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Commentary (Author Response) to Correspondence entitled "Importance of Angioedema-free Days in Patients with Chronic Idiopathic/Spontaneous Urticaria"

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Motivated by the manuscript of Zazzali et. al.¹ my editorial² was intended to elaborate on the possibility of having conflicting conclusions concerning clinical significance versus statistical significance. I would like to thank the authors for their constructive letter³ in support of clinical significance of the effects of omalizumab on angioedema in patients with chronic idiopathic/spontaneous urticaria. The statistical significance of the collective primary outcome differences in patients treated with an active intervention compared against a control is often assessed in terms of the difference in the outcome means for the treatments. Interpretation of the statistical significance of this difference may be obscured by inherent variability in individual responses, irrespective of the magnitude of treatment effectiveness. On the other hand, even when the active intervention has no effect whatsoever and a well-designed randomization plan has been used to assign patients to either active or control, it is possible to find by chance statistical significance. Following traditional statistical procedures, a p-value is calculated, under the assumption that there is no active treatment effect and the means are in fact identical, to estimate the probability of obtaining a difference in means at least as large as the observed difference. Small differences are expected to yield large p-values and large differences are expected to yield small p-values. However, large differences are expected to be rare if there is no active effect and the underlying "population" means are identical. Thus, experimental results that yield small p-values cast doubt on the assumption of identical means used in calculating the p-value. Typically, differences that yield p-values that are less than or equal to 0.05 are defined to be statistically significant. However, as noted in my editorial², differences that are statistically significant are not necessarily clinically significant. For example, if the samples are comprised of large numbers of patients or the variability among patient responses is very small, observed differences that are not clinically significant may be deemed statistically significant.³ The point of my editorial was not to "advise the readers on the importance of sufficiently large sample size in randomized clinical trials to ensure the outcomes are captured appropriately", but rather to caution against reporting statistical significance

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without discussing clinical significance. Although clinical and statistical significance are both important, it is my view that investigators often rely too heavily on the statistical significance of their findings and fail to fully develop a discussion of clinical relevance.

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