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Dupilumab improves asthma outcomes irrespective of frequency of previous asthma exacerbation history



Lack of control of moderate-to-severe asthma results in a substantial disease burden and poor quality of life for affected patients and represents a significant unmet clinical need.¹

Dupilumab is a fully human monoclonal antibody inhibiting the signaling of interleukin (IL)-4 and IL-13, key drivers of inflammation in type 2 inflammatory diseases such as asthma, allergic rhinitis, atopic dermatitis, and food allergies—conditions that frequently manifest as comorbidities²—and is approved in the United States for patients aged 12 years or older with moderate-to-severe eosinophilic or oral corticosteroid-dependent asthma^{3–5} and for the treatment of adults with inadequately controlled moderate-to-severe atopic dermatitis in several countries.^{6–8} In a pivotal, placebo-controlled, phase 2b study of uncontrolled persistent asthma in 769 adults without restrictions for absolute eosinophil count as an inclusion or exclusion criterion (NCT01854047), dupilumab administered subcutaneously at doses of 200 mg or 300 mg every 2 weeks or every 4 weeks with medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 -agonist (ICS+LABA) improved lung function, as measured by the forced expiratory volume in 1 second (FEV₁), reduced annualized rates of severe asthma exacerbation, improved asthma control and measures of asthma-related quality of life, and was generally well tolerated.³

Asthma exacerbation history, particularly number of recent exacerbations, is considered a significant independent predictor of future exacerbation risk,⁹ and frequent exacerbations (defined as a deterioration of asthma requiring use of systemic corticosteroids for ≥ 3 days, or hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids and confirmed by chart review) tend to be associated with poorer lung function, worse asthma control, and greater use of high-dose ICS+LABA.³ Other factors associated with frequent exacerbations include blood eosinophil count, bronchodilator responsiveness, body mass index, and comorbid chronic rhinosinusitis and gastroesophageal reflux disease.¹⁰

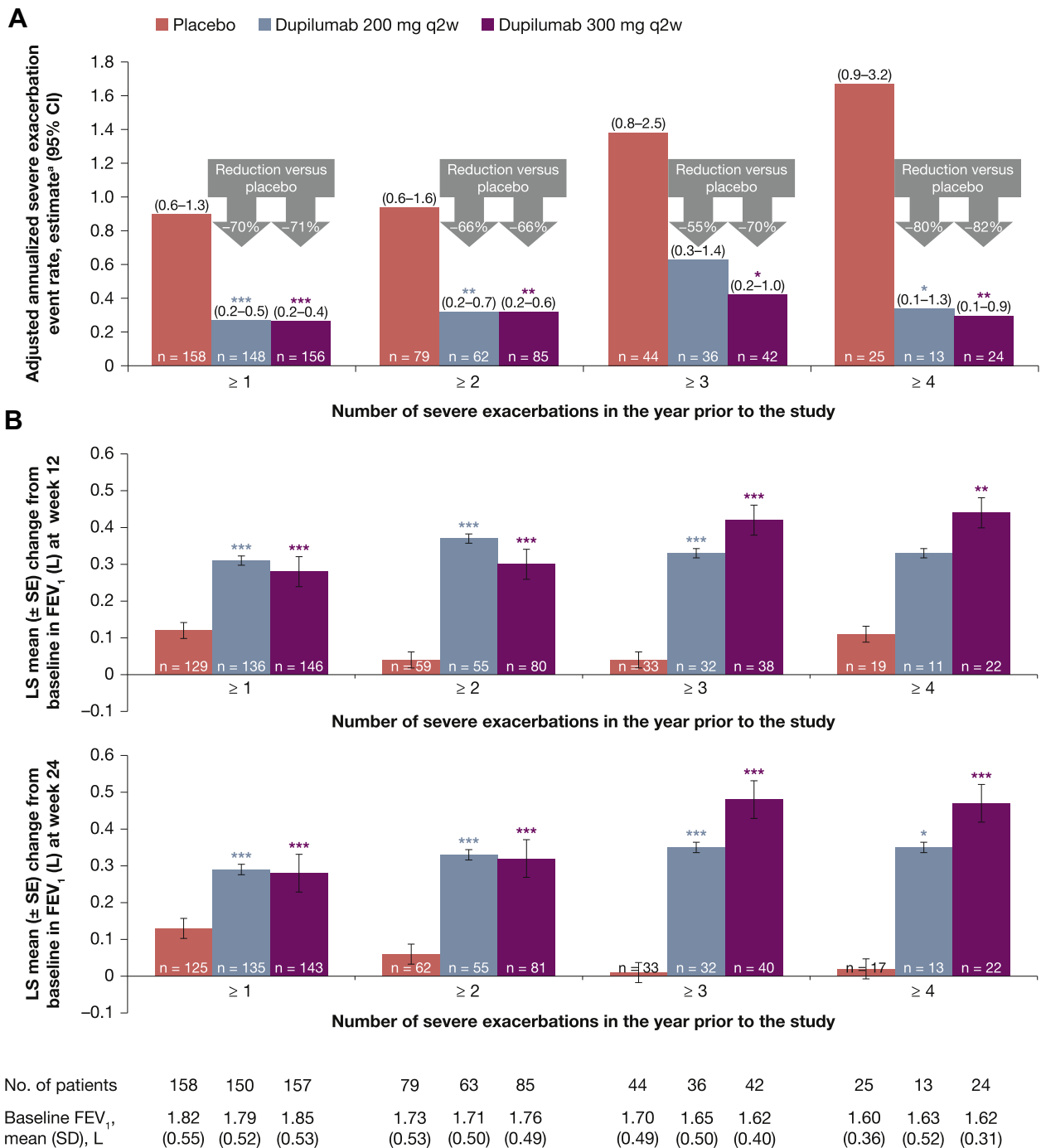
This post hoc analysis of the phase 2b asthma study (NCT01854047) assessed the effects of dupilumab (200 mg or 300 mg every 2 weeks), compared with placebo, on annualized rates of

severe asthma exacerbations, changes in lung function, asthma control, and quality of life in patients categorized by the number of exacerbations they had experienced in the year before study entry. In the study, 465 patients had had 1 or more exacerbations; 227, 2 or more; 122, 3 or more; and 62, 4 or more. The highest number of exacerbations in the year prior to the study was 20 in the overall study population, 20 in the placebo group, 15 in the dupilumab 300 mg group, and 12 in the dupilumab 200 mg group. The annualized rate of severe exacerbations during the 24-week treatment period was derived from a negative binomial model. Change from baseline in lung function, measured by FEV₁ at weeks 12 and 24, was analyzed using a mixed-effects model with a repeated-measures approach to determine least squares (LS) mean and standard error (SE), as previously described.⁷ Asthma control was assessed using the 5-item Asthma Control Questionnaire (ACQ-5), and patient-reported quality of life was assessed with the Asthma Quality of Life Questionnaire (AQLQ); again, a mixed-effects repeated-measures model was used to determine the LS mean ($\pm$ SE).⁴ Because this was an exploratory analysis, no attempt was made to control for type I errors. Safety was also evaluated across subgroups by using adverse event reports and laboratory assessments.

Treatment with either dose of dupilumab significantly reduced the annualized rate of severe exacerbations to a similar extent ($P < .05$ vs placebo), with greatest treatment effect observed in patients with the highest number of exacerbations in the previous year (Fig 1A). In patients receiving placebo, the number of exacerbations during the study increased with the number of historical exacerbations during the previous year (Fig 1A). Treatment with dupilumab 200 mg and 300 mg every 2 weeks dose regimens significantly improved FEV₁ at weeks 12 and 24 ($P < .05$ vs placebo) in all patients, except at week 12 in patients who received dupilumab 200 mg every 2 weeks and had experienced 4 or more exacerbations in the previous year ($P = .1227$; Fig 1B). In patients receiving dupilumab, the higher the number of prior exacerbations, the greater the improvement observed. In the placebo group, however, the higher the number of exacerbations in the previous year, the lesser were the improvements in FEV₁. At week 24, all patients receiving dupilumab experienced significantly improved asthma control ($P < .05$ vs placebo). The largest improvements in asthma control occurred in patients who had experienced the highest numbers of exacerbations in the previous year (eFig 1). Findings were similar for asthma-related quality of life; LS mean changes in AQLQ scores from baseline to week 24 showed improvement with both dupilumab regimens in all patients. Again, improvements increased with the number of prior exacerbations, particularly in patients receiving the higher dose of dupilumab (eFig 1). In the overall study population, dupilumab was well tolerated at either dose during the study; the incidence of treatment-emergent adverse events was similar across treatment groups and independent of exacerbation history.

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* $P < .05$; ** $P < .01$; *** $P < .001$ vs placebo.

^aEstimate derived using negative binomial model with the total number of events onset between first dose date and last dose date + 14 days as the response variable; treatment, baseline eosinophil strata, pooled countries/regions, and number of asthma events prior to the study as covariates; and log-transformed standardized treatment duration as an offset variable.

Figure 1. Effect of dupilumab on the annualized severe exacerbation rate (A) and FEV₁ (L) (B) according to the history of exacerbations in the year prior to the study. Differences in the patient subgroup numbers exist because of censoring/dropout at week 12. CI, confidence interval; FEV₁, forced expiratory volume in 1 second; LS, least squares; q2w, every 2 weeks; SD, standard deviation, SE, standard error.

To conclude, our results show that dupilumab significantly reduced the rate of severe asthma exacerbations and improved lung function, asthma control, and quality of life in patients with uncontrolled, persistent, moderate-to-severe asthma, regardless of their exacerbation frequency in the previous year. Treatment effects tended to be better with higher number of exacerbations in the

year before the study. This analysis was limited in that it is a retrospective analysis using data from only a small number of patients. Analysis of a larger data set should confirm the present findings that systemic immunomodulatory therapy with dupilumab every 2 weeks may be beneficial for patients with poorly controlled asthma, irrespective of severity.

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Supplementary Data

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Occupational asthma, rhinitis, contact dermatitis, and severe milk allergy caused by primary occupational exposure to casein



Respiratory allergy to milk proteins, including casein, remains rare in adults, and only a few case reports have been made in the context of occupational allergy.^{1,2} Moreover, casein is not listed as a substance that can cause occupational asthma.³

We report a case of occupational asthma, rhinitis, contact dermatitis, and severe milk allergy that started in adult life from occupational exposure.

A 22-year microbiology laboratory worker developed sneezing, watering eyes, cough, wheeze, chest tightness, and flushing within 5 minutes of exposure to culture media powder, despite wearing a basic dust mask. This happened on a weekly basis while preparing the culture medium. He began experiencing these symptoms 12 months after starting the job, and they took 12 hours to improve. He also reported worsening nasal congestion and chest tightness during the week, improving over the weekend and resolving completely on holidays.

Six months later, he developed allergic reactions after eating cheese and milk chocolate, developing generalized urticaria, lip swelling, abdominal pain, cough, and wheezing. This required admissions to the emergency department, where he was treated with

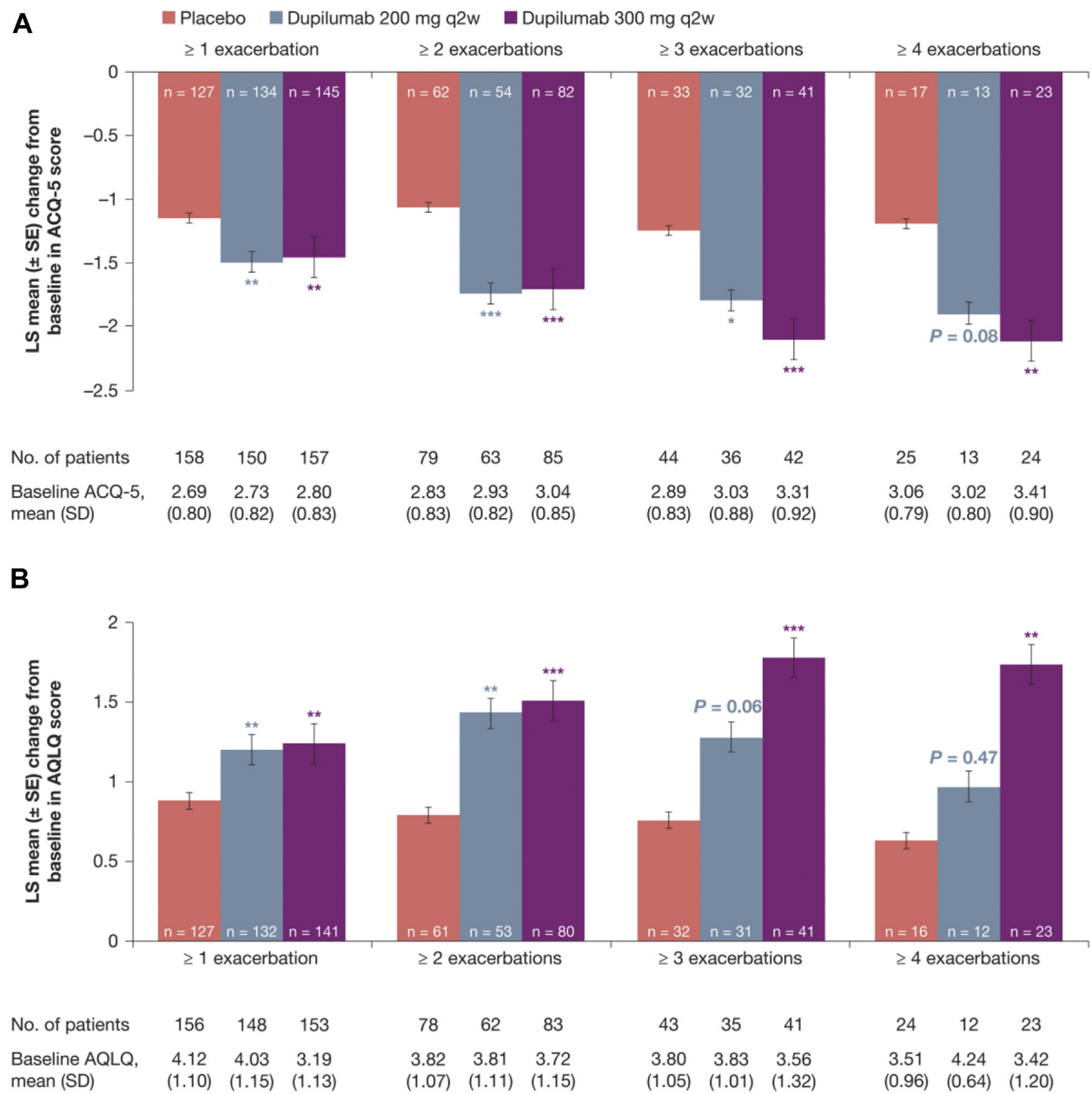
antihistamine, inhaled and systemic steroids, and intravenous fluids. Until this time, he was able to consume milk and milk products without any adverse reaction.

He also had episodes of acute allergic contact dermatitis whilst wearing latex gloves (Triflex, Baxter) with a clearly demarcated area of erythema under the glove. These latex gloves contain casein as a stabilizer.

He had no medical history of asthma, hay fever, or eczema.

CT-SMAC (0157 media powder) contains casein and is used in procedures for selective and differential isolation of Shiga toxin-producing *Escherichia coli* serotype O157:H7 from stool specimens. This powder can plume into the air when being mixed, easily coming into contact with mucous membranes, or be inhaled.⁴

Skin prick tests (SPT) to a standard panel of aeroallergens and latex were negative. The SPTs to milk proteins (raw and boiled milk, cheddar cheese) and to culture media containing casein were strongly positive (Table 1), whereas SPT to these reagents (containing casein) in 7 healthy negative control subjects were all negative. Specific immunoglobulin E (IgE; ISAC ImmunoCAP, Thermo Scientific, Uppsala, Sweden) to casein was elevated, and other milk proteins were negative (Table 1). Results of his routine spirometry were normal. Peak expiratory flow (PEF) variability was



* $P < .05$; ** $P < .01$; *** $P < .001$ vs placebo.

eFigure 1. Effect of dupilumab on the least squares (LS) mean difference in ACQ-5 score (A) and AQLQ score (B), by history of exacerbations in the year before the study. ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; q2w, every 2 weeks; SD, standard deviation; SE, standard error.