Type 2 Biomarkers Associated With Dupilumab Efficacy in Patients With Uncontrolled, Moderate-To-Severe Asthma Enrolled in the Phase 3 Study LIBERTY ASTHMA QUEST

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BACKGROUND

- Dupilumab, a fully human VelocImmune®-derived anti-interleukin (IL)-4 receptor α monoclonal antibody, inhibits IL-4 and IL-13, which are key drivers of Type 2 inflammation[1]
- Dupilumab is approved for treatment of adults with inadequately controlled moderate-to-severe atopic dermatitis[2–4]
- In a phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), dupilumab 200 mg and 300 mg every 2 weeks (q2w) vs matched placebo reduced annualized severe exacerbation rates and improved pre-bronchodilator (BD) forced expiratory volume in 1 second (FEV_1), % change in FEV_1, asthma symptoms, and quality of life measures, and was generally well tolerated in the intent-to-treat (ITT) population

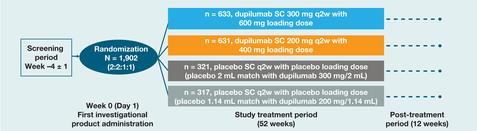
OBJECTIVE

- **This post hoc analysis of the phase 3 LIBERTY ASTHMA QUEST study evaluates associations between baseline Type 2 inflammatory biomarkers and therapeutic responses to dupilumab**

METHODS

Study design

Figure 1. Study design (NCT02414854).



Eligible patients were allowed to continue on to the extension study LTS12551 after completion of treatment; thus, they would have had no post-treatment follow-up period. SC, subcutaneous.

Main inclusion criteria

- Adults and adolescents (aged ≥ 12 years) with physician-diagnosed persistent asthma for ≥ 12 months (based on the Global Initiative for Asthma 2014 Guidelines[5]), on medium-to-high dose inhaled corticosteroids (ICS) plus up to 2 additional controllers; pre-BD FEV_1 ≤ 80% predicted normal (≤ 90% for adolescents) at screening and baseline; FEV_1 reversibility ≥ 12% and 200 mL post-short-acting β_2-agonist administration prior to randomization; 5-item Asthma Control Questionnaire (ACQ-5) score ≥ 1.5 at screening and baseline; ≥ 1 exacerbation during the previous year; without a minimum requirement for baseline blood eosinophil count or any other Type 2 biomarkers (e.g. fractional exhaled nitric oxide [FeNO] or serum total IgE)

Main exclusion criteria

- Diagnosis of chronic obstructive pulmonary disease or other lung disease that might impair lung function; severe asthma exacerbation within 1 month prior to screening and baseline; current smoker or smoker who stopped within 6 months before screening or with a smoking history of > 10 pack-years; diagnosis of a comorbid disease that might interfere with the evaluation of the study drug

Study assessments

- Primary efficacy endpoints were the annualized rate of severe exacerbations during the 52-week treatment period and the absolute change from baseline to Week 12 in pre-BD FEV_1 in the overall population
  - These endpoints were also examined in patients with baseline blood eosinophil counts of ≥ 300 cells/μL and < 300 cells/μL and those with baseline levels of FeNO ≥ 25 ppb and < 25 ppb
- Treatment-by-biomarker interactions between baseline levels of Type 2 inflammatory biomarkers for change from baseline in pre-BD FEV_1 and annualized rate of severe exacerbations were assessed

RESULTS

Patient characteristics

- Baseline demographics and clinical characteristics were generally similar across the treatment groups (**Table 1**)

Table 1. Baseline demographic and clinical characteristics of the patients: ITT population.

	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Overall population (N = 1,902)
	Placebo (n = 317)	Dupilumab (n = 631)	Placebo (n = 321)	Dupilumab (n = 633)	
Age, mean (SD), years	48.2 (15.6)	47.9 (15.3)	48.2 (14.7)	47.7 (15.6)	47.9 (15.3)
Age < 18 years, n (%)	21 (6.6)	34 (5.4)	18 (5.6)	34 (5.4)	107 (5.6)
Female sex, n (%)	198 (62.5)	387 (61.3)	218 (67.9)	394 (62.2)	1,197 (62.9)
Pre-bronchodilator FEV_1, mean (SD), L	1.76 (0.61)	1.78 (0.62)	1.75 (0.57)	1.78 (0.60)	1.78 (0.60)
Pre-bronchodilator FEV_1, mean (SD), % predicted	58.43 (13.22)	58.38 (13.52)	58.35 (13.87)	58.51 (13.52)	58.43 (13.52)
Exacerbations in past year, mean (SD), n	2.07 (1.58)	2.07 (2.66)	2.31 (2.07)	2.02 (1.86)	2.09 (2.15)
High-dose ICS+LABA use, n (%)	172 (54.3)	317 (50.2)	167 (52.0)	323 (51.0)	979 (51.5)
ACQ-5[a] score, mean (SD)	2.71 (0.73)	2.76 (0.80)	2.77 (0.77)	2.77 (0.76)	2.76 (0.77)

[a]ACQ-5 is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Higher scores indicate less control; a global score ranging from 0 to 6 is calculated.
LABA, long-acting β_2-agonist; SD, standard deviation.

- Baseline values for biomarkers associated with Type 2 inflammation were generally similar across treatment groups (**Table 2**)
- Patients treated with dupilumab showed greater reduction from baseline over the 52-week treatment period in FeNO, total IgE, thymus and activation regulated chemokine (TARC), periostin, and eotaxin-3 (nominal $P < 0.001$ vs placebo) (**Table 2**)
- Transient elevations in blood eosinophil counts were observed in both dupilumab treatment groups that decreased to close to baseline levels by Week 52 (**Table 2**)

Relationship between annualized rate of severe exacerbations and baseline Type 2 inflammatory biomarkers

- Dupilumab 200 or 300 mg q2w vs placebo significantly reduced annualized severe exacerbation rates in the overall ITT population with greater benefits in patients with elevated baseline blood eosinophil counts (≥ 300 cells/μL) and in patients with elevated baseline FeNO levels (≥ 25 ppb) (all $P < 0.001$) (**Figures 2A–2C**)
- Significant treatment-by-baseline biomarker interactions were observed between both blood eosinophil counts ($P < 0.0001$) and FeNO ($P = 0.0001$) and the annualized rate of severe exacerbations during the 52-week treatment period (**Figures 3A** and **3B**); all other interactions were non-significant (**Figures 3C–3G**)

Relationship between change from baseline pre-BD FEV_1 and baseline Type 2 inflammatory biomarkers

- Improvement in pre-BD FEV_1 was rapid (with significant differences vs placebo seen at Week 2) and was sustained throughout the 52-week treatment period ($P < 0.001$ for both regimens) (**Figure 4A**)
- Dupilumab 200 or 300 mg q2w vs placebo significantly improved pre-BD FEV_1 at Week 12 in the overall ITT population with greater benefits in patients with elevated baseline blood eosinophil counts (≥ 300 cells/μL) and in patients with elevated baseline FeNO levels (≥ 25 ppb) (all $P < 0.001$) (**Figure 4**)
- Significant treatment-by-baseline biomarker interactions were observed between blood eosinophil counts ($P < 0.0001$), FeNO ($P < 0.0001$), total IgE ($P = 0.0245$), periostin ($P = 0.0009$), ECP ($P = 0.0102$), and eotaxin-3 ($P = 0.0151$) and change from baseline pre-BD FEV_1 at Week 12 (**Figures 5A–C** and **E–G**)
  - The treatment-by-baseline interaction for TARC ($P = 0.3759$) was non-significant (**Figure 5D**)

Safety

- The incidence of treatment-emergent adverse events (TEAEs) was similar across treatment groups (81% vs 83% for dupilumab- and placebo-treated patients, respectively) in the safety population
- The most frequent (> 10%) TEAEs in dupilumab-treated patients vs placebo-treated patients were viral upper respiratory tract infection (18% vs 20%), upper respiratory tract infection (12% vs 14%), injection-site erythema (14% vs 6%), and bronchitis (11% vs 14%)

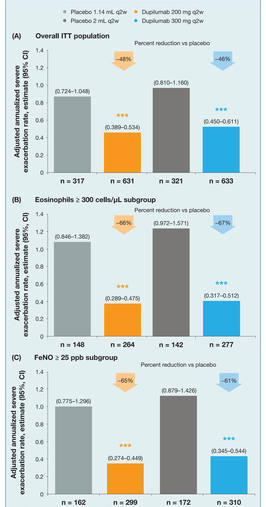
Table 2. Type 2 biomarker concentrations at baseline and change from baseline at Week 52.

	1.14 mL/200 mg q2w		2 mL/300 mg q2w	
	Placebo (n = 313)	Dupilumab (n = 631)	Placebo (n = 321)	Dupilumab (n = 632)
Blood eosinophil count, cells/μL				
Baseline				
Mean (SD)	369 (334)	351 (348)	391 (419)	351 (370)
Median (min to max)	280 (0 to 2,200)	250 (0 to 3,610)	265 (0 to 3,580)	250 (0 to 4,330)
Change from baseline at Week 52				
Mean (SD)	−3 (313)	20 (397)	−48 (347)	−7 (419)
Median (min to max)	0 (−1,670 to 1,540)	−20 (−1,690 to 3,170)	−30 (−2,330 to 1,740)	−30 (−3,670 to 3,420)
FeNO, ppb				
Baseline				
Mean (SD)	34.5 (28.7)	34.4 (34.9)	38.4 (38.0)	34.0 (29.8)
Median (min to max)	26.0 (3.0 to 197.0)	23.0 (3.0 to 387.0)	27.0 (5.0 to 351.0)	24.0 (4.0 to 202.0)
Change from baseline at Week 52				
Mean (SD)	−2.1 (20.2)	−16.0*** (27.1)	−5.5 (36.2)	−16.2*** (26.8)
Median (min to max)	−1.0 (−76.0 to 103.0)	−8.0*** (−188.0 to 46.0)	−2.0 (−307.0 to 218.0)	−8.0*** (−177.0 to 54.0)
Total IgE, IU/mL				
Baseline				
Mean (SD)	394.2 (626.2)	460.6 (816.6)	448.5 (796.7)	415.0 (701.4)
Median (min to max)	174.5 (1.0 to 5,000.0)	154.0 (1.0 to 5,000.0)	178.5 (3.0 to 5,000.0)	174.0 (1.0 to 5,000.0)
Change from baseline at Week 52				
Mean (SD)	0.6 (427.5)	−313.4*** (576.7)	−4.0 (322.1)	−294.8*** (519.4)
Median (min to max)	−2.0 (−1,704.0 to 4,925.0)	−109.0*** (−4,637.0 to 573.0)	−2.5 (−1,000.0 to 3,246.0)	−116.5*** (−4,994.0 to 862.0)
TARC, pg/mL				
Baseline				
Mean (SD)	377.8 (289.0)	393.8 (457.4)	398.0 (344.2)	364.7 (295.4)
Median (min to max)	296.0 (33.0 to 1,970.0)	314.5 (16.0 to 8,600.0)	300.0 (34.0 to 3,210.0)	295.0 (16.0 to 3,170.0)
Change from baseline at Week 52				
Mean (SD)	−10.4 (194.9)	−157.4*** (445.9)	137.7 (2,156.4)	−122.8*** (218.0)
Median (min to max)	−5.0 (−1,456.0 to 1,090.0)	−100.0*** (−8,187.0 to 885.0)	8.5 (−669.0 to 33,650.0)	−85.0*** (−2,196.0 to 590.0)

	1.14 mL/200 mg q2w		2 mL/300 mg q2w	
	Placebo (n = 313)	Dupilumab (n = 631)	Placebo (n = 321)	Dupilumab (n = 632)
Periostin, ng/mL				
Baseline				
Mean (SD)	79.83 (36.60)	79.85 (39.12)	80.94 (40.73)	78.42 (37.94)
Median (min to max)	71.7 (27.8 to 244.9)	70.6 (20.5 to 368.2)	71.0 (25.1 to 312.8)	69.7 (19.2 to 298.5)
Change from baseline at Week 52				
Mean (SD)	−4.58 (22.00)	−18.64*** (34.67)	−5.05 (27.89)	−18.90*** (30.84)
Median (min to max)	−3.6 (−108.4 to 75.7)	−11.4*** (−260.0 to 70.4)	−4.1 (−110.3 to 189.5)	−12.45*** (−202.4 to 130.1)
ECP, ng/mL				
Baseline				
Mean (SD)	25.5 (27.2)	26.6 (30.8)	27.1 (30.0)	24.2 (27.1)
Median (min to max)	17.0 (1.0 to 200.0)	16.0 (1.0 to 200.0)	17.0 (1.0 to 198.0)	16.0 (1.0 to 200.0)
Change from baseline at Week 52				
Mean (SD)	−4.1 (20.9)	−2.9 (29.0)	−4.5 (25.6)	−3.8 (26.8)
Median (min to max)	−2.0 (−108 to 78)	−2.0 (−164 to 183)	−1.0 (−106 to 131)	−2.0 (−177 to 166)
Eotaxin-3, pg/mL				
Baseline				
Mean (SD)	52.172 (86.619)	78.202 (339.495)	50.892 (57.855)	69.516 (481.528)
Median (min to max)	36.5 (1.95 to 1,180.0)	38.2 (1.95 to 6,430.0)	37.45 (1.95 to 723.0)	38.3 (1.95 to 12,000.0)
Change from baseline at Week 52				
Mean (SD)	−1.426 (51.882)	60.847*** (2,197.545)	−1.086 (42.110)	−48.750*** (526.878)
Median (min to max)	0.000 (−528.00 to 337.30)	−12.700*** (−3,178.00 to 48,070.00)	−0.800 (−312.10 to 205.90)	−13.800*** (−11,374.00 to 222.50)

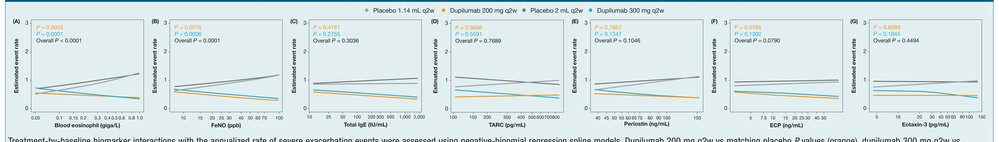
***Nominal $P < 0.001$ vs placebo. Biomarkers assessed: blood eosinophil counts (measured as part of the standard 5-part white blood count differential cell count on a hematology autoanalyzer); FeNO (NIOX® instrument; Aerocrine AB, Solna, Sweden, using a flow rate of 50 mL/s); serum total IgE (ImmunoCAP® fluorescence enzyme immunoassay method; Phadia AB, Uppsala, Sweden); serum TARC (Human TARC Quantikine ELISA kit; R&D Systems, Minneapolis, MN, USA); serum periostin (ELISA kit; Shino-Test, Kanagawa, Japan); serum eosinophil cationic protein (ECP) (ImmunoCAP® fluorescence enzyme immunoassay method; Phadia AB, Uppsala, Sweden); and plasma eotaxin-3 (Human Eotaxin-3 Quantikine ELISA kit; R&D Systems, Minneapolis, MN, USA). All biomarker comparisons were tested non-parametrically. IU, international unit; min to max, minimum to maximum; ppb, parts per billion.

Figure 2. Dupilumab significantly reduced the annualized rate of severe asthma exacerbations during the 52-week treatment period in the ITT population (A), in subgroups defined by baseline blood eosinophil counts ≥ 300 cells/μL (B), and by baseline FeNO levels ≥ 25 ppb (C).



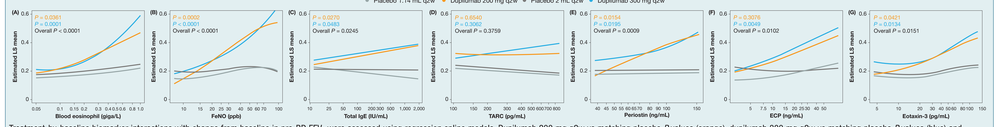
***$P < 0.001$ vs placebo. The annualized rate of severe exacerbations was analyzed using a negative binomial regression model. CI, confidence interval.

Figure 3. Dupilumab treatment effect on the annualized rate of severe exacerbations during the 52-week treatment period was influenced by baseline Type 2 inflammatory biomarkers, blood eosinophils and FeNO only: blood eosinophil counts (A), FeNO (B), total IgE (C), TARC (D), periostin (E), ECP (F), and eotaxin-3 (G).



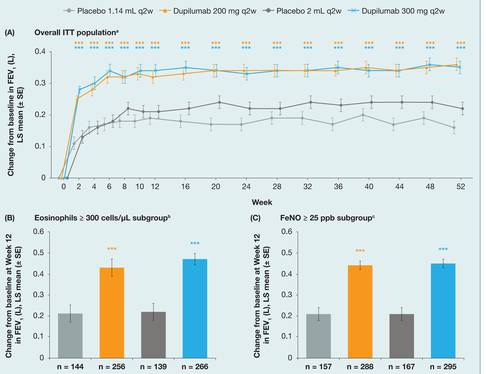
Treatment-by-baseline biomarker interactions with the annualized rate of severe exacerbation events were assessed using negative-binomial regression spline models. Dupilumab 200 mg q2w vs matching placebo *P* values (orange), dupilumab 300 mg q2w vs matching placebo *P* values (blue) and overall *P* values are indicated.

Figure 5. Dupilumab treatment effect on the change from baseline in pre-BD FEV_1 (L) at Week 12 was influenced by several baseline Type 2 inflammatory biomarkers: blood eosinophil counts (A), FeNO (B), total IgE (C), TARC (D), periostin (E), ECP (F), and eotaxin-3 (G).



Treatment-by-baseline biomarker interactions with change from baseline in pre-BD FEV_1 were assessed using regression spline models. Dupilumab 200 mg q2w vs matching placebo *P* values (orange), dupilumab 300 mg q2w vs matching placebo *P* values (blue) and overall *P* values are indicated.

Figure 4. Dupilumab significantly improved change from baseline in FEV_1 during the 52-week treatment period in the ITT population (A), and to Week 12 in subgroups defined by baseline blood eosinophil counts ≥ 300 cells/μl (B), and by baseline FeNO levels ≥ 25 ppb (C).



***$P < 0.0001$ vs matched placebo. [b]$P < 0.0001$ at Week 12, and nominal $P < 0.0001$ at all other time points. [b]$P < 0.0001$ for dupilumab 300 mg q2w vs matched placebo; nominal $P < 0.0001$ for dupilumab 200 mg vs matched placebo. [c]Nominal $P < 0.0001$ vs matched placebo. Change from baseline in pre-BD FEV_1 was analyzed using a mixed-effect model with repeated measures approach. SE, standard error.

CONCLUSIONS

- **Baseline Type 2 biomarkers, blood eosinophil counts, FeNO, total IgE, periostin, ECP, and eotaxin-3 showed significant treatment-by-baseline biomarker interactions with change from baseline in pre-BD FEV_1 at Week 12**
  - **Only baseline blood eosinophil counts and FeNO showed treatment interactions with annualized rate of severe exacerbations**
- **These data indicate that differences exist in the biological pathways for dupilumab's efficacy in improving lung function and reducing severe exacerbations, but blood eosinophil counts and FeNO are common to both and may be better biomarkers for the treatment decision for patients with uncontrolled moderate-to-severe asthma**

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NOTE: Dupilumab is in clinical development for treatment of asthma and currently has no marketing authorization for this indication.

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