



LETTER

A Response to: Letter to the Editor Regarding Long-Term Benefit–Risk Profiles of Treatments for Moderate-to-Severe Plaque Psoriasis: A Network Meta-analysis

April W. Armstrong · Ahmed M. Soliman · Keith A. Betts ·
Yan Wang · Yawen Gao · Vassilis Stakias · Luis Puig

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We thank the journal for the opportunity to respond to the letter to the editor regarding “Long-Term Benefit–Risk Profiles of Treatments for Moderate-to-Severe Plaque Psoriasis: A Network Meta-Analysis” [1]. The analyses reported in Armstrong et al. [2] and Shear et al. [3] were conducted following a rigorous and well-accepted methodology. Therefore, the authors believe that the conclusion that risankizumab was associated with the most favorable long-

term benefit–risk profile is well supported by the analyses and the results.

Pettitt et al. suggest that the analysis based on the Surface Under the Cumulative Ranking (SUCRA) score does not support the benefit–risk profile summarized in our conclusion. However, this approach is well in line with prevailing methodological conventions applied in other recently published network meta-analyses (NMAs) that also described the benefit–risk profiles of psoriasis treatments [4, 5]. For example, the NMAs by the British Association of Dermatologists used the bidimensional SUCRA plot to cluster treatments into high vs. low efficacy and high vs. low tolerability [4]; similar interpretations were given to the bidimensional SUCRA plots in the Cochrane systematic review of systemic treatments for psoriasis [5]. These examples used SUCRA for efficacy and safety outcomes to characterize the benefit–risk profiles of psoriasis treatments. Additionally, the novel approach developed by Mavridis et al. (a method suggested by Pettitt et al.) is an extension of the bidimensional SUCRA plots in the present study [6]. Moreover, Salanti et al. [7] examined multiple ranking metrics for NMAs and concluded that the SUCRA score is the proper metric to address the treatment hierarchy question of “*which treatment has the largest fraction of competitors that it beats*”. To summarize, our methodology to compare the benefit–risk profile of treatments using SUCRA is well

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A. W. Armstrong (✉)
Department of Dermatology, Keck School of
Medicine, University of Southern California, Health
Sciences Campus, HC4 2000 1450 San Pablo, Los
Angeles, CA 90033, USA
e-mail: armstrongpublication@gmail.com

A. M. Soliman
AbbVie, Inc., 1 N. Waukegan Road, North Chicago,
IL 60064, USA

K. A. Betts · Y. Wang · Y. Gao
Analysis Group, Inc., 333 South Hope Street 27th
Floor, Los Angeles, CA 90071, USA

V. Stakias
AbbVie, Inc., 26525 N. Riverwoods Blvd, Mettawa,
IL 60045, USA

L. Puig
Department of Dermatology, IIB SANTPAU,
Hospital de la Santa Creu i Sant Pau, Universitat
Autònoma de Barcelona, Carrer de Sant Quintí, 89,
08041 Barcelona, Spain

established and is in line with prevailing methodological conventions [4, 5, 7].

Moreover, although SUCRA is agnostic to the magnitude of treatment effects, Armstrong et al. [2] also identified and reported many clinically meaningful, statistically significant contrasts based on the rates of Psoriasis Area and Severity Index (PASI) response and any adverse event (AE) across treatments. Both outcomes are well established, commonly used for assessing the efficacy and safety of psoriasis treatments. Detailed results have been reported in the original publication. Briefly, as summarized in Table 1, risankizumab is significantly superior to all other included treatments in either or both of long-term efficacy and long-term safety. Specifically, compared with brodalumab, guselkumab, ixekizumab, secukinumab, ustekinumab, adalimumab, and etanercept, risankizumab has statistically significantly higher PASI response rates by week 48–56. Risankizumab

also has a statistically significantly lower rate of any AE compared with secukinumab, ustekinumab, and bimekizumab by week 48–56. These results are consistent with and augment the superiority of risankizumab over other treatments based on SUCRA. Additionally, while Pettitt et al. mention that the treatment-specific PASI response rates and safety event rates have overlapped credible intervals (CrIs), these estimates are correlated, and thus overlapped CrIs do not necessarily translate to high uncertainty for their joint distribution or statistically insignificant contrasts between treatments. A formal assessment based on odds ratios had been reported in Armstrong et al. (2022), which informs whether the contrast between a pair of treatments is statistically significant [2].

Pettitt et al. further suggest that random-effects models or meta-regression models should be used instead. At the same time, they admit that such models are not possible for the sparse networks in this study. Because applying a random-effects model to sparse networks would generate unreasonably wide CrIs, using the random-effects model in this study would not be in line with the recommendation by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group: “reviewers conducting NMAs who believe that the common between-study heterogeneity across comparisons is unrealistic, or that it cannot be estimated reliably in their sparse networks—and that it is causing some network estimates to have CIs much wider than appears sensible—may reasonably assume that such between-study heterogeneity across comparisons is zero by conducting the NMA using fixed rather than random effects models—if, that is, results make more intuitive sense than those of random effect models” [8]. Additionally, for sparse networks, meta-regression models would produce statistically insignificant coefficients for adjusted covariates, which would then not support such adjustment. Armstrong et al. (2022) had transparently acknowledged that the sparsity of the networks precludes the use of random-effects or meta-regression models, making the adjustment for heterogeneities infeasible [2].

Table 1 Summary of statistical comparisons (pairwise odds ratios) of risankizumab versus other treatments in terms of PASI response rates and any AE rates in the long term (Tables 2 and 3 and Supplementary Table 2 in Armstrong et al. [2])

| Treatments | PASI response rates (week 48–56) | |
|--|--|--|
| | Risankizumab significantly superior to | Risankizumab statistically comparable to |
| Any AE (week 48–56) | | |
| Risankizumab significantly safer than | SEC, UST | BKZ |
| Risankizumab statistically comparable to | GUS, ADA, IXE | – |
| Other treatments without safety data | BRO, ETA | – |

ADA adalimumab, AE adverse event, BKZ bimekizumab, BRO brodalumab, ETA etanercept, GUS guselkumab, IXE ixekizumab, PASI Psoriasis Area and Severity Index, SEC secukinumab, UST ustekinumab

We agree with Pettitt et al. that an open dialogue about the standards for conducting and interpreting NMA would be useful. Overall, the interpretations of meta-analyses by Armstrong et al. [2] and Shear et al. [3] are based on rigorous and accepted methodology also used by professional dermatology societies such as the British Association of Dermatologists and the Cochrane group.

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Compliance with ethics guidelines. This article is based on previously conducted studies.

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