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Article type : Letter to the Editor

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

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To the Editor,

Asthma prevalence has increased globally among adolescents in recent years, yet this population remains understudied.¹Dupilumab, 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 (FEV₁) 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 change from baseline in pre-bronchodilator FEV₁ and annualized severe exacerbation rate (AER). Changes from baseline were assessed post hoc for post-bronchodilator FEV₁, percentage predicted FEV₁ (ppFEV₁), Asthma Control Questionnaire (ACQ-5) response, fractional exhaled nitric oxide (FeNO) levels, blood eosinophil counts, and serum total IgE.

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Subgroups of adolescent and adult patients with elevated type 2 biomarkers (blood eosinophils ≥ 150 cells/ μ L 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 population⁶ (Figures S1 and S2).

In the adolescent population, dupilumab (200 and 300 mg) vs matched placebo significantly improved pre-bronchodilator FEV₁ at Week 12 by 0.37 L (95% CI, 0.13-0.61; $P=0.003$) and 0.27 L (95% CI, 0.02-0.52; $P=0.037$) (Figure 1A). In the 80% of adolescent patients with elevated baseline type 2 biomarker levels treated with 200 mg dupilumab, the magnitude of this improvement was greater (0.43 L; 95% CI, 0.17-0.69; $P=0.002$) 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 FEV₁ (Figure 1C) and ppFEV₁ (Figure 1D) in both dupilumab groups vs placebo in the adolescent population. Improvements in ppFEV₁ 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 300 mg dupilumab 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 FEV₁ observed for adolescents in both the 200 mg 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), which would affect the adjusted exacerbation rate. Unadjusted AER was numerically lower with both dupilumab doses vs matched placebo in both 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.

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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, 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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TRIAL REGISTRATION

ClinicalTrials.gov Identifier: NCT0414854.

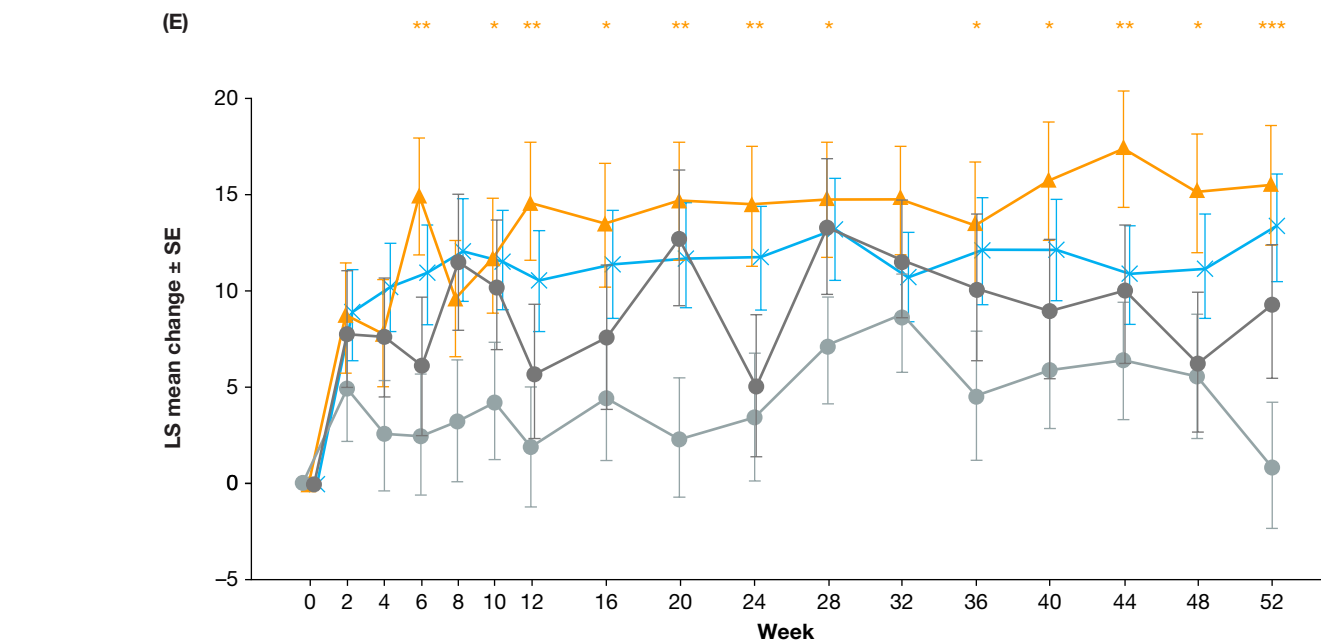
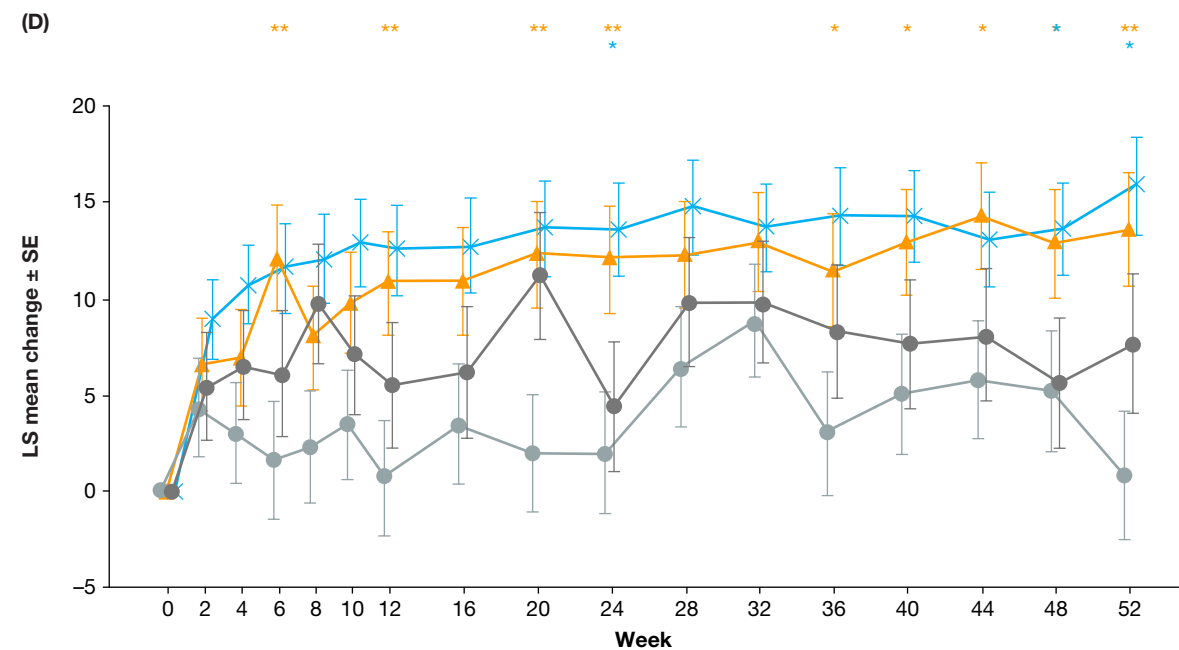
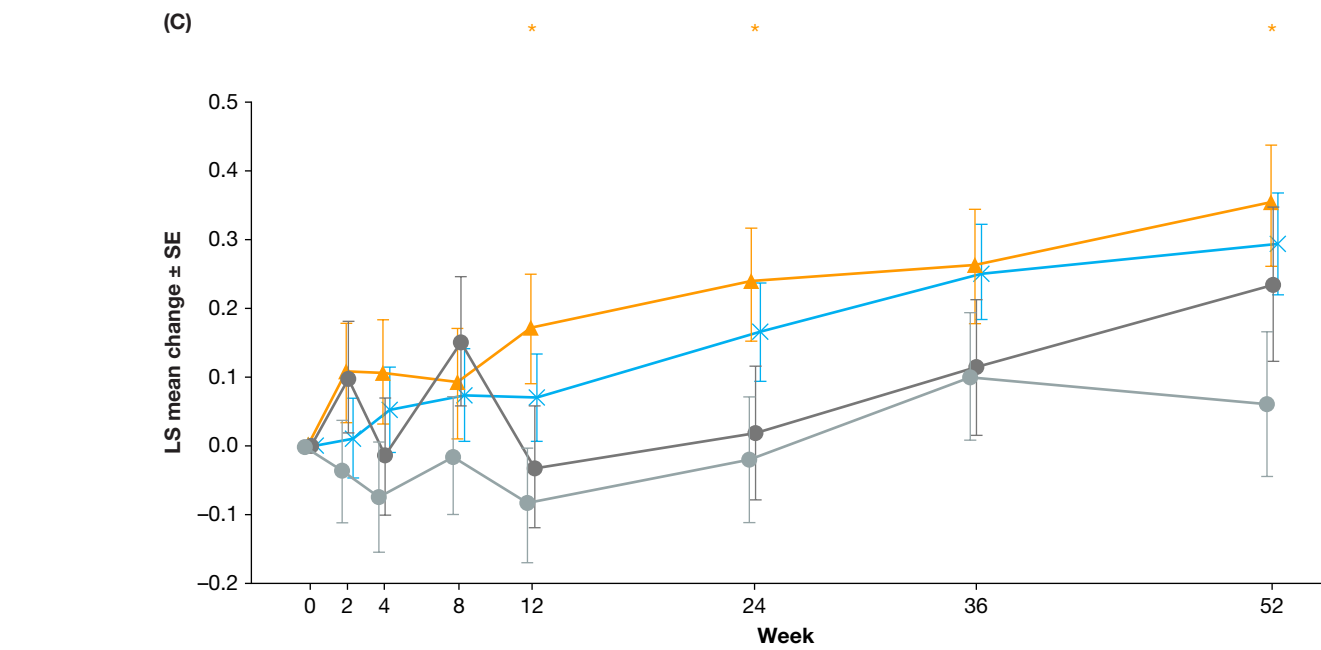
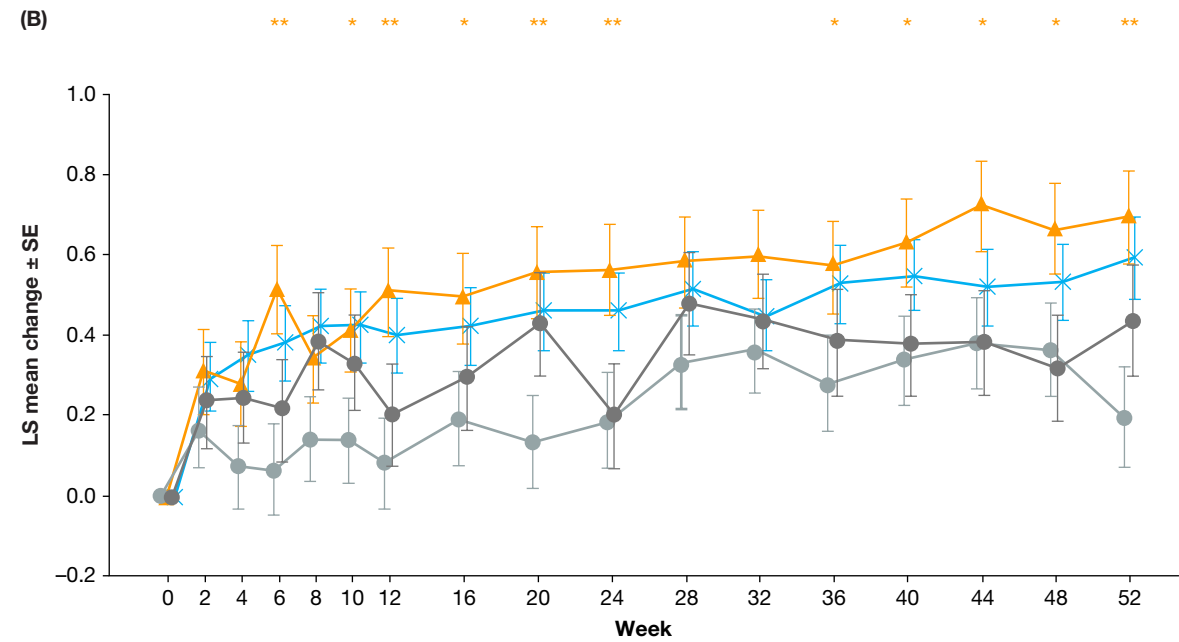
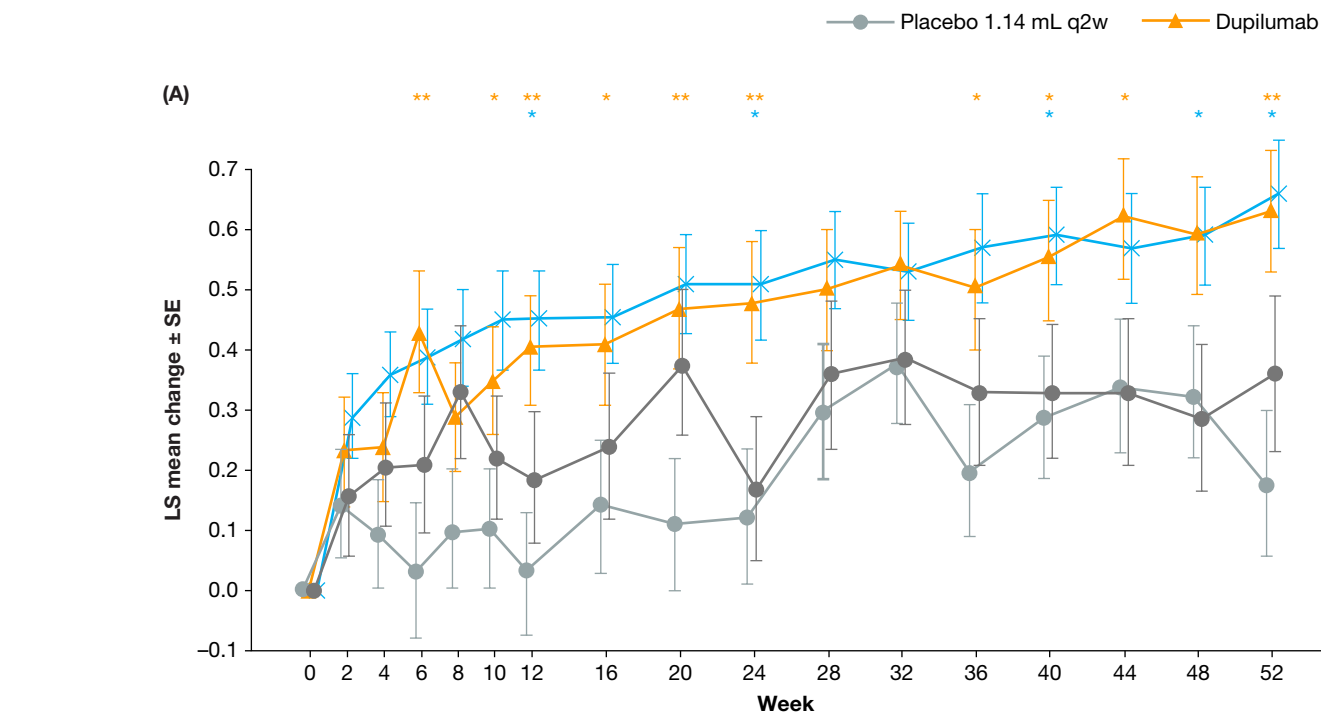
FIGURE LEGENDS

Figure 1. LS mean change from baseline during the 52-week treatment period in: pre-bronchodilator FEV₁ (L) in (A) the ITT QUEST adolescent population and (B) the subgroup of adolescents with baseline blood eosinophils ≥ 150 cells/ μ L or FeNO ≥ 20 ; (C) post-bronchodilator FEV₁ (L) in the ITT QUEST adolescent population; percent predicted pre-bronchodilator FEV₁ (L) in (D) the ITT QUEST adolescent population and (E) the subgroup with baseline blood eosinophils ≥ 150 cells/ μ L 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 versus matched (P values based on change from baseline vs placebo).

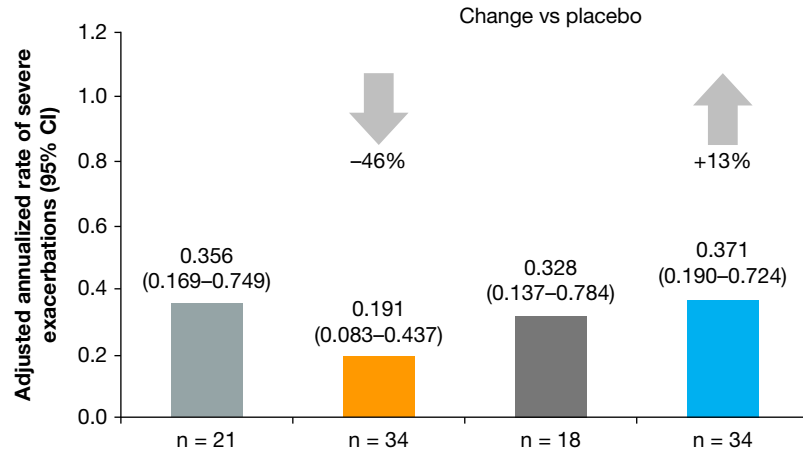
Figure 2. Annualized severe exacerbation rate (AER) during the 52-week treatment period. Adjusted AER in (A) the ITT QUEST adolescent population and (B) the subgroup of adolescents with baseline blood eosinophils ≥ 150 cells/ μ L or FeNO ≥ 20 ; unadjusted AER in (C) adolescents and (D) the subgroup with baseline blood eosinophils ≥ 150 cells/ μ L or FeNO ≥ 20 ppb.

CI, confidence interval; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat; q2w, every 2 weeks.

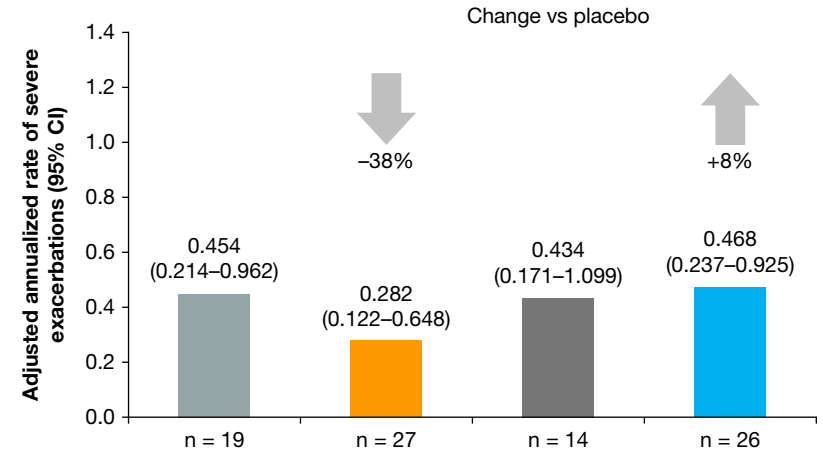


■ Placebo 1.14 mL ■ Dupilumab 200 mg q2w ■ Placebo 2 mL ■ Dupilumab 300 mg q2w

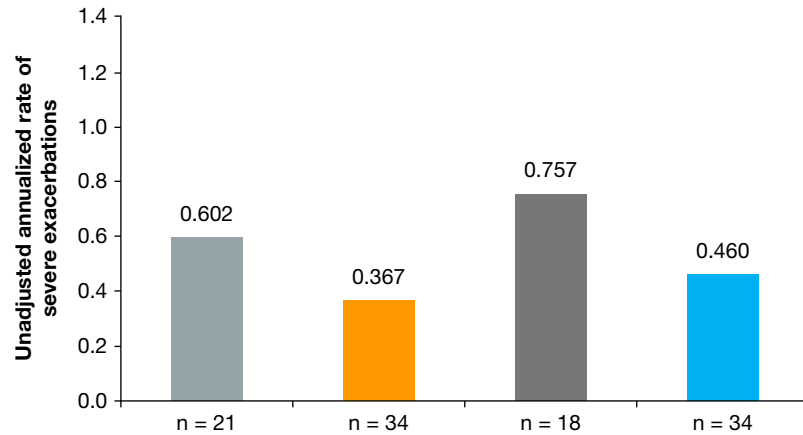
(A)



(B)



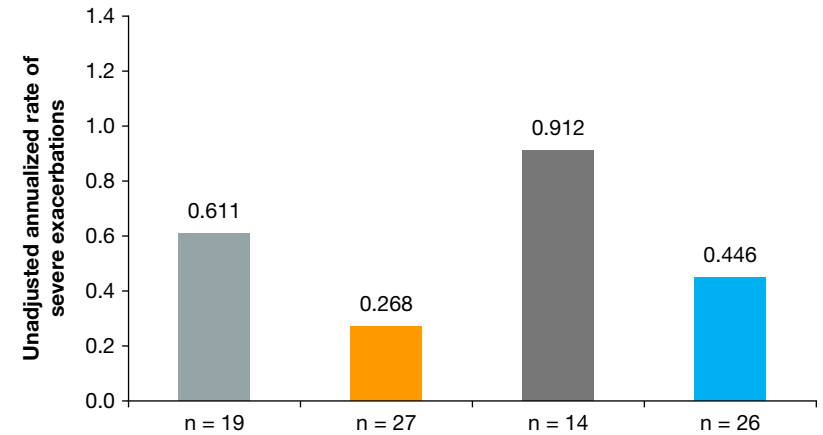
(C)



Total no. of severe exacerbation events
Total patient-years followed

12	12	13	15
19.9	32.7	17.2	32.6

(D)



Total no. of severe exacerbation events
Total patient-years followed

11	7	12	11
18.0	26.1	13.2	24.7

SUPPLEMENTAL INFORMATION

These data are provided as a supplement to the Letter by Maspero JF, Fitzgerald JM, Pavord ID et al. entitled ‘Dupilumab efficacy in adolescents with uncontrolled, moderate-to-severe asthma: LIBERTY ASTHMA QUEST study’ to provide additional information about the analysis of QUEST described.

Table S1. Baseline demographic and disease characteristics in adolescent and adult patients in the LIBERTY ASTHMA QUEST study

	Adolescents (n = 107)				Adults (n = 1795)			
	Placebo 1.14mL (n = 21)	Dupilumab 200mg q2w (n = 34)	Placebo 2mL (n = 18)	Dupilumab 300mg q2w (n = 34)	Placebo 1.14mL (n = 296)	Dupilumab 200mg q2w (n = 597)	Placebo 2mL (n = 303)	Dupilumab 300mg q2w (n = 599)
Age (y), mean (SD)	14.2 (1.8)	14.1 (1.9)	14.6 (1.4)	14.1 (1.8)	50.6 (13.2)	49.8 (13.4)	50.1 (12.6)	49.6 (13.7)
Female sex, n (%)	4 (19.0)	10 (29.4)	9 (50.0)	15 (44.1)	194 (65.5)	377 (63.1)	209 (69.0)	379 (63.3)
BMI (kg/m ²), mean (SD),	20.9 (4.5)	22.6 (5.2)	21.2 (3.3)	22.4 (6.7)	30.4 (7.0)	29.4 (6.4)	26.7 (6.8)	29.4 (6.5)
Age at asthma onset (y), mean (SD)	4.3 (4.3)	6.4 (4.1)	5.3 (3.1)	3.8 (3.3)	28.9 (18.7)	28.3 (19.0)	28.7 (18.3)	27.9 (19.2)
Pre-bronchodilator FEV ₁ (L), mean (SD)	2.42 (0.67)	2.21 (0.58)	2.54 (0.64)	2.29 (0.43)	1.72 (0.58)	1.76 (0.61)	1.70 (0.53)	1.76 (0.60)
Pre-bronchodilator FEV ₁ (% predicted), mean (SD)	71.71 (9.65)	67.15 (13.36)	72.61 (11.39)	71.82 (9.40)	57.49 (12.94)	57.88 (13.37)	57.50 (13.56)	57.75 (13.32)
Post-bronchodilator FEV ₁ (L), mean (SD)	2.93 (0.85)	2.68 (0.63)	3.03 (0.75)	2.85 (0.61)	2.10 (0.66)	2.13 (0.74)	2.08 (0.65)	2.14 (0.71)
Exacerbations in previous year (n), mean (SD)	2.14 (1.62)	1.97 (1.68)	2.22 (2.29)	1.53 (0.71)	2.06 (1.58)	2.07 (2.71)	2.32 (2.06)	2.05 (1.90)
High-dose ICS use, n (%)	6 (28.6)	6 (17.6)	3 (16.7)	11 (32.4)	166 (56.1)	311 (52.1)	164 (54.1)	312 (52.1)
ACQ-5 score, mean (SD)	2.47 (0.72)	2.60 (0.57)	2.58 (0.59)	2.38 (0.67)	2.73 (0.73)	2.77 (0.81)	2.78 (0.78)	2.79 (0.76)
AQLQ score, mean (SD)	5.17 (0.78)	4.38 (0.96)	4.90 (0.97)	5.02 (0.97)	4.19 (1.00)	4.30 (1.08)	4.27 (1.02)	4.24 (1.04)
Blood eosinophil count (cells/μL), median (IQR)	360 (200–740)	200 (150–450)	215 (120–400)	315 (11–620)	270 (130–470)	250 (120–470)	270 (140–480)	250 (130–450)
FeNO (ppb), median (IQR)	45.0 (24.0–73.0)	19.5 (15.0–46.0)	30.5 (18.0–56.0)	29.5 (13.0–55.0)	25.0 (15.0–43.0)	23.5 (14.0–42.0)	27.0 (16.0–47.0)	24.0 (14.0–42.0)
Serum total IgE (IU/mL), median (IQR)	356.0 (127.0–771.0)	290.5 (123.0–1116.0)	860.5 (288.0–1,938.0)	465.0 (233.0–1390.0)	170.0 (58.0–440.0)	150.5 (59.5–434.0)	159.5 (54.0–398.5)	165.0 (62.0–429.0)
Any comorbid medical history, [*] n (%)	20 (95.2)	30 (88.2)	18 (100.0)	33 (97.1)	238 (80.4)	461 (77.2)	236 (77.9)	465 (77.6)

ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroid(s); IQR, interquartile range; ppb, parts per billion; q2w, every 2 weeks; SD, standard deviation.

^{*}Patients were considered to have a relevant comorbid medical history if they had any of the following diseases: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyposis, eosinophilic esophagitis, food allergy, or hives.

Table S2. LS mean change from baseline in ACQ-5 during the 52-week treatment period in adolescents and adults – ITT population

	Adolescents (n=107)				Adults (n=1795)			
	Placebo 1.14 mL (n = 21)	Dupilumab 200 mg q2w (n = 34)	Placebo 2 mL (n = 18)	Dupilumab 300 mg q2w (n = 34)	Placebo 1.14 mL (n = 296)	Dupilumab 200 mg q2w (n = 597)	Placebo 2 mL (n = 303)	Dupilumab 300 mg q2w (n = 599)
ACQ-5								
Baseline (SD)	2.47 (0.72)	2.60 (0.57)	2.58 (0.59)	2.38 (0.67)	2.73 (0.73)	2.77 (0.81)	2.78 (0.78)	2.79 (0.76)
<i>Week 12</i>								
LS mean change (SE)	-1.04 (0.19)	-1.19 (0.17)	-0.99 (0.21)	-1.25 (0.15)	-1.02 (0.06)	-1.36 (0.04)	-1.11 (0.06)	-1.37 (0.04)
LS mean difference vs placebo (95% CI)		-0.15 (-0.62 – 0.32)		-0.26 (-0.75 – 0.22)		-0.34 (-0.48 – -0.21)		-0.26 (-0.39 – -0.12)
P value vs placebo		.5303		.2870		< .0001		.0002
<i>Week 24</i>								
LS mean change (SE)	-1.25 (0.20)	-1.14 (0.17)	-1.19 (0.22)	-1.40 (0.16)	-1.08 (0.06)	-1.46 (0.04)	-1.20 (0.06)	-1.39 (0.04)
LS mean difference vs placebo (95% CI)		0.11 (-0.37 – 0.59)		-0.20 (-0.71 – 0.30)		-0.38 (-0.52 – -0.24)		-0.19 (-0.33 – -0.05)
P value vs placebo		.6520		.4264		< .0001		.0073
<i>Week 52</i>								
LS mean change (SE)	-1.00 (0.24)	-1.50 (0.20)	-1.35 (0.27)	-1.36 (0.19)	-1.15 (0.06)	-1.54 (0.04)	-1.29 (0.06)	-1.52 (0.04)
LS mean difference vs placebo (95% CI)		-0.50 (-1.09 – 0.09)		-0.00 (-0.63 – 0.62)		-0.39 (-0.53 – -0.24)		-0.24 (-0.38 – -0.09)
P value vs placebo		.0945		.9878		< .0001		.0012
AQLQ								
Baseline (SD)	5.17 (0.78)	4.38 (0.96)	4.90 (0.97)	5.02 (0.97)	4.19 (1.00)	4.30 (1.08)	4.27 (1.02)	4.24 (1.04)
<i>Week 12</i>								
LS mean change (SE)	0.95 (0.20)	1.08 (0.19)	0.84 (0.23)	1.05 (0.17)	0.88 (0.06)	1.11 (0.04)	0.96 (0.05)	1.11 (0.04)
LS mean difference vs placebo (95% CI)		0.12 (-0.38 – 0.63)		0.21 (-0.29 – 0.70)		0.23 (0.10 – 0.36)		0.15 (0.02 – 0.28)
P value vs placebo		.6262		.4145		.0008		.0215
<i>Week 24</i>								
LS mean change (SE)	1.10 (0.20)	0.97 (0.19)	1.19 (0.23)	1.14 (0.17)	0.94 (0.06)	1.15 (0.04)	1.01 (0.06)	1.16 (0.04)
LS mean difference vs placebo (95% CI)		-0.13 (-0.63 – 0.36)		-0.05 (-0.54 – 0.44)		0.22 (0.07 – 0.36)		0.16 (0.02 – 0.30)
P value vs placebo		.5980		.8371		.0029		.0261
<i>Week 52</i>								
LS mean change (SE)	1.08 (0.23)	1.36 (0.19)	1.06 (0.25)	1.33 (0.17)	0.99 (0.06)	1.28 (0.04)	1.04 (0.06)	1.30 (0.04)
LS mean difference vs placebo (95% CI)		0.28 (-0.24 – 0.81)		0.27 (-0.27 – 0.82)		0.29 (0.14 – 0.44)		0.26 (0.12 – 0.41)
P value vs placebo		.2875		.3185		.0002		.0004

ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; ITT, intention-to-treat; LS, least squares; SD, standard deviation; SE, standard error.

TABLE S3. Summary of TEAEs in subpopulations of adolescent and adult patients – safety population

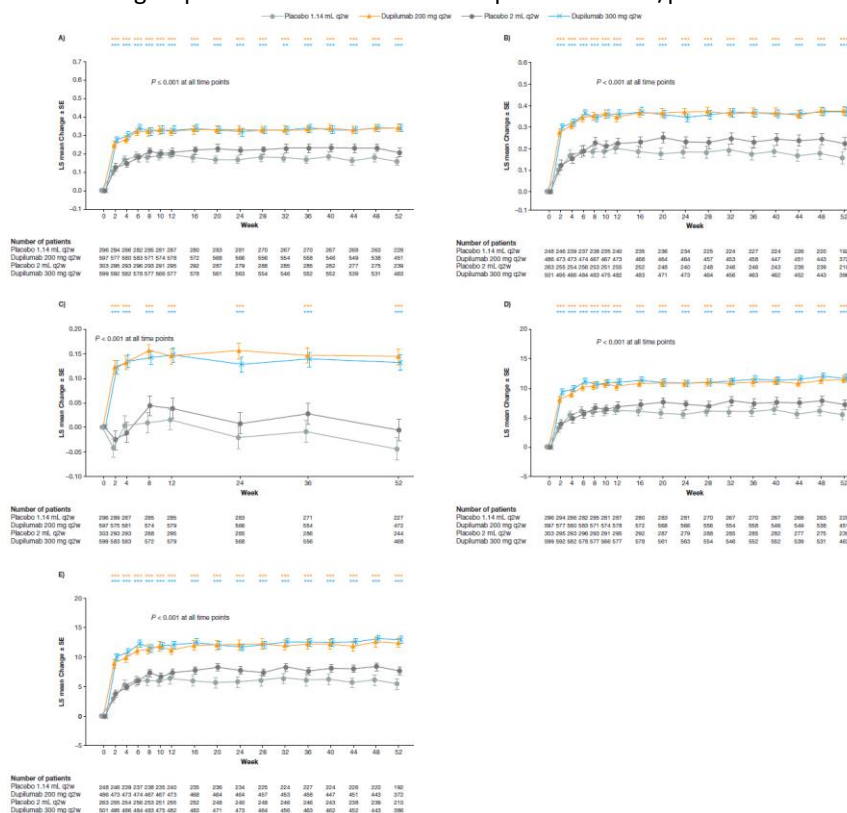
n (%)	Adolescents (n=107)				Adults (n=1795)			
	Placebo 1.14mL (n = 21)	Dupilumab 200mg q2w (n = 34)	Placebo 2mL (n = 18)	Dupilumab 300mg q2w (n = 34)	Placebo 1.14mL (n = 292)	Dupilumab 200mg q2w (n = 597)	Placebo 2mL (n = 303)	Dupilumab 300mg q2w (n = 598)
Any TEAE	16 (76.2)	24 (70.6)	16 (88.9)	26 (76.5)	241 (82.5)	484 (81.1)	254 (83.8)	489 (81.8)
Treatment-emergent SAE	0	3 (8.8)	2 (11.1)	1 (2.9)	26 (8.9)	46 (7.7)	25 (8.3)	54 (9.0)
Any TEAE leading to death	0	0	0	0	3 (1.0)	1 (0.2)	0	4 (0.7)
Any TEAE leading to treatment discontinuation	0	1 (2.9)	1 (5.6)	2 (5.9)	19 (6.5)	18 (3.0)	9 (3.0)	42 (7.0)
AEs occurring in ≥5% of patients in any group (MedDRA PT)[†]								
Viral respiratory tract infection	0	3 (8.8)	2 (11.1)	4 (11.8)	9 (3.1)	12 (2.0)	1 (0.3)	6 (1.0)
Viral upper respiratory tract infection	6 (28.6)	2 (5.9)	7 (38.9)	10 (29.4)	54 (18.5)	117 (19.6)	57 (18.8)	101 (16.9)
Upper respiratory tract infection	0	4 (11.8)	1 (5.6)	2 (5.9)	37 (12.7)	65 (10.9)	48 (15.8)	75 (12.5)
Bronchitis	1 (4.8)	4 (11.8)	0	2 (5.9)	46 (15.8)	69 (11.6)	42 (13.9)	69 (11.5)
Injection-site reactions (HLT) [‡]	0	3 (8.8)	1 (5.6)	4 (11.8)	17 (5.8)	93 (15.6)	32 (10.6)	112 (18.7)

AE, adverse event; HLT, High Level Term; MedDRA, Medical Dictionary for Regulatory Activities; PT, MedDRA Preferred Term; q2w, every 2 weeks; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[†]Adverse events in this category were reported according to the PTs in the MedDRA, version 20.0, unless otherwise indicated.

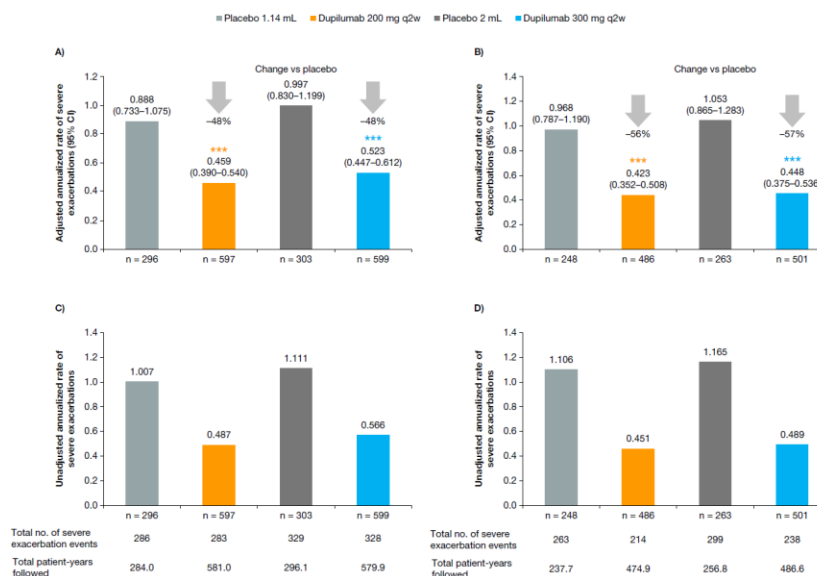
[‡]Injection-site reaction is an HLT in MedDRA.

Figure S1. LS mean change from baseline during the 52-week treatment period in: pre-bronchodilator FEV1 (L) in (A) the ITT QUEST adult population, and in (B) the subgroup with baseline blood eosinophils ≥ 150 cells/ μ L or FeNO ≥ 20 ; (C) post-bronchodilator FEV1 (L) in the ITT QUEST adult population; percent predicted pre-bronchodilator FEV1 (L) in (D) the ITT QUEST adult population, and (E) in the subgroup with baseline blood eosinophils ≥ 150 cells/ μ L or FeNO ≥ 20 .



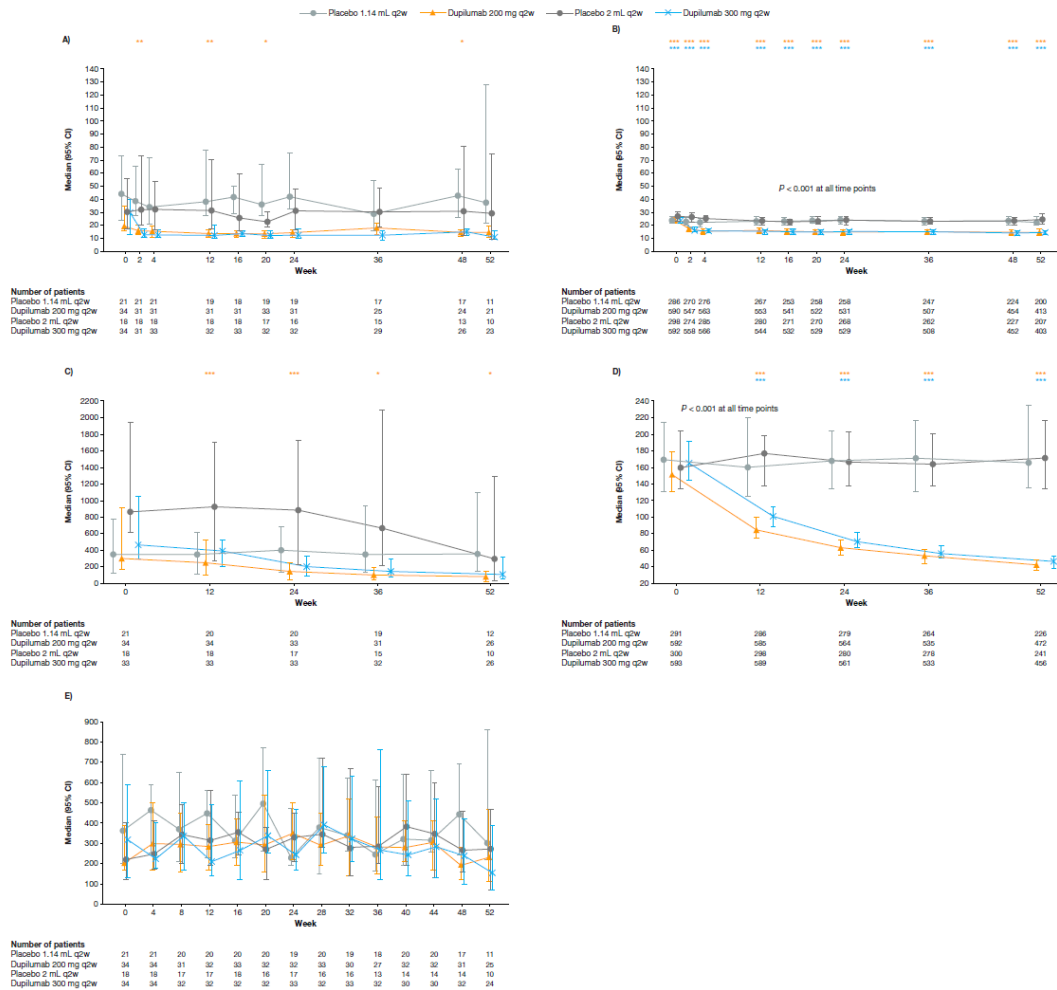
P<.05, **P<.01, ***P<.001 versus matched (P values based on change from baseline vs placebo). FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; ITT, intention-to-treat; LS, least squares; ppb, parts per billion; q2w, every 2 weeks; SE, standard error.

Figure S2. Annualized severe exacerbation rate (AER) during the 52-week treatment period. Adjusted AER in (A) the ITT QUEST adult population, and (B) in the subgroup with baseline blood eosinophils ≥ 150 cells/ μ L or FeNO ≥ 20 ; unadjusted AER in (C) adult and (D) in the subgroup with baseline blood eosinophils ≥ 150 cells/ μ L or FeNO ≥ 20 ppb.



CI, confidence interval; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat; q2w, every 2 weeks.

Figure S3. Median levels of type 2 biomarkers during the 52-week treatment period in the exposed population: median FeNO levels in (A) adolescents and (B) adults; median serum total IgE levels in (C) adolescents and (D) adults; (E) median eosinophil concentrations in adolescents.



* $P < .05$, ** $P < .01$, *** $P < .001$ versus matched placebo (P values based on change from baseline versus placebo). CI, confidence interval; FeNO, fractional exhaled nitric oxide; q2w, every 2 weeks.