR outcomes

Table 4 Deviance information criterion for reported model and reference arm response-adjusted model

Model	DIC
Week 12 network	
ACR random-effects	441.5
ACR reference arm response-adjusted random-effects	442.7
Week 24 network	
ACR random-effects	325.1
ACR reference arm response-adjusted random-effects	326.4

ACR American College of Rheumatology, *DIC* deviance information criterion

clinically useful evidence in regards to the comparative efficacy among the different JAK inhibitors.

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