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Dupilumab efficacy in adolescents with uncontrolled, moderate-to-severe asthma: LIBERTY ASTHMA QUEST

To the Editor,

Asthma prevalence has increased globally among adolescents in recent years, yet this population remains understudied.[1] Dupilumab, a fully human VelocImmune®-derived monoclonal antibody,[2,3] blocks the shared receptor component for interleukin (IL)-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases.[4,5] In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab 200/300 mg every 2 weeks vs placebo significantly reduced severe asthma exacerbations and improved pre-bronchodilator forced expiratory volume in 1 second (FEV_1) in patients with uncontrolled, moderate-to-severe asthma. Treatment effects were greater in patients with elevated type 2 biomarkers at baseline.[6]

This post hoc analysis of QUEST assessed the efficacy of dupilumab in adolescent patients aged 12–17 years compared with adults aged ≥18 years. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline and approved by local institutional review boards or ethics committees. All patients provided written informed consent before participating in the trial. Prespecified endpoints were changed from baseline in pre-bronchodilator FEV_1 and annualized severe exacerbation rate (AER). Changes from baseline were assessed post hoc for post-bronchodilator FEV_1, percentage predicted FEV_1 ($ppFEV_1$), Asthma Control Questionnaire (ACQ-5) response, fractional exhaled nitric oxide (FeNO) levels, blood eosinophil counts, and serum total immunoglobulin E (IgE). Subgroups of adolescent and adult patients with elevated type 2 biomarkers (blood eosinophils ≥150 cells/μL or FeNO ≥20 ppb) at baseline were also examined post hoc.

107 adolescents aged 12–17 years (5.6% of total population) and 1795 (94.4%) adults were randomized. Due to the small proportion of adolescents in the overall population, differences in baseline characteristics between patients receiving dupilumab and placebo were observed (Table S1); results should be interpreted within the context of these limitations. Dupilumab significantly improved lung function and exacerbation rates in adults, as previously observed in the overall QUEST population (Figures S1 and S2).[6]

In the adolescent population, dupilumab (200 and 300 mg) vs matched placebo significantly improved pre-bronchodilator FEV_1 at Week 12 by 0.37L (95% CI, 0.13–0.61; p=.003) and 0.27L (95% CI, 0.02–0.52; p=.037) (Figure 1A). In the 80% of adolescent patients with elevated baseline type 2 biomarker levels treated with dupilumab 200 mg, the magnitude of this improvement was greater (0.43L; 95% CI, 0.17–0.69; p=.002) than in the corresponding intention-to-treat (ITT) adolescent subgroup (Figure 1B). At almost all visits during the treatment period, numerically or statistically significant improvements were observed in post-bronchodilator FEV_1 (Figure 1C) and $ppFEV_1$ (Figure 1D) in both dupilumab groups vs placebo in the adolescent population. Improvements in $ppFEV_1$ with dupilumab vs placebo were also observed for adolescents with elevated baseline type 2 biomarkers (Figure 1E).

In adolescents, a 46% numerical reduction in adjusted AER (95% CI, 0.24–1.21) was observed with dupilumab 200 mg vs placebo. Adjusted AER in the dupilumab 300 mg group was 13% (95% CI, 0.48–2.69) higher vs matched placebo (Figure 2A). Similar results were seen in adolescents with elevated baseline type 2 biomarkers (Figure 2B). The increased AER seen in adolescents treated with dupilumab 300 mg is in marked contrast to the AER in adults as well as adolescents exposed to 200 mg q2w, and also contrasts with the improvement in FEV_1 observed for adolescents in both the 200 and 300 mg groups. This may be due to the imbalance observed in the number of severe exacerbations in the previous year between the dupilumab 300 mg group and the matched placebo group (mean 1.53 and 2.22, respectively) that would affect the adjusted exacerbation rate. Unadjusted AER was numerically lower with both dupilumab doses vs matched placebo in the overall adolescent population and patients with elevated baseline type 2 biomarkers (Figure 2C,D).

Dupilumab treatment numerically reduced median FeNO levels and serum total IgE vs placebo in adolescents and adults; median eosinophil concentrations remained constant over time in adolescent patients (Figure S3). Dupilumab treatment numerically improved ACQ-5 scores vs placebo by Week 52 (Table S2). Health-related quality-of-life improvements (measured by AQLQ scores) mirrored those seen in ACQ-5 scores (Table S2).

Dupilumab was generally well tolerated, with safety consistent with the known dupilumab safety profile (Table S3).

In conclusion, dupilumab improved lung function and reduced levels of type 2 biomarkers in the subpopulation of adolescents with uncontrolled, moderate-to-severe asthma, supporting the use of dupilumab in this population.

Trial registration: ClinicalTrials.gov Identifier: NCT02414854.

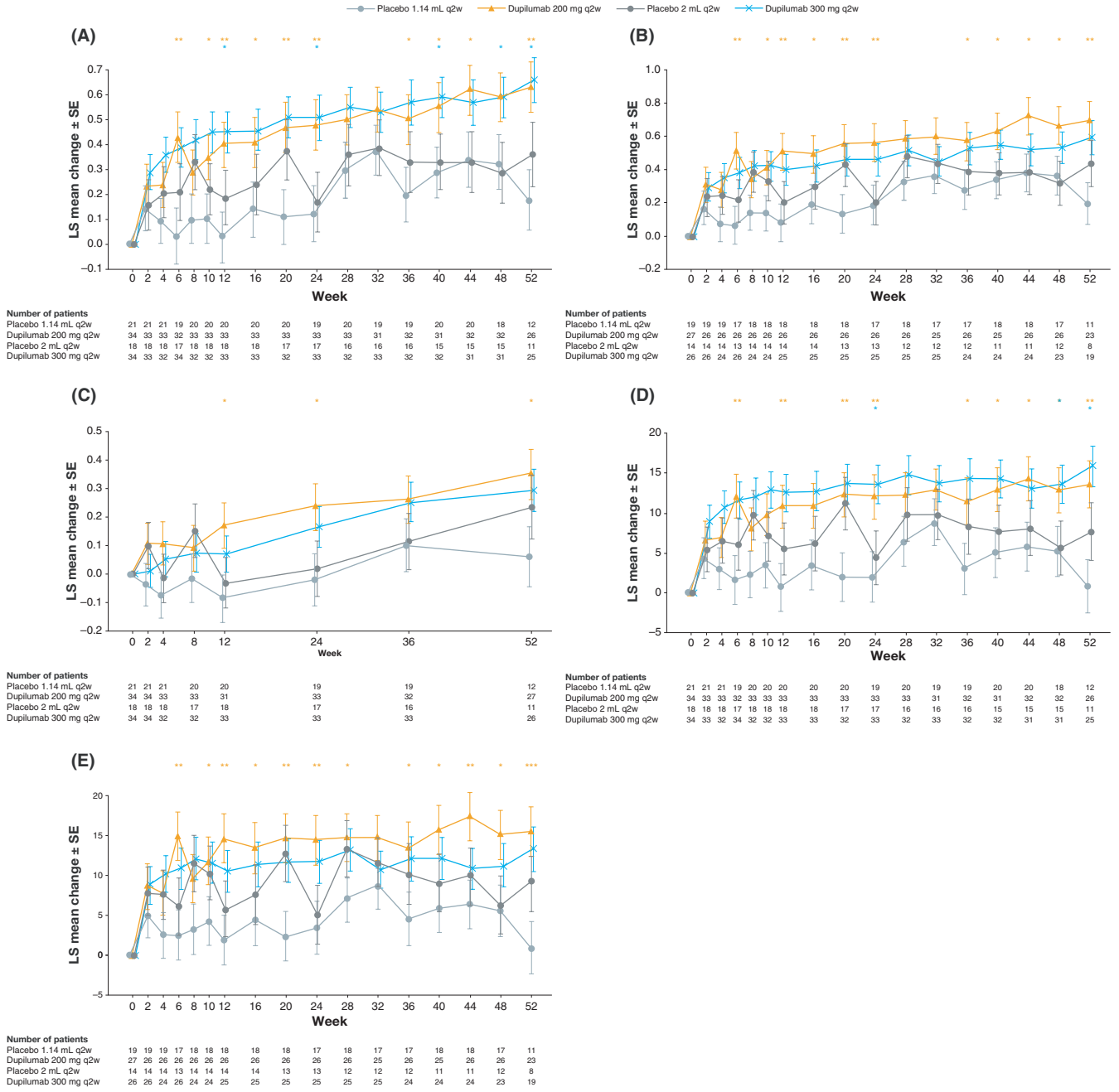

FIGURE 1 LS mean change from baseline during the 52-week treatment period in: pre-bronchodilator FEV_1 (L) in (A) the ITT QUEST adolescent population and (B) the subgroup of adolescents with baseline blood eosinophils ≥150 cells/μL or FeNO ≥20; (C) post-bronchodilator FEV_1 (L) in the ITT QUEST adolescent population; percent predicted pre-bronchodilator FEV_1 (L) in (D) the ITT QUEST adolescent population and (E) the subgroup with baseline blood eosinophils ≥150 cells/μL or FeNO ≥20. FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; ITT, intention-to-treat; LS, least squares; ppb, parts per billion; q2w, every 2 weeks; SE, standard error. *p < .05, **p < .01, ***p < .001 vs matched (p values based on change from baseline vs placebo)

KEYWORDS

asthma, asthma treatment, biologics, biomarkers, interleukins

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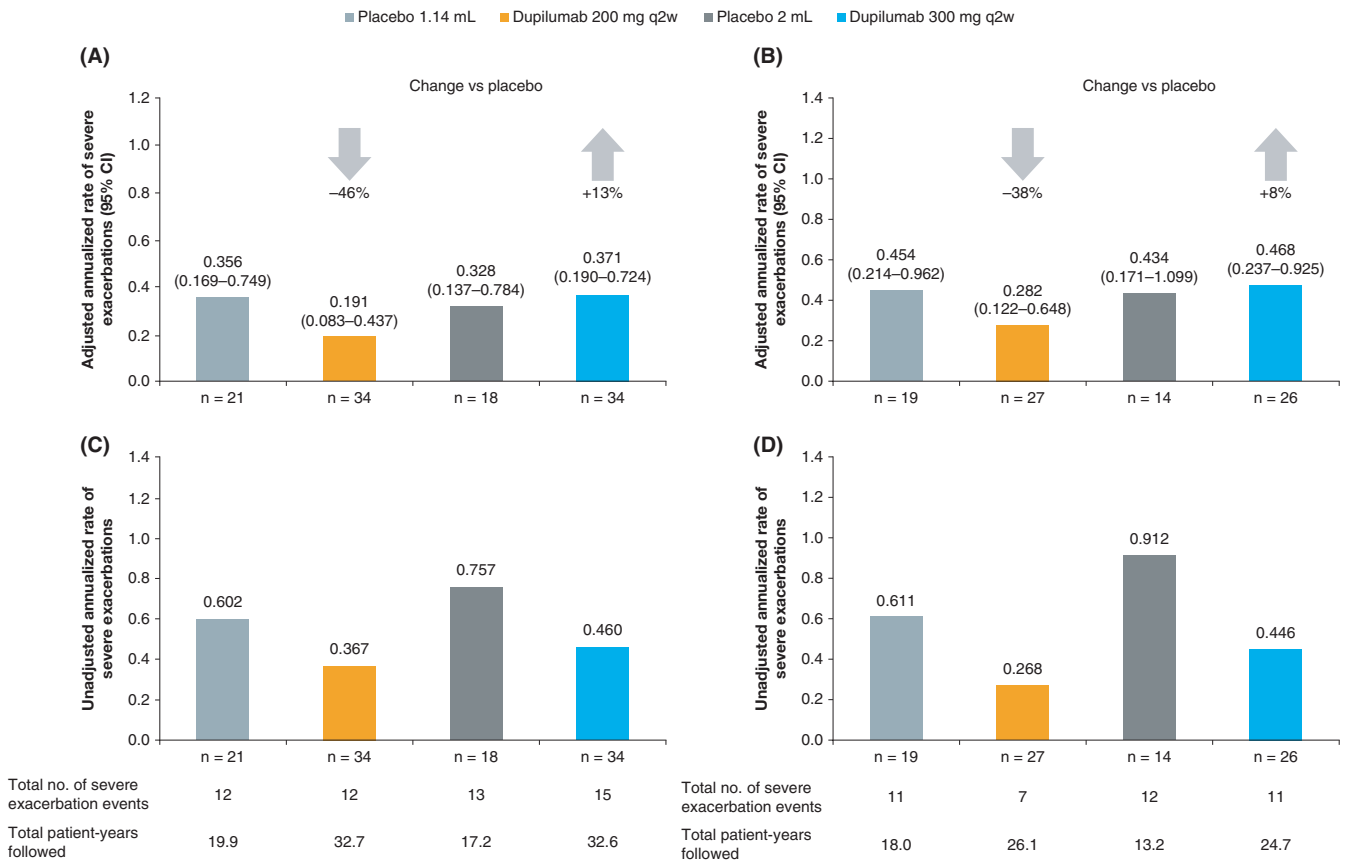

FIGURE 2 Annualized severe exacerbation rate (AER) during the 52-week treatment period. Adjusted AER in (A) the ITT QUEST adolescent population and (B) the subgroup of adolescents with baseline blood eosinophils ≥150 cells/μl or FeNO ≥20; unadjusted AER in (C) adolescents and (D) the subgroup with baseline blood eosinophils ≥150 cells/μl or FeNO ≥20 ppb. CI, confidence interval; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat; q2w, every 2 weeks

CONFLICTS OF INTEREST

Maspero JF: AstraZeneca, Sanofi—consultant; GlaxoSmithKline, Menarini, Novartis, Uriach—speaker fees; Novartis—research grants. **FitzGerald JM:** AstraZeneca, GlaxoSmithKline, Novartis, Teva—advisory board; AstraZeneca, GlaxoSmithKline, Regeneron Pharmaceuticals, Inc., Sanofi—research funding paid directly to UBC; GlaxoSmithKline—unrestricted grants; AstraZeneca, GlaxoSmithKline, Novartis—speaker honoraria; Vancouver Coastal Health—educational material. **Pavord ID:** Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, Teva—speakers' honoraria; AstraZeneca, Teva—organization of educational events; Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Dey Pharma, Genentech, GlaxoSmithKline, Knopp Biosciences, Merck, Merck Sharp & Dohme, Napp Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, Inc., RespiVert, Sanofi, Schering-Plough, Teva—advisory boards; AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Napp Pharmaceuticals, Teva—traveling grants; Chiesi—clinical trial support. **Rice MS, Rowe P, Hardin M:** Sanofi—employees, may hold stock and/or stock options in the company. **Maroni J, Amin N, Ruddy M:** Regeneron Pharmaceuticals, Inc.—employees and shareholders. **Pirozzi G, Teper A**: Sanofi—former employees, may hold stock and/or stock options in the company. **Graham NMH**: Regeneron Pharmaceuticals, Inc.—former employee and shareholder.

AUTHOR CONTRIBUTIONS

J.F. Maspero and J.M. Fitzgerald acquired data and provided interpretation of data (ICMJE Criterion #1), provided critical feedback (ICMJE Criterion #2), gave final approval for submission (ICMJE Criterion #3), and agreed to be accountable for the accuracy and integrity of this work (ICMJE Criterion #4). I.D. Pavord provided interpretation of data (#1), provided critical feedback (#2), gave final approval for submission (#3), and agreed to be accountable for the accuracy and integrity of this work (#4). M.S. Rice, J. Maroni, P. Rowe, G. Pirozzi, N. Amin, M. Ruddy, N.M.H. Graham, A. Teper and M. Hardin contributed to the conception and design of the study and provided interpretation of the data (#1), provided critical feedback (#2), gave final approval for submission (#3), and agreed to be accountable for the accuracy and integrity of this work (#4).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Anaphylaxis in the Emergency Department Unit: Before and during COVID-19

To the Editor,

After the declaration of coronavirus disease 2019 (COVID-19) as a global health emergency, healthcare systems have faced unprecedented challenges worldwide.[1] During the same period, emergency departments have reported a significant drop in the average number of daily accident and emergency (A&E) visits and admissions.[2]

We undertook a retrospective audit (registration number: 10952)and enrolled patients attending our Emergency Department Unit (EDU) to investigate how this pandemic has affected the lives of patients experiencing systemic allergic reactions requiring A&E admission.[3] We compared adult patients attending with clinical findings of a systemic allergic reaction and mast cell tryptase elevation in the first half of 2019 from January until the end June with the same period in 2020. This period was chosen as the first cases of COVID-19 in the UK were diagnosed in January 2020.[4]

Demographics, severity of reaction according to the Brown classification being mild, moderate or severe,[5] existence of a possible trigger for anaphylaxis according to the EDU discharge letter, tryptase values during the acute reaction, management and follow-up strategies in the EDU have been evaluated.

There was a significant reduction from 62 to 10 in the number of patients attending EDU with systemic allergic reactions between 2019 and 2020, respectively (Table 1). There were no differences in age or gender between the two groups. The majority of patients in 2019 (52%) experienced mild symptoms and presented with skin and/or mucosal involvement. In 2020, 80% of attendances were with moderate reactions affecting multiple systems. The difference between these two rates was significant suggesting a reduction in the number of EDU attendances of patients with likely milder spontaneous reactions.

Existence of an obvious allergic trigger was lower in 2019 at 54%. However, in 2020 according to EDU discharge letters, 8 of the 10 patients had exposure to a possible culprit trigger shortly before the reaction. Among the reactions occurring in 2020, 60% were likely drug related and followed administration of amoxicillin in four cases. Nitrofurantoin and ibuprofen were identified in single cases. Suspected food triggers in 2020 were walnut and celery each associated with a single case. Adrenaline was used in 80% of cases in 2020 and patients have all been referred to the Allergy Service.