A Randomized, Controlled Phase 3 Study, LIBERTY ASTHMA QUEST, Evaluating the Efficacy and Safety of Dupilumab in Uncontrolled, Moderate-to-Severe Asthma

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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 the treatment of adults with inadequately controlled moderate-to-severe atopic dermatitis[2–4]
- In a pivotal phase 2b dose-ranging study (NCT01854047), dupilumab significantly reduced annualized severe exacerbation rates, improved pre-bronchodilator (BD) forced expiratory volume in 1 second (FEV_1), asthma symptoms, and quality of life measures, and was generally well tolerated in patients with uncontrolled persistent asthma despite the use of medium-to-high-dose inhaled corticosteroids (ICS) and long-acting β_2-agonists[5]
- LIBERTY ASTHMA QUEST (NCT02414854) was designed to confirm these findings in a phase 3 study

OBJECTIVE

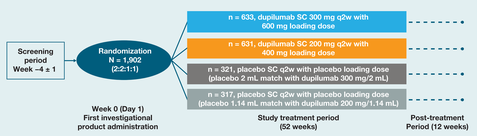
- **To evaluate the efficacy and safety of dupilumab in patients with uncontrolled, moderate-to-severe asthma**

METHODS

Study design

- The design of the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854) 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. q2w, every 2 weeks; 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[6]), on medium-to-high-dose 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, and ≥ 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 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 ≤ 6 months before screening or who had a smoking history of > 10 pack-years; diagnosis of a comorbid disease that might interfere with 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 as secondary endpoints in subgroups of patients with baseline blood eosinophil counts of ≥ 300, < 300 to ≥ 150, and < 150 cells/μL
  - These endpoints were also examined in subgroups of patients with baseline levels of FeNO ≥ 50, < 50 to ≥ 25, and < 25 parts per billion (ppb)
- Safety and tolerability were reported according to incidence of treatment-emergent adverse events (TEAEs) and serious TEAEs

Statistical analysis

- Efficacy analyses were performed on the intent-to-treat (ITT) population
- The safety population included all patients who actually received at least 1 dose or part of a dose of the dupilumab, analyzed according to the treatment that patients actually received
- The annualized rate of severe exacerbations was analyzed using a negative binomial regression model
- Change from baseline in pre-BD FEV_1 was analyzed using a mixed-effects model with repeated measures approach
- All endpoints after the hierarchy break or were not part of the hierarchical testing order, and as such were not multiplicity controlled and were nominal

RESULTS

Patient characteristics

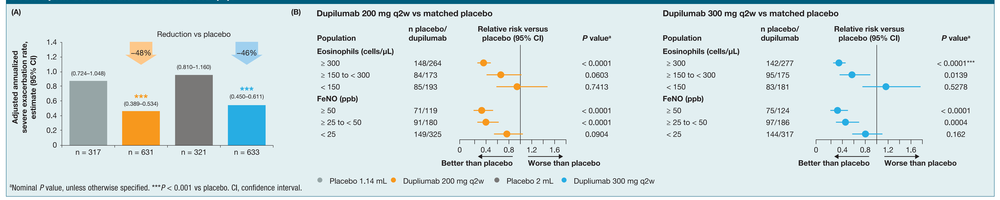
- Of 1,902 patients randomized, 1,897 received treatment
- Baseline demographics and clinical characteristics were generally similar across the treatment groups (**Table 1**)

Table 1. Baseline demographic and clinical characteristics: ITT population.

	Placebo (n = 317)	Dupilumab 200 mg q2w (n = 631)	Placebo (n = 321)	Dupilumab 300 mg q2w (n = 633)	Overall population (N = 1,902)
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, 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)
FEV_1 reversibility, mean (SD), %	25.06 (18.76)	27.39 (22.79)	26.45 (17.65)	25.73 (23.79)	26.29 (21.73)
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 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)
Blood eosinophil count, mean (SD), cells/μL	370 (338)	349 (345)	391 (419)	351 (370)	360 (366)
FeNO, mean (SD), ppb	34.47 (28.54)	34.45 (34.91)	38.39 (38.00)	34.01 (29.74)	34.97 (32.85)
Total IgE, mean (SD), IU/mL	393.90 (624.70)	460.96 (817.75)	448.47 (796.66)	415.08 (701.40)	432.40 (746.66)

[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. SD, standard deviation.

Figure 2. Annualized rate of severe asthma exacerbations during the 52-week treatment period in the ITT population (A) and in subgroups defined by baseline blood eosinophil counts and FeNO levels (B).



[a]Nominal *P* value, unless otherwise specified. ***$P < 0.001$ vs placebo. CI, confidence interval.

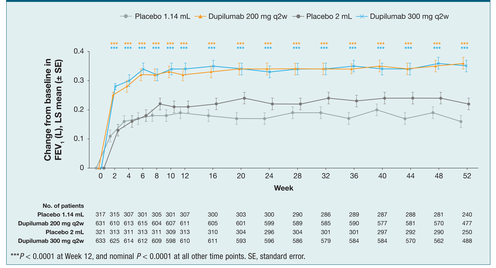
Annualized rate of severe asthma exacerbations during the 52-week treatment period

- In the overall population, dupilumab 200 mg/300 mg q2w vs placebo significantly reduced annualized severe exacerbation rates by 48%/46% (both $P < 0.001$) (**Figure 2A**)
  - Larger reductions vs placebo in annualized exacerbation rates were also observed in patients with baseline blood eosinophil counts ≥ 300 cells/μL (66% with dupilumab 200 mg q2w, nominal $P < 0.001$; 67% with dupilumab 300 mg q2w, $P < 0.001$) (**Figure 2B**)
  - Reductions in annualized exacerbation rates were also observed in patients with FeNO ≥ 25 ppb (nominal $P < 0.001$) (**Figure 2B**)
  - Patients treated with dupilumab 200 mg q2w with baseline blood eosinophil counts of < 300 cells/μL or baseline FeNO < 25 ppb saw a trend in exacerbation rate reductions vs placebo

Change from baseline to Week 12 in pre-bronchodilator FEV_1

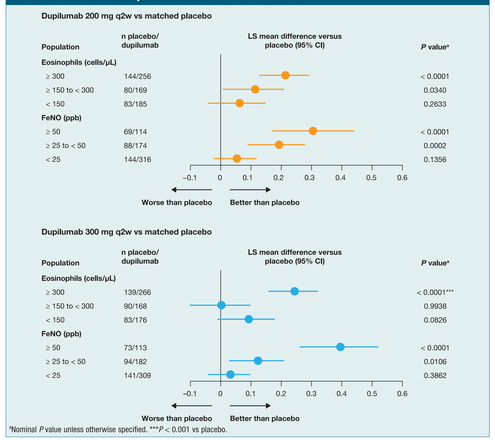
- In the overall population, dupilumab 200 mg/300 mg q2w vs placebo improved FEV_1 at Week 12 by 0.32/0.34 L (least squares [LS] mean difference vs placebo 0.14 L/0.13 L; both $P < 0.001$) (**Figure 3**)
  - Improvement in FEV_1 was rapid (with differences vs placebo seen at the first evaluation at Week 2) and was sustained throughout the 52-week treatment period (nominal $P < 0.001$ for both regimens) (**Figure 3**)
  - Larger FEV_1 improvements at Week 12 vs placebo were observed in patients with baseline eosinophil counts of ≥ 300 cells/μL (0.21 L with dupilumab 200 mg q2w, nominal $P < 0.001$; 0.24 L with dupilumab 300 mg q2w, $P < 0.001$) (**Figure 4**)
  - Improvements in FEV_1 at Week 12 were also observed in patients with baseline FeNO ≥ 25 ppb (nominal $P < 0.001$) (**Figure 4**)
  - Patients with baseline blood eosinophil counts of < 300 cells/μL or baseline FeNO < 25 ppb saw numerical improvements vs placebo in FEV_1 from baseline to Week 12

Figure 3. Change from baseline over 52 weeks in FEV_1 in the ITT population[a].



***$P < 0.0001$ at Week 12, and nominal $P < 0.0001$ at all other time points. SE, standard error.

Figure 4. Change from baseline to Week 12 in FEV_1 in subgroups defined by baseline blood eosinophil counts and FeNO levels.



[a]Nominal *P* value unless otherwise specified. ***$P < 0.001$ vs placebo.

Safety

- The incidence of TEAEs was similar across treatment groups (81% vs 83% for dupilumab- and placebo-treated patients) in the safety population (**Table 2**)
- The most frequent (> 10%) TEAEs in dupilumab-treated patients were viral upper respiratory tract infection (18% vs 20% for placebo), injection-site erythema (14% vs 6%), upper respiratory tract infection (12% vs 14%), and bronchitis (11% vs 14%)
- Blood eosinophilia occurred in 52 (4.1%) dupilumab-treated versus 4 (0.6%) placebo-treated patients

Table 2. 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 significantly reduced severe asthma exacerbations and improved lung function (FEV_1) in uncontrolled moderate-to-severe asthma patients in the overall study population; treatment effects were similar for both dupilumab doses**
  - **More robust results were observed for both reduction in severe asthma exacerbations and FEV_1 improvement in patients with higher baseline blood eosinophil counts (≥ 300 cells/μL) or higher baseline FeNO levels (≥ 25 ppb)**
  - **Significant improvement in FEV_1 in the overall population with dupilumab treatment was seen as early as Week 2, and was sustained throughout the 52-week treatment period**
- **Dupilumab was generally well tolerated in this patient population**

References

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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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