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LETTER

Letter to the Editor Regarding 'Matching-Adjusted Indirect Comparison of the Long-Term Efficacy Maintenance and Adverse Event Rates of Lebrikizumab Versus Dupilumab in Moderate-to-Severe Atopic Dermatitis'

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Dear Editor,

We read with interest the article by Rand et al. [1], reporting the results of a matching-adjusted indirect comparison (MAIC) between dupilumab and lebrikizumab maintenance therapy for patients with moderate-to-severe atopic dermatitis (AD). The authors used individual patient data from the ADvocate 1 and 2 lebrikizumab trials maintenance phase (NCT04146363 and NCT04178967) [2] and aggregate data from the SOLO-CONTINUE dupilumab trial (NCT02395133) [3]. However, several methodological issues challenge the appropriateness and thus robustness of the analyses published in Rand et al. [1].

First, anchored comparison is the more appropriate method and should be favored over the unanchored approach for indirect treatment comparison (ITC) as recommended by Health Technology Assessment agencies like NICE [4] and by the ISPOR task force [5]. The benefit of conducting an ITC on the relative effect is well established, and the protection from bias achieved by patient randomization in a clinical trial should be preserved for ITC purposes to ensure that imbalance of prognostic factors does not bias the analysis. Unanchored ITC is correctly regarded as the last resort, where there is no possibility to anchor the comparison.

The choice of an unanchored MAIC approach in Rand et al. [1] was based on the rationale that the placebo arms were unsuitable for comparison because of prior treatment with dupilumab or lebrikizumab for 16 weeks in these two similarly designed trials. However, based on their pharmacokinetic profiles, no active substance would be detectable 36 weeks after the withdrawal of either drug. Consequently, placebo data could and should have been employed for anchoring to facilitate the

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ITC. For example, using a simple and widely accepted Bucher ITC approach [6], the placebo-corrected treatment effects for dupilumab versus lebrikizumab are numerically in favor of dupilumab for both outcomes reported: Eczema Area and Severity Index (EASI)-75 and Investigator Global Assessment (IGA) 0/1.

Applying the Bucher ITC method to the EASI-75 results for dupilumab and placebo, as well as the results for lebrikizumab and placebo, using similar non-responder imputation (NRI) from respective sources ([3], Table 2; [2], Table S4), we find consistent results for the following comparisons with odds ratios (OR) numerically favoring dupilumab:

- Dupilumab weekly (QW)/twice a week (Q2W) versus lebrikizumab Q2W (OR 3.78, 95% confidence interval [CI] 1.05–13.61)
- Dupilumab QW/Q2W versus lebrikizumab Q4W (OR 3.22, 95% CI 0.90–11.57)
- Dupilumab Q4W versus lebrikizumab Q4W (OR 1.79, 95% CI 0.47–6.82)

Theses analyses of EASI-75 show ORs that are significantly in favor of dupilumab QW/Q2W compared with lebrikizumab Q2W, as indicated by a positive OR and a CI that excludes 1; scenarios comparing dupilumab QW/Q2W or Q4W with lebrikizumab Q4W found numerically higher OR.

Utilizing the published IGA 0/1 results using NRI from both sources in the Bucher ITC analysis reveals a similar pattern, with all scenarios reporting ORs that numerically favor dupilumab:

- Dupilumab QW/Q2W versus lebrikizumab Q2W (OR 3.27, 95% CI 0.34–31.54)
- Dupilumab QW/Q2W versus lebrikizumab Q4W(OR 2.35, 95% CI 0.24–22.53)
- Dupilumab Q4W versus lebrikizumab Q4W (OR 1.56, 95% CI 0.15–16.07)

Second, both studies are similar in study design, except for intermittent use of topical anti-inflammatory therapy that was permitted during the ADvocate 1 and 2 maintenance period, but not in SOLO-CONTINUE, which was a strict monotherapy trial where patients who used topical therapies were considered non-responders. Topical therapy can significantly improve efficacy outcomes and was used in up to 18.3% of patients in the ADvocate 1 and 2 trials, [2]. It is not clear whether these patients were considered non-responders in Rand et al. [1].

Third, the dupilumab maintenance baseline values (n, %) for EASI-75 (116, 71.6%) and IGA 0/1 (68, 54%) shown in Table 1 of Rand et al. [1] are wrong; the correct values are EASI-75 (162, 95.9%) and IGA 0/1 (129, 76.3%) [3]. The use of incorrect baseline data calls into question the results of the entire analysis, as the MAIC analysis is meant to be employed for correcting the imbalances between trials in patients' characteristics at baseline.

Fourth, based on the data in Table 2 in Rand et al. [1], we note that baseline differences remain, raising issues as to how the prognostic factors/effect modifiers were identified, included, and weighted by Rand et al. in their model. It is possible that the weighting may not have been conducted appropriately or may have omitted some important prognostic factors.

In conclusion, there are significant methodological flaws in the analysis by Rand et al. [1], rendering the results unsuitable for decision-making. A re-evaluation employing an anchored approach would provide a more accurate picture concerning the relative efficacy of dupilumab and lebrikizumab. Using a simple and widely accepted anchored Bucher ITC approach showed that the probability of maintaining EASI-75 and IGA 0/1 is higher in patients treated with dupilumab versus lebrikizumab across all dose comparisons.

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Declarations

Conflict of interest. Mike Bastian: Sanofi—employee and may hold stock and/or stock options in the company; Nick Freemantle: grants from the National Institute for Health and Care Research, the Medical Research Council, Cure Parkinson's Trust, and the European Union, consultancy fees from ALK, Sanofi Aventis, Gedeon Richter, Abbott, Galderma, AstraZeneca, Ipsen, Vertex, Thea, Novo Nordisk, Aimmune, and Ipsen, and honorarium from Abbott Singapore; Ana B Rossi: Sanofi—employee and may hold stock and/or stock options in the company; Brad Shumel: Regeneron—employee and shareholder; Gaelle Bego Le Bagousse: Sanofi—employee and may hold stock and/or stock options in the company; Zhixiao Wang: Regeneron—employee and shareholder; Yingxin Xu: Regeneron—employee and shareholder; Patricia Guyot: Sanofi—employee and may hold stock and/or stock options in the company.

Ethical Approval. This letter is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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