Impact of baseline patient characteristics on dupilumab efficacy in type 2 asthma

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To the Editor:

Severe asthma affects an estimated 5–10% of the total asthma patient population [1]. Various demographic factors, such as sex, age, obesity and age of onset, have been associated with asthma disease severity [2, 3], and the efficacy of asthma treatments has previously been found to vary depending on patient demographics [4, 5].

Approximately 50% of asthma patients are affected by type 2 inflammatory asthma, characterised by increased production of interleukin (IL)-4, IL-5 and IL-13 [6]. Dupilumab, a fully human VelocImmune-derived monoclonal antibody [7, 8], blocks the shared receptor component for IL-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases [9]. In the European Union, dupilumab is indicated as an add-on maintenance treatment in patients aged ⩾12 years with severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fractional exhaled nitric oxide (F_{eNO}) that is inadequately controlled with high-dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment [10–12]. In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab 200 mg or 300 mg every 2 weeks, *versus* placebo, significantly reduced severe asthma exacerbations, improved pre-bronchodilator forced expiratory volume in 1 s (FEV_1), and was generally well tolerated in the overall population of patients with uncontrolled, moderate-to-severe asthma. Treatment effects were greater in patients with elevated type 2 biomarkers at baseline (blood eosinophils or F_{eNO}) [11].

In this non-prespecified *post hoc* analysis of the phase 3 QUEST study, we assessed efficacy of dupilumab in the population of patients with elevated baseline type 2 biomarker levels (blood eosinophils ⩾150 cells·μL^{-1} and/or F_{eNO} ⩾20 ppb), and stratified them into subgroups by demographic and disease characteristics at baseline (gender, geographical region, body mass index, age, age at asthma onset, medication use, pre-bronchodilator FEV_1, number of severe asthma exacerbations in the year before study start, smoking history, blood eosinophil levels, F_{eNO} levels) to evaluate whether the response to dupilumab was affected by these characteristics. Patients were randomised 2:2:1:1 to receive add-on subcutaneous dupilumab 200 mg or 300 mg or matched-volume placebo every 2 weeks for 52 weeks. Injections were administered during patient study visits until week 12 and could be administered by patients and/or caregivers later. Full details of the study design and methodology have been reported previously [11]. Annualised rate of severe exacerbations during the 52-week treatment period was analysed using negative binomial regression models, with the total number of events occurring during the observation period as the response variable; and treatment group, age, region, baseline eosinophil strata, baseline ICS dose level, number of severe exacerbation events within 1 year prior to the study, subgroup (demographic or disease characteristic if different than the aforementioned) and treatment by subgroup interaction as covariates. Least squares mean change from baseline in pre-bronchodilator FEV_1 at week 12 was assessed using mixed-effects models with repeated measures. The model included change from baseline in pre-bronchodilator FEV_1 values up to week 12 as response variable; and treatment group, age, patient sex and height, region, baseline eosinophil strata, baseline ICS dose level, visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV_1 value, baseline-by-visit interaction, subgroup (demographic or disease characteristic if different than the aforementioned covariates), subgroup-by-treatment interaction, and subgroup-by-treatment-by-visit interaction as covariates.

Shareable abstract (@ERSpublications)
Dupilumab treatment *versus* placebo improved exacerbation rate and lung function outcomes in patients with uncontrolled moderate-to-severe asthma and high type 2 biomarkers at baseline, regardless of baseline characteristics in the phase 3 QUEST study https://bit.ly/3yR7MlD

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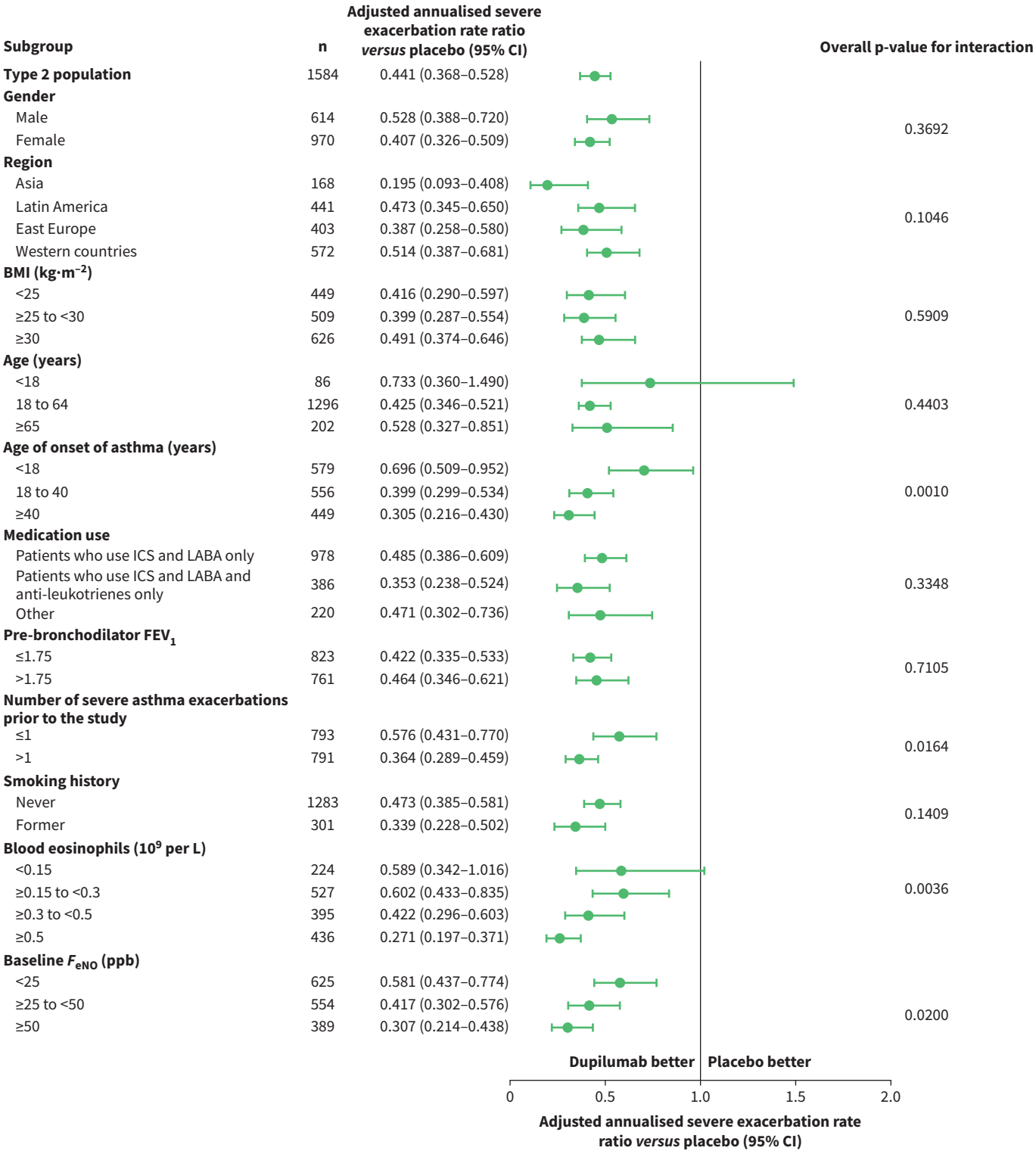

FIGURE 1 a) Adjusted annualised severe exacerbation rate.

Of the 1902 patients randomised in the study, 1584 (dupilumab: 1040; placebo: 544) had baseline blood eosinophils $\geqslant 150$ cells·μL^{-1} or F_{eNO} $\geqslant 20$ ppb. Among these patients, demographic and disease characteristics at study initiation were comparable between treatment groups.

Subgroup	n	LS mean difference *versus* placebo, L (95% CI)	Overall p-value for interaction
Type 2 population	1533	0.15 (0.11–0.19)	
Gender			
Male	593	0.18 (0.11–0.26)	0.2200
Female	940	0.13 (0.09–0.18)	
Region			
Asia	166	0.26 (0.13–0.39)	
Latin America	434	0.15 (0.07–0.23)	0.4345
East Europe	385	0.15 (0.07–0.24)	
Western countries	548	0.12 (0.06–0.19)	
BMI (kg·m^{-2})			
<25	434	0.20 (0.11–0.28)	
≥25 to <30	496	0.13 (0.05–0.20)	0.2687
≥30	603	0.12 (0.07–0.18)	
Age (years)			
<18	83	0.33 (0.14–0.52)	
18 to 64	1255	0.15 (0.11–0.20)	0.1241
≥65	195	0.07 (–0.02–0.16)	
Age of onset of asthma (years)			
<18	562	0.11 (0.04–0.18)	
18 to 40	535	0.17 (0.11–0.24)	0.4261
≥40	436	0.16 (0.09–0.23)	
Medication use			
Patients who use ICS and LABA only	944	0.14 (0.09–0.19)	
Patients who use ICS and LABA and anti-leukotrienes only	376	0.17 (0.09–0.25)	0.8094
Other	213	0.14 (0.03–0.24)	
Pre-bronchodilator FEV_1			
≤1.75	800	0.17 (0.11–0.22)	0.3689
>1.75	733	0.13 (0.07–0.19)	
Number of severe asthma exacerbations prior to the study group 1			
≤1	767	0.11 (0.05–0.17)	0.0920
>1	766	0.19 (0.13–0.24)	
Smoking history			
Never	1244	0.15 (0.11–0.20)	0.6126
Former	289	0.13 (0.04–0.22)	
Blood eosinophils (10^9 per L)			
<0.15	219	0.09 (–0.02–0.20)	
≥0.15 to <0.3	507	0.05 (–0.02–0.12)	0.0002
≥0.3 to <0.5	379	0.17 (0.09–0.25)	
≥0.5	426	0.29 (0.21–0.37)	
Baseline F_{eNO} (ppb)			
<25	610	0.04 (–0.02–0.09)	
≥25 to <50	538	0.15 (0.09–0.22)	< 0.0001
≥50	369	0.35 (0.26–0.44)	

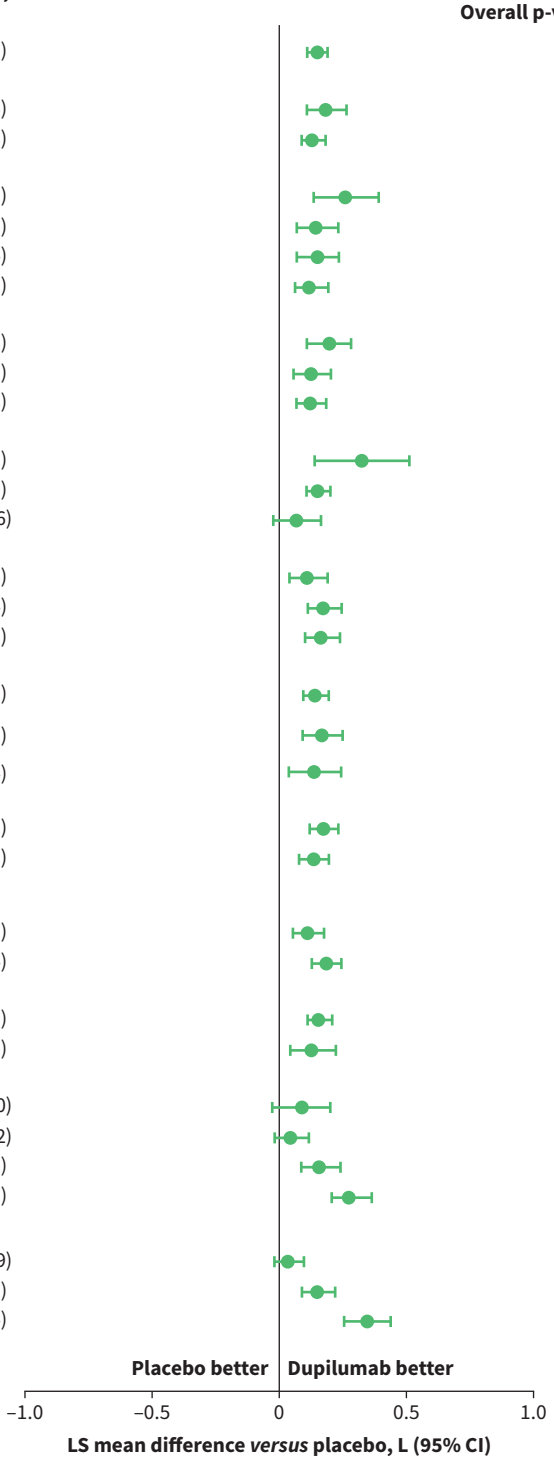

FIGURE 1 b) Least squares (LS) mean difference in the change in pre-bronchodilator forced expiratory volume in 1 s (FEV_1) from baseline at week 12 between dupilumab and placebo by baseline patient demographic and disease characteristic subgroup. BMI: body mass index; F_{eNO}: fractional exhaled nitric oxide; ICS: inhaled corticosteroids; LABA: long-acting β2-agonists; ppb: parts per billion.

Dupilumab *versus* placebo reduced the annualised rate of severe exacerbations, irrespective of demographic or disease characteristics at baseline (figure 1a). In general, efficacy of dupilumab was comparable between demographic and disease characteristic subgroups. Dupilumab efficacy was greater in patients with >1

exacerbation in the year prior to study initiation (p=0.0164), and age at asthma onset >18 years (p=0.0010). Dupilumab had a greater treatment effect in patients with higher baseline blood eosinophil concentrations (p=0.0036) and F_{eNO} levels (p=0.0200) in line with previous observations [11].

In this *post hoc* analysis, dupilumab improved pre-bronchodilator FEV_1 12 weeks after treatment initiation in all demographic and disease characteristic subgroups examined (figure 1b). No significant treatment-by-subgroup interactions were detected, with the exception of baseline blood eosinophil concentration (p=0.0002) and F_{eNO} levels (p<0.0001), suggesting a comparable treatment benefit for all patients, irrespective of their demographic or disease characteristics.

Our findings suggest that in this population of patients with elevated type 2 biomarkers at baseline, dupilumab reduced the annualised rate of severe exacerbations and improved pre-bronchodilator FEV_1 consistently across most patient demographic and disease characteristics at baseline. This included patients with differing gender, geographical region, body mass index, age, age at asthma onset, medication use, pre-bronchodilator FEV_1, number of severe asthma exacerbations in the year before study start, smoking history, blood eosinophil levels, and F_{eNO} levels. Previous studies have found the efficacy of some asthma treatments to vary depending on patient demographics, for example age and age of asthma onset, with limited efficacy observed in patients with asthma onset <18 years [4, 5]. Although patients with differing age at asthma onset and exacerbation history showed variations in the degree to which the exacerbation rate was reduced, dupilumab was efficacious in reducing severe exacerbations *versus* placebo in all demographic and disease characteristic subgroups evaluated, including those in whom asthma started before age 18 years. Benefits of dupilumab on patient lung function were not impacted by demographic and disease characteristics. Taken together, these findings add to the body of knowledge guiding treatment decisions for asthma patients. Current EAACI guidelines recommend the use of dupilumab as an add-on treatment for adult and adolescent patients with severe uncontrolled asthma with a type 2 phenotype [13–15]. This analysis supports these recommendations, demonstrating that dupilumab treatment is efficacious in all patients with moderate-to-severe, type 2 asthma, regardless of demographics or disease characteristics.

In conclusion, the response to dupilumab treatment in patients with uncontrolled, moderate-to-severe, type 2 asthma was unaffected by patient demographic or disease characteristics at baseline.

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Conflict of interest: W.W. Busse is a consultant for AstraZeneca, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, Inc. and Sanofi; and is on the data safety monitoring board for Boston Scientific. P. Paggiaro received research grants and is an advisory board member for AstraZeneca, Chiesi, GlaxoSmithKline, Novartis and Sanofi. X. Muñoz is a speaker, scientific advisor for and has received clinical trial investigator fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Faes Farma, GlaxoSmithKline, Menarini, Mundipharma, Novartis and Teva. T.B. Casale received research support from American Lung Association, Genentech, NIH, Novartis, PCORI and Sanofi; is a consultant for AstraZeneca, Boehringer Ingelheim, Genentech, Novartis and Regeneron Pharmaceuticals, Inc.; is on the speakers bureau of Genentech. M. Castro received research support from American Lung Association, AstraZeneca, GlaxoSmithKline, NIH, Novartis, PCORI, Pulmatrix, sanofi-aventis and Shionogi; is a

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References

1 Chung KF, Wenzel SE, Brozek JL, *et al.* International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014; 43: 343–373.
2 Zein JG, Denson JL, Wechsler ME. Asthma over the adult life course: gender and hormonal influences. *Clin Chest Med* 2019; 40: 149–161.
3 Khalid F, Holguin F. A review of obesity and asthma across the life span. *J Asthma* 2018; 55: 1286–1300.
4 Harrison TW, Chanez P, Menzella F, *et al.* Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial. *Lancet Respir Med* 2021; 9: 260–274.
5 Sposato B, Scalese M, Latorre M, *et al.* Effects of omalizumab in severe asthmatics across ages: a real life Italian experience. *Respir Med* 2016; 119: 141–149.
6 Fahy JV. Type 2 inflammation in asthma—present in most, absent in many. *Nat Rev Immunol* 2015; 15: 57–65.
7 Macdonald LE, Karow M, Stevens S, *et al.* Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc Natl Acad Sci USA* 2014; 111: 5147–5152.
8 Murphy AJ, Macdonald LE, Stevens S, *et al.* Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. *Proc Natl Acad Sci USA* 2014; 111: 5153–5158.
9 Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. *Expert Rev Clin Immunol* 2017; 13: 425–437.
10 Wenzel S, Castro M, Corren J, *et al.* Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet* 2016; 388: 31–44.
11 Castro M, Corren J, Pavord ID, *et al.* Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018; 378: 2486–2496.
12 Rabe KF, Nair P, Brusselle G, *et al.* Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018; 378: 2475–2485.
13 Agache I, Akdis CA, Akdis M, *et al.* EAACI Biologicals Guidelines-Recommendations for severe asthma. *Allergy* 2021; 76: 14–44.
14 Agache I, Song Y, Rocha C, *et al.* Efficacy and safety of treatment with dupilumab for severe asthma: a systematic review of the EAACI guidelines-Recommendations on the use of biologicals in severe asthma. *Allergy* 2020; 75: 1058–1068.
15 Doroudchi A, Pathria M, Modena BD. Asthma biologics: comparing trial designs, patient cohorts and study results. *Ann Allergy Asthma Immunol* 2020; 124: 44–56.