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Response to: 'Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria: a critical appraisal'

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Durack and Matin¹ have written a critical appraisal of our article² and we appreciate the opportunity to respond to their concerns regarding our study methodology. We would like to thank the authors for their thorough evaluation of our phase 3 study of omalizumab in patients with chronic idiopathic urticaria or chronic spontaneous urticaria (CIU/CSU) and appreciate their bringing this analysis to the attention of a dermatology audience.

With regard to the exclusion of German participants < 18 years of age, German health authorities do not allow the participation of adolescents in phase 3 studies unless the study drug is being used for an approved indication. However, there are data from adolescents from other countries that would allow for generalization to the German adolescent population.

Regarding the concerns raised regarding eligibility, recruitment and assessment during the screening period, the Study Design section of the article indicates the length of the screening period (14 days before randomization, and two visits conducted at day –14 and day –7 to assess eligibility). During screening, patients had to have an in-clinic physician-assessed Urticaria Activity Score (UAS) ≥ 4 on one of the screening-visit days, had to use an approved dose of an H₁-antihistamine for the treatment of CIU/CSU for at least three consecutive days immediately before day –14, and had to complete an electronic symptom diary (eDiary) twice daily throughout the screening period to establish the patient's UAS over 7 days (UAS7). Patients were eligible for inclusion in the study if they had no missing eDiary entries in the 7 days before randomization, to ensure accurate capture of the severity of disease. All patients were recruited from specialty and/or research centres.

Use of H₁-antihistamines and other medications for CIU/CSU before enrolment was collected as part of the patient-reported history during screening.

Concerns were raised regarding the randomization and medications used before enrolment. The authors are confident that the Interactive Voice and Web Response System (IxRS) used to randomize patients successfully distributed patients evenly across the four treatment groups. Please note that patients who were enrolled in the trial may not have received immunosuppressants or steroids for 30 days before the first day of screening. The differences in medication before enrolment were not stratified; however, we did evaluate previous

and concomitant use of CIU/CSU medication in patients treated with omalizumab 300 mg in another phase 3 study³ that demonstrated similar efficacy across patient subgroups with different previous concomitant use.

An additional concern was raised by Durack and Matin that the study blinding could have been inadvertently broken by unblinded clinicians caring for the study patients. As in protocol sections 4.2 and 4.3, the placebo had the same ingredients as the omalizumab formulation (with the exception of omalizumab) and all drugs were shipped to study centres in a blinded fashion. The study drug was reconstituted at each site by an unblinded pharmacist (or other qualified designee), who had no contact with the patient. The study drug was administered by an individual who was not involved in patient evaluation, and treatment allocation remained blinded. Other than the unblinded pharmacist, only the IxRS provider, the sponsor's unblinding statistician and the independent data coordinating centre statistician had access to the unblinding code during the study.

Durack and Matin also point out that a modified intention-to-treat (mITT) population was used for our evaluations and that the acceptability of the mode of drug administration may have been an issue. We would like to note that there was only one patient from the total enrolled population excluded from the mITT analysis. This patient withdrew before receiving study treatment because she had a history of serum sickness.

With regard to external validity, we have addressed limitations to the study in our article.² However, the study population was reflective of the known epidemiology of patients with CIU/CSU. A pooled analysis of this study and its sister studies from the phase 3 programme has been planned and should provide more robust data for patient subgroups.

While our study found the mean $\pm$ SD time since CIU/CSU diagnosis to be 6.5 $\pm$ 8.6 years, the median time was 3.3 years (range 0.5–66.5), which is consistent with the cited general persistence of the disease of 1–5 years.⁴

As Durack and Matin have noted, six patients randomized to omalizumab 75 mg received more than one dose of omalizumab 150 mg and were therefore included in the omalizumab 150-mg group in the safety and pharmacokinetic evaluable populations. These patients were included in the omalizumab 75-mg group for the efficacy analyses as stated in the Statistical Analysis section.

The timing of protocol changes on ClinicalTrials.gov was also highlighted. The protocol and statistical analysis plan for this study, which are available online at *The New England Journal of Medicine* (<http://www.nejm.org/>), detail the amendment and timing of amendment to the protocol. In sum, the protocol was revised once on 11 January 2011, based on feedback from the U.S. Food and Drug Administration, internal Genen-

tech, Inc. staff and external experts. This revision occurred before the start of the study (the first patient entered on 10 March 2011). The outcomes reported in our article were consistent with the predesignated outcomes in the final protocol for the study.

We remain confident that we appropriately minimized bias in our study and have provided results that are generalizable to the populations represented. Future planned pooled analyses examining efficacy and safety in subgroups of patients should provide additional data for consideration.

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