Dupilumab Produces Rapid and Sustained Improvements in Asthma-Related Symptoms in Patients With Uncontrolled, Moderate-to-Severe Asthma From the LIBERTY ASTHMA QUEST Study

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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

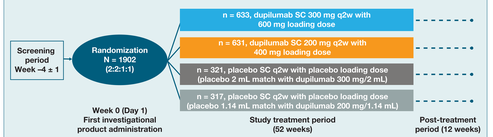
- **This pre-specified analysis of the phase 3 LIBERTY ASTHMA QUEST study evaluates the effect of dupilumab on asthma symptoms over the 52-week treatment period**

METHODS

Study design

- The design of the phase 3 LIBERTY ASTHMA QUEST study is shown in **Figure 1**

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 annualized rate of severe exacerbations during the 52-week treatment period and 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
- Patients recorded overall asthma symptom scores in an electronic diary twice a day
  - Symptoms experienced during the waking hours were recorded in the evening (PM symptom score); symptoms experienced during the night were recorded upon arising (AM symptom score); scores range between 0 and 4, with 0 indicating milder symptoms and 4 indicating more severe symptoms
- Patients also recorded the number of nocturnal awakenings due to asthma and the number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations in an electronic diary once daily
- Baseline values of efficacy assessments presented are an average of the scores recorded in the 7 days prior to randomization
- Pre-specified endpoints were change from baseline in AM and PM asthma symptom score, nocturnal awakenings, and use of daily puffs of rescue medication at Weeks 2, 4, 8, 12, 24, 36, and 52
  - Weeks 10, 16, 20, 28, 32, 40, 44, and 48 were also assessed
  - Periodical averages were generated based on time between visits
- Additional pre-specified endpoints were change from baseline in ACQ-5 score at Weeks 2, 4, 8, 12, 24, 36, and 52 and change from baseline in Asthma Quality Of Life Questionnaire with Standardized Activities [AQLQ(S)] Self-Administered (≥ 12 years) at Weeks 12, 24, 36, and 52

Statistical analysis

- Change from baseline in asthma symptom scores, number of nocturnal awakenings, and use of daily puffs of rescue medication were analyzed using a mixed-effect model with repeated measures approach
- Correlations between change from baseline in AM/PM symptom scores and change from baseline in ACQ-5 and AQLQ scores were assessed at Week 52 using the Pearson's correlation coefficient (r)

RESULTS

Patient characteristics

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

Annualized rate of severe asthma exacerbations during the 52-week treatment period and change from baseline to Week 12 in pre-bronchodilator FEV_1

- Dupilumab 200 mg/300 mg q2w vs placebo significantly reduced annualized severe exacerbation rates by 48%/46% (both $P < 0.001$) and improved pre-BD FEV_1 at Week 12 by 0.32/0.34 L (least squares [LS] mean difference vs placebo 0.14 L/0.13 L; both $P < 0.001$), with greater benefits in patients with elevated baseline blood eosinophils (≥ 300 cells/μL) and in patients with elevated baseline FeNO levels (≥ 25 ppb) (data not shown)

Change from baseline in AM asthma symptoms during the 52-week treatment period

- There were small improvements in AM asthma symptom scores in dupilumab-treated patients (**Figure 2**)
  - Improvements were reported as early as Week 2 (LS mean change –0.19 vs –0.07 and –0.16 vs –0.09 for dupilumab 200 mg and 300 mg vs matched placebo, respectively) and continued through Week 52 (nominal $P < 0.05$ at all time points)

Change from baseline in PM asthma symptoms during the 52-week treatment period

- There were small improvements in PM asthma symptom scores in dupilumab-treated patients (**Figure 3**)
  - Improvements were reported as early as Week 2 (LS mean change –0.18 vs –0.05 and –0.17 vs –0.07 for dupilumab 200 mg and 300 mg vs matched placebo, respectively) and continued through Week 52 (nominal $P < 0.05$ at all time points)

Relationship between change from baseline in AM/PM symptom scores and change from baseline in ACQ-5 and AQLQ scores

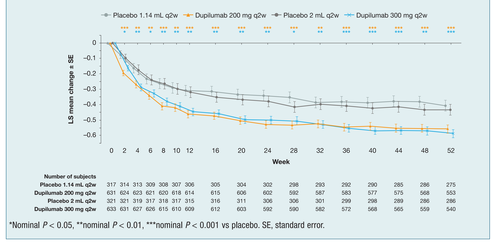
- Dupilumab improved ACQ-5 as early as Week 2 and the effect was sustained over the course of treatment (nominal $P < 0.01$ at all time points) (data not shown)
- Likewise, AQLQ was improved at Week 24 and 52 (nominal $P < 0.05$) (data not shown)
- At Week 52, moderate positive correlations were observed between change from baseline AM and PM asthma symptom scores and ACQ-5 mean score in both the placebo- and dupilumab-treated groups ($r = 0.40$ to 0.59) (**Table 2**)
- At Week 52, moderate negative correlations were observed between change from baseline AM and PM asthma symptom scores and AQLQ global score in both the placebo- and dupilumab-treated groups ($r = –0.40$ to –0.59) (**Table 2**)

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)
AQLQ global score,[b] mean (SD)	4.26 (1.02)	4.31 (1.08)	4.30 (1.03)	4.28 (1.05)	4.29 (1.05)
AM asthma symptom score, mean (SD)	1.16 (0.81)	1.14 (0.85)	1.12 (0.84)	1.12 (0.87)	1.14 (0.85)
PM asthma symptom score, mean (SD)	1.27 (0.82)	1.26 (0.85)	1.23 (0.82)	1.27 (0.84)	1.26 (0.84)
Atopic/allergic medical history, n (%)	266 (83.9)	509 (80.7)	266 (82.9)	524 (82.8)	1,565 (82.3)
Atopic dermatitis	35 (11.0)	61 (9.7)	38 (11.8)	62 (9.8)	196 (10.3)
Allergic rhinitis	221 (69.7)	421 (66.7)	225 (70.1)	438 (69.2)	1,305 (68.6)
Nasal polyposis and/or chronic rhinosinusitis	73 (23.0)	141 (22.3)	80 (24.9)	145 (22.9)	439 (23.1)

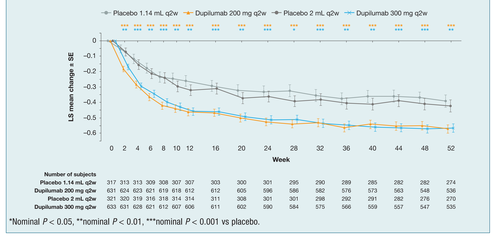
[a]ACQ-5 is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Higher scores indicate less control; a global score ranging from 0 to 6 is calculated. [b]AQLQ is a patient-reported measure of the functional impairments that are most troublesome to patients as a result of their asthma. Higher scores indicate better quality of life; a global score ranging from 1 to 7 and a score by domain is calculated. LABA, long-acting β_2-agonist; SD, standard deviation.

Figure 2. Change from baseline in asthma-related AM symptom scores for dupilumab 200 mg and 300 mg regimens during the 52-week treatment period.



*Nominal $P < 0.05$, **nominal $P < 0.01$, ***nominal $P < 0.001$ vs placebo. SE, standard error.

Figure 3. Change from baseline in asthma-related PM symptom scores for dupilumab 200 mg and 300 mg regimens during the 52-week treatment period.



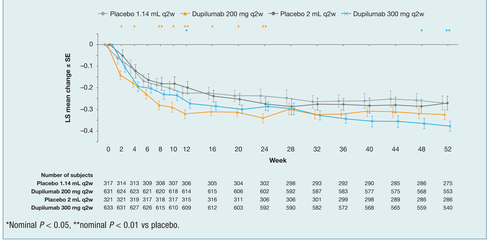
*Nominal $P < 0.05$, **nominal $P < 0.01$, ***nominal $P < 0.001$ vs placebo.

Table 2. Correlations between change from baseline in AM/PM symptom scores and change from baseline in ACQ-5 and AQLQ scores.

	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
	Placebo (n = 317)	Dupilumab (n = 631)	Placebo (n = 321)	Dupilumab (n = 633)	Placebo (n = 638)	Dupilumab (n = 1,264)
Change from baseline in AM Asthma Symptom Scores at Week 52						
vs change from baseline in ACQ-5 mean score at Week 52						
Number of patients	279	524	277	528	556	1,052
Correlation coefficient (r) (95% CI)	0.3435 (0.2350 to 0.4426)	0.4921 (0.4240 to 0.5541)	0.4384 (0.3374 to 0.5284)	0.4556 (0.3848 to 0.5203)	0.3905 (0.3173 to 0.4585)	0.4730 (0.4245 to 0.5184)
P value[a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
vs change from baseline in AQLQ(S) global score at Week 52						
Number of patients	266	516	275	506	541	1,022
Correlation coefficient (r) (95% CI)	–0.3813 (–0.4790 to –0.2729)	–0.4501 (–0.5160 to –0.3781)	–0.4334 (–0.5242 to –0.3314)	–0.4592 (–0.5250 to –0.3871)	–0.4082 (–0.4758 to –0.3351)	–0.4548 (–0.5019 to –0.4045)
P value[a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
Change from baseline in PM Asthma Symptom Scores at Week 52						
vs change from baseline in ACQ-5 mean score at Week 52						
Number of patients	275	506	264	521	539	1,027
Correlation coefficient (r) (95% CI)	0.3757 (0.2688 to 0.4724)	0.4800 (0.4096 to 0.5441)	0.4579 (0.3562 to 0.5477)	0.4619 (0.3912 to 0.5266)	0.4163 (0.3436 to 0.4835)	0.4706 (0.4214 to 0.5167)
P value[a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
vs change from baseline in AQLQ(S) global score at Week 52						
Number of patients	262	499	261	500	523	999
Correlation coefficient (r) (95% CI)	–0.3670 (–0.4669 to –0.2566)	–0.4349 (–0.5031 to –0.3605)	–0.4513 (–0.5423 to –0.3482)	–0.4752 (–0.5400 to –0.4040)	–0.4096 (–0.4782 to –0.3353)	–0.4548 (–0.5024 to –0.4039)
P value[a]	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

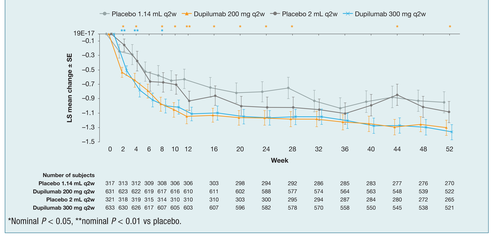
[a]Nominal P value. CI, confidence interval.

Figure 4. Change from baseline in number of nocturnal awakenings per night and for dupilumab 200 mg and 300 mg regimens during the 52-week treatment period.



*Nominal $P < 0.05$, **nominal $P < 0.01$ vs placebo.

Figure 5. Change from baseline in number of puffs of reliever medication per 24 hours for dupilumab 200 mg and 300 mg regimens during the 52-week treatment period.



*Nominal $P < 0.05$, **nominal $P < 0.01$ vs placebo.

Change from baseline in the number of nocturnal awakenings per night during the 52-week treatment period

- Dupilumab-treated patients showed numerically fewer nocturnal awakenings compared with matched placebo during the 52-week treatment period (**Figure 4**)

Change from baseline in the use of daily puffs of rescue medication during the 52-week treatment period

- Dupilumab-treated patients showed numerically less use of daily puffs of rescue medication compared with matched placebo during the 52-week treatment period (**Figure 5**)

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 (**Table 3**)
- 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 3. Overview of TEAEs (MedDRA PT) and injection-site reactions (MedDRA HLT) in the safety population.

n (%)	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
	Placebo (n = 313)	Dupilumab (n = 631)	Placebo (n = 321)	Dupilumab (n = 632)	Placebo (n = 634)	Dupilumab (n = 1,263)
Any TEAE	257 (82.1)	508 (80.5)	270 (84.1)	515 (81.5)	527 (83.1)	1,023 (81.0)
Any serious TEAE	26 (8.3)	49 (7.8)	27 (8.4)	55 (8.7)	53 (8.4)	104 (8.2)
Any TEAE leading to death[a]	3 (1.0)	1 (0.2)	0	4 (0.6)	3 (0.5)	5 (0.4)
Any TEAE leading to permanent treatment discontinuation	19 (6.1)	19 (3.0)	10 (3.1)	44 (7.0)	29 (4.6)	63 (5.0)
TEAEs (PT) occurring in ≥ 10% of patients						
Viral upper respiratory tract infection	60 (19.2)	119 (18.9)	64 (19.9)	111 (17.6)	124 (19.6)	230 (18.2)
Upper respiratory tract infection	37 (11.8)	69 (10.9)	49 (15.3)	77 (12.2)	86 (13.6)	146 (11.6)
Bronchitis	47 (15.0)	73 (11.6)	42 (13.1)	71 (11.2)	89 (14.0)	144 (11.4)
Injection-site erythema	13 (4.2)	76 (12.0)	22 (6.9)	98 (15.5)	35 (5.5)	174 (13.8)
Injection-site reaction (HLT)	17 (5.4)	96 (15.2)	33 (10.3)	116 (18.4)	50 (7.9)	212 (16.8)

[a]5 dupilumab-treated patients (0.4%; 1 using the 200 mg dose, 4 using the 300 mg dose) and 3 placebo patients (0.5%; all in the 1.14 mL group) experienced a TEAE leading to death; all deaths were considered unrelated to study medication. HLT, MedDRA High Level Term; MedDRA, Medical Dictionary for Regulatory Activities; PT, MedDRA Preferred Term.

CONCLUSIONS

- **Dupilumab q2w vs placebo significantly (nominal $P < 0.05$) and rapidly improved both morning and evening daily asthma symptoms in adult and adolescent patients (aged ≥ 12 years) with uncontrolled moderate-to-severe asthma**
  - **Improvements in asthma symptom scores were maintained over the 52-week treatment period**
- **Dupilumab q2w vs placebo also reduced nocturnal awakenings and use of rescue medication over the treatment period**
- **Improvements in morning and evening daily asthma symptoms were moderately correlated with improvements in both ACQ-5 and AQLQ scores**
- **Dupilumab was generally well tolerated**

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Disclosures

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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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