Dupilumab efficacy and safety in patients with asthma and blood eosinophils ⩾500 cells·μL^{-1}

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To the Editor:

Uncontrolled, moderate-to-severe asthma in patients with high baseline blood eosinophils (⩾500 cells·μL^{-1}) can be difficult to treat [1]. Global Initiative for Asthma guidelines recommend biologics as add-on therapy for patients with severe type 2 inflammatory asthma that remains uncontrolled despite treatment with high-dose inhaled corticosteroids [2]. Surrogate markers of type 2 inflammation, such as elevated levels of blood or sputum eosinophils and fractional exhaled nitric oxide (F_{eNO}) can be used to identify patients with a type 2 signature who might be eligible for such treatment [1–3]. Several biologics are now available that target different molecules in type 2 inflammatory pathways, notably IgE and type 2 cytokines [1–3]. One of these, dupilumab, is a fully human VelocImmune-derived [4, 5] monoclonal antibody that blocks the shared receptor component for interleukin-4 and -13, cytokines that are key and central drivers of type 2 inflammation in multiple diseases, thus inhibiting their signalling [6, 7].

In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab 200 mg and 300 mg every 2 weeks *versus* matched placebo significantly reduced severe asthma exacerbations and improved pre-bronchodilator forced expiratory volume in 1 s (FEV_1) in the overall population of patients with uncontrolled, moderate-to-severe asthma [8]. In this, and other studies, the magnitude of these benefits was greater in subgroups of patients with a type 2 signature (eosinophils ⩾150 or ⩾300 cells·μL^{-1}, and/or F_{eNO} ⩾25 ppb or ⩾50 ppb) [8–12]. Asthma control, assessed using the patient-reported 5-item Asthma Control Questionnaire (ACQ-5), was also significantly improved with dupilumab *versus* placebo in patients with elevated baseline eosinophil counts [10]. Moreover, dupilumab is effective in lowering biomarkers of type 2 inflammation in both the airway (F_{eNO}) and blood compartments (serum thymus and activation-regulated chemokine and serum IgE) [8, 10, 11]. However, the efficacy and safety of dupilumab in patients with high eosinophil levels (⩾500 cells·μL^{-1}) is not well understood.

In this *post hoc* analysis, we assessed the efficacy of dupilumab in patients enrolled in QUEST who had baseline blood eosinophils ⩾500 cells·μL^{-1}. QUEST was a phase 3, randomised, controlled trial that evaluated the efficacy and safety of dupilumab in patients aged ⩾12 years with uncontrolled, moderate-to-severe asthma [8]. QUEST was open to patients irrespective of minimum baseline blood eosinophil count or any other biomarker requirement. Patients were randomised 2:2:1:1 to receive 52 weeks of add-on therapy with subcutaneous dupilumab at a dose of 200 mg or 300 mg every 2 weeks or a matched-volume placebo (1.14 mL or 2.00 mL, respectively) for each active dose. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guideline and was approved by local institutional review boards or ethics committees. All patients provided written informed consent before participating in the trial.

The efficacy endpoints in this analysis were the annualised severe exacerbation rate over the treatment period, mean change from baseline in pre-bronchodilator FEV_1 over time, and change from baseline at week 52 in ACQ-5 score in the subgroup of patients with baseline blood eosinophils ⩾500 cells·μL^{-1}. Annualised severe exacerbation rates were determined using a negative binomial model. Least squares mean change from baseline in pre-bronchodilator FEV_1 and ACQ-5 values were derived from a linear mixed-effect model with repeated measures. Spline regression analyses were performed on the overall

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Dupilumab is well tolerated and improves clinical outcomes in patients with asthma and high eosinophils (⩾500 cells·μL^{-1}). Improvements in clinical outcomes correlate with eosinophil counts, demonstrating dupilumab efficacy in those with high eosinophils. https://bit.ly/3Jxvicb

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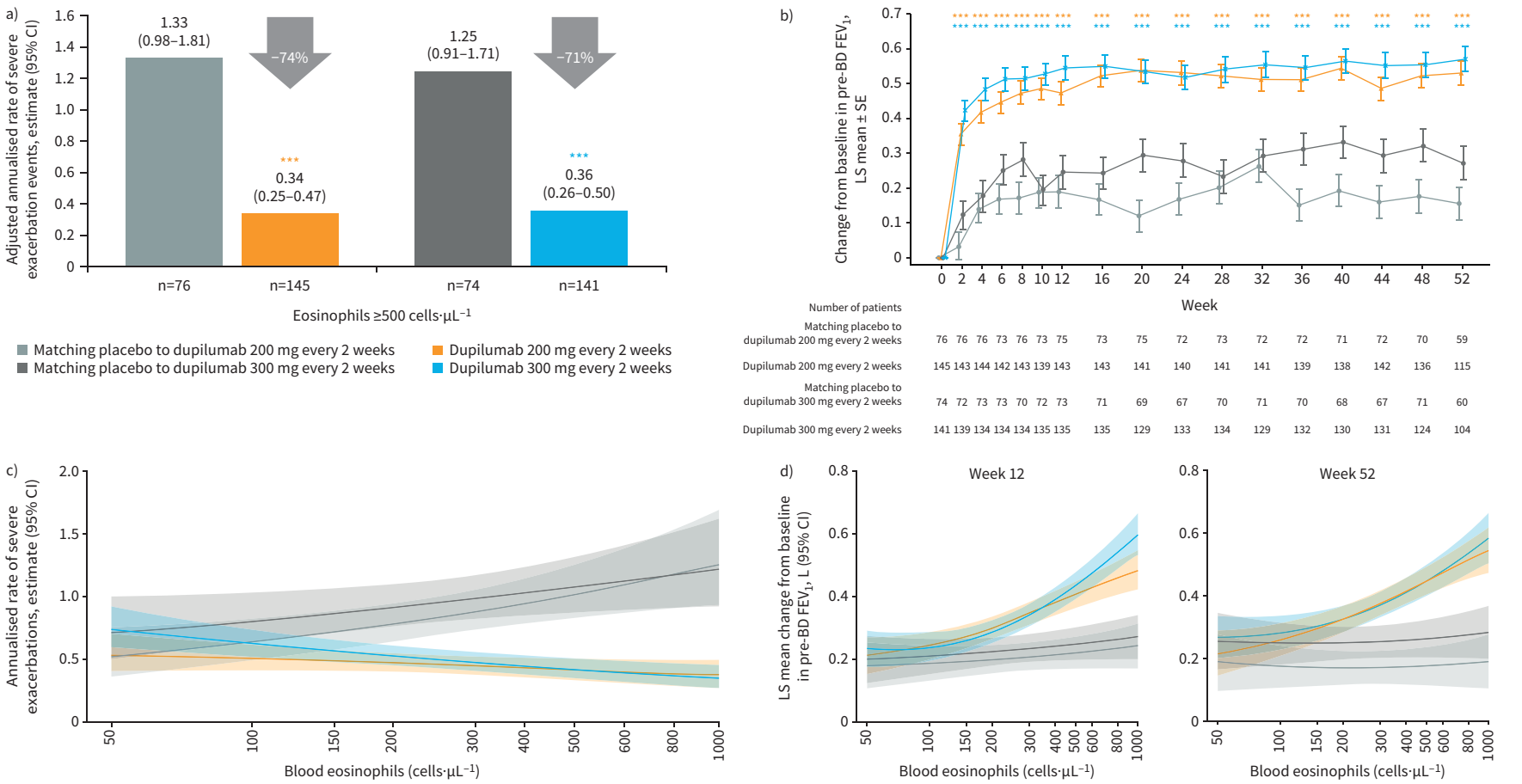

FIGURE 1 a) Annualised severe exacerbation rates over the treatment period and b) least squares (LS) mean change from baseline in pre-bronchodilator (pre-BD) forced expiratory volume in 1 s (FEV_1) over time in patients with blood eosinophils ⩾500 cells·μL^{-1} at baseline. c) Annualised severe exacerbation rates and d) LS mean change from baseline in pre-BD FEV_1 in the overall intention-to-treat population by baseline eosinophil count. ***: p<0.001.

intention-to-treat (ITT) population of QUEST to assess the effects of treatment by baseline eosinophil count on annualised severe exacerbation rates and change from baseline in pre-bronchodilator FEV_1 at weeks 12 and 52.

The ITT population of QUEST comprised 1902 patients. Of these, 436 (23%) had baseline eosinophil counts $\geqslant$500 cells·μL^{-1} (145 randomised to dupilumab 200 mg every 2 weeks, 76 to placebo matched to dupilumab 200 mg, 141 to dupilumab 300 mg every 2 weeks and 74 to placebo matched to dupilumab 300 mg). Baseline demographics and clinical characteristics were comparable across the four treatment groups. The mean age of the patients ranged from 46.0 to 49.0 years across treatment groups, and 48.7%–63.1% were female. The mean number of severe exacerbations experienced in the previous year ranged from 2.3 to 2.6, baseline pre-bronchodilator FEV_1 from 1.70 to 1.72 L and ACQ-5 scores from 2.7 to 2.8 across treatment groups. Baseline median levels (interquartile range) of blood eosinophils and baseline F_{eNO} across treatment groups ranged from 690.0 (600.0–950.0) to 795.0 (630.0–1030.0) cells·μL^{-1} and from 35.0 (22.0–61.5) to 42.5 (29.0–72.5) ppb, respectively, indicative of, and confirming, the type 2 signature of the patients.

In patients with blood eosinophils $\geqslant$500 cells·μL^{-1} at baseline, dupilumab 200 mg and 300 mg every 2 weeks *versus* placebo significantly reduced severe exacerbations by 74% and 71%, respectively (both $p<0.0001$ *versus* matched placebo) (figure 1a), and improved pre-bronchodilator FEV_1 at week 52 by 0.37 L (95% CI 0.26–0.49) and 0.30 L (95% CI 0.18–0.42), respectively (both $p<0.0001$). As described in other dupilumab studies [8–12], improvements in FEV_1 were rapid, with significant differences *versus* placebo achieved as early as at the first evaluation at week 2 and were then sustained throughout the 52-week treatment period for both doses (both $p<0.0001$ *versus* matched placebo at all timepoints) (figure 1b). Spline regression analyses revealed that, for both dupilumab doses, the estimated rate of severe exacerbations decreased and improvements in pre-bronchodilator FEV_1 at weeks 12 and 52 increased with increasing levels of baseline blood eosinophils (figure 1c and d). Asthma control, as assessed using the ACQ-5, was also significantly improved at week 52 *versus* placebo (least squares mean change from baseline −0.59 (95% CI −0.88 to −0.30) and −0.62 (95% CI −0.92 to −0.33), respectively; $p<0.0001$ *versus* matched placebo), achieving the minimal clinically important difference of 0.5 [13] for both doses.

The incidence of adverse events was similar across dupilumab- and placebo-treated patients with uncontrolled moderate-to-severe asthma with blood eosinophils $\geqslant$500 cells·μL^{-1} at baseline. The most common treatment-emergent adverse events reported overall in these patients were viral upper respiratory tract infection (20.2%), injection-site reactions (20.0%), upper respiratory tract infection (12.8%) and bronchitis (12.2%). In patients with blood eosinophils $\geqslant$500 cells·μL^{-1}, on-treatment eosinophilia (defined as >3000 cells·μL^{-1}) was reported by 10.3% and 9.2% of patients receiving 200 and 300 mg dupilumab, respectively, and by <3% of patients in the matching placebo groups. Elevated eosinophils and clinical symptoms were not correlated; one of the 28 dupilumab-treated patients with eosinophilia developed eosinophilic granulomatosis with polyangiitis.

Patients with asthma with high blood eosinophil counts experience more severe exacerbations and have poorer asthma control; moreover, this relationship is continuous and linear with asthma outcomes worsening progressively with increasing baseline eosinophil count [14]. Findings from spline regression analyses concur with the literature, showing that dupilumab benefits increase with increasing baseline eosinophil concentration. Alongside previous data showing that the magnitudes of improvements in exacerbation rates, lung function and asthma control with dupilumab treatment *versus* placebo are greater in patients with a type 2 signature [8–12], the data presented here suggest that dupilumab may provide the greatest benefit to patients with a high type 2 signature, though results should be interpreted with caution as this was a *post hoc* analysis. Despite this limitation, the data also suggest that baseline eosinophil count has clinical utility in guiding treatment by identifying the patients who could benefit most from dupilumab treatment.

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This clinical trial was prospectively registered at ClinicalTrials.gov with identifier NCT02414854. Qualified researchers may request access to patient level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan and dataset specifications. Patient level data will be anonymised, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: http://www.clinicalstudydatarequest.com/

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