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Liberty Asthma QUEST: Phase 3 Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate Dupilumab Efficacy/Safety in Patients with Uncontrolled, Moderate-to-Severe Asthma

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ABSTRACT

Introduction: Dupilumab, a fully human anti-IL-4Rα monoclonal antibody, inhibits signaling of both interleukin (IL)-4 and IL-13, which are key drivers of type 2-mediated inflammation. Dupilumab is approved in the EU, USA, and other countries for the treatment of adults with inadequately controlled moderate-to-severe atopic dermatitis. Following positive phase 2 results in asthma, the phase 3 Liberty Asthma QUEST trial was initiated to provide further evidence for dupilumab efficacy and safety in patients with uncontrolled, moderate-to-severe asthma.

Methods: Liberty Asthma QUEST is a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial (NCT02414854) in patients with persistent asthma who are receiving continuous treatment with inhaled corticosteroids (ICS) plus one or two other asthma controller medicines. A total of 1902 patients (aged $\geq$ 12 years) were randomized in a 2:2:1:1 ratio to receive 52 weeks of add-on therapy with subcutaneously administered dupilumab 200 or 300 mg every 2 weeks or matched placebo. The study consisted of a 4 ± 1-week screening period, 52-week randomized treatment period, and 12-week post-treatment follow-up period. All patients continued

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to receive their prescribed ICS plus up to two additional controller medications. The primary efficacy endpoints were annualized rate of severe exacerbation events during the 52-week treatment period and absolute change from baseline in pre-bronchodilator FEV_1 at week 12. **Conclusion**: Uncontrolled asthma patients with persistent symptoms represent a population of significant unmet need, for whom new treatments are required. Patients with severe asthma are at high risk of asthma exacerbations, and face an accelerated decline in lung function and impaired quality of life. QUEST examines the efficacy of dupilumab in this at-risk patient population; it is the largest placebo-controlled study in uncontrolled, moderate-to-severe asthma with a biologic agent to date, and the only phase 3 study of a biologic therapy of asthma that enrolled patients irrespective of baseline type 2 inflammatory biomarker levels.

INTRODUCTION

Asthma is a chronic inflammatory airway disease characterized by airway hyper-responsiveness, bronchoconstriction, airway edema, and mucus plugging. Approximately 5–10% of patients with asthma remain uncontrolled despite receiving the maximum recommended treatment. These patients are at increased risk of frequent and severe exacerbations, have impaired lung function and impaired quality of life, and account for a high healthcare cost burden [1]. As such, they represent a population with unmet needs, for whom new treatments are required.

Asthma phenotypes, including inflammatory, clinical, and trigger-related subtypes, have been identified and defined by interactions between genetic and environmental factors [2–5]. Type 2-high asthma is a common subtype, characterized by the release of the inflammatory prototypical cytokines interleukin (IL)-4, IL-5,

and IL-13 from immune cells [6]. Several biomarkers are linked to type 2 airway inflammation, including fractional exhaled nitric oxide (FeNO), serum immunoglobulin E (IgE), periostin, and blood and sputum eosinophils [5]. Identification of inflammatory pathways involved in asthma pathophysiology has produced therapeutic approaches to severe asthma that target type 2 inflammatory mediators, including antibodies directed at IL-5, a key cytokine involved in eosinophil proliferation and recruitment to sites of inflammation.

Dupilumab is a fully human monoclonal antibody (mAb) directed against IL-4 receptor alpha (IL-4Rα). Dupilumab inhibits signaling of IL-4 and IL-13, cytokines that are key drivers of type 2 immune diseases (e.g. atopic/allergic diseases) such as atopic dermatitis (AD), asthma, allergic rhinitis, chronic rhinosinusitis (with or without nasal polyps), and food allergies that are often associated as comorbidities [7]. Dupilumab is approved in the EU, USA, and other countries for the treatment of adults with inadequately controlled moderate-to-severe AD.

In a phase 2a proof-of-concept study, dupilumab added to medium-to-high-dose inhaled corticosteroids (ICS) plus a long-acting β_2-agonist (LABA) in patients with uncontrolled persistent eosinophilic asthma [8] significantly reduced the number of patients with asthma exacerbation by 87% and improved lung function compared to placebo. Given these promising findings, a phase 2b dose-ranging study assessed dupilumab as add-on therapy in a patient population including both eosinophilic and non-eosinophilic patients. Dupilumab was well tolerated, and doses given every 2 weeks improved lung function (least squares [LS] mean change in forced expiratory volume in 1 s [FEV_1] from baseline to week 12 of 0.31 and 0.28 L for 200 and 300 mg of dupilumab, respectively, and 0.12 L for placebo), reduced severe exacerbations (70.0% to 70.5% risk reduction vs. placebo), improved asthma control (LS mean change in the 5-item asthma control questionnaire [ACQ-5] score from baseline to week 24 of − 1.49 and − 1.45 for 200 and 300 mg of dupilumab, respectively, and − 1.14 for placebo) [9], and reduced levels of type 2 inflammatory biomarkers including FeNO (LS

mean change − 18.69 and − 20.86 ppb for 200 and 300 mg doses, respectively, and − 3.90 ppb for placebo), plasma eotaxin-3 (− 32.45 and − 30.63 pg/mL in dupilumab doses, − 1.84 pg/mL in placebo), and serum IgE (− 235.40 and − 207.95 IU/mL in dupilumab doses, 6.21 IU/mL increase in placebo) over a 24-week treatment period. While this study established that a 2-weekly dosing regimen was optimum, it did not establish the most appropriate dose [9].

Following positive phase 2 results, a phase 3 program was initiated with the objective of providing further evidence of the efficacy and safety of dupilumab in patients with uncontrolled, moderate-to-severe asthma.

METHODS

Liberty Asthma QUEST Study Design

QUEST is a phase 3 multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial in patients with uncontrolled, moderate-to-severe asthma who are receiving continuous treatment with ICS plus one or two other asthma controller medicines (Clinical Trials.gov Identifier: NCT02414854). Database lock was planned to have data on the 52-week treatment period of at least 1638 randomized patients. Patients were randomized at 413 sites in 22 countries globally, making QUEST the largest placebo-controlled study ever performed to date in uncontrolled persistent asthma with a biologic agent. Subsequent to the findings of the phase 2b study that dupilumab was effective for patients with eosinophilic and non-eosinophilic asthma, the primary enrolled patient population in QUEST was based on clinical criteria alone, without any pre-specified biomarker requirement (an upper baseline blood eosinophil count limit of $> 1500/\mu L$ was included). This enabled a full, unbiased analysis of the influence of baseline biomarker and clinical characteristics on treatment response. The key inclusion and exclusion criteria for QUEST are listed in Table 1.

The study consisted of three periods: a 4 ± 1-week screening period, a 52-week randomized treatment period, and a 12-week post-treatment follow-up period (unless patients entered an open-label extension study) (Fig. 1). Patient eligibility and level of asthma control were established during the screening period. The study was sponsored by Sanofi and Regeneron Pharmaceuticals, Inc., and conducted in accordance with the principles established in the Declaration of Helsinki and the International Conference on Harmonization guidelines for good clinical practice. All study documents and procedures were approved by the appropriate institutional review board/ethics committees at each study site, and written informed consent was obtained from all patients before initiation into the study.

Treatment/Dosing

A total of 1902 patients (≥ 12 years) were randomized in a 2:2:1:1 ratio to receive 52 weeks of add-on therapy with subcutaneously administered dupilumab 200 mg (loading dose 400 mg) or 300 mg (loading dose 600 mg) every 2 weeks (q2w), or matched placebo corresponding to the respective volumes of each dupilumab pre-filled syringe (1.14 and 2 mL for the 200 and 300 mg doses, respectively). Hence, approximately 634 patients for each dupilumab dose group and 317 patients for each matching placebo group were randomized.

Patients were stratified at randomization by age (< 18, ≥ 18 years), blood eosinophil count at screening (< 300, ≥ 300 cells/μL), baseline ICS dose (medium versus high), and country. For the duration of the study, all patients continued to receive their prescribed ICS plus up to two additional asthma controller medications, without change. Throughout the study, patients were permitted to use a short-acting β_2-adrenergic receptor agonist (either salbutamol or levosalbutamol) as relief medication for asthma symptoms as needed.

Objectives and Outcome Measures

A summary of the study outcome measures is provided in Table 2. The two primary efficacy endpoints were annualized rate of severe exacerbation events during the 52-week treatment

Table 1 Patient eligibility criteria

Key inclusion criteria

Adults and adolescent pts ($\geq$ 12 years)

Physician-diagnosed asthma for $\geq$ 12 months, based on GINA 2017 Guidelines [23]

Existing treatment with medium-to-high-dose ICS ($\geq$ 250 µg of fluticasone propionate twice daily or equipotent ICS
  daily dosage to a maximum of 2000 µg/day of fluticasone propionate or equivalent) in combination with a second
  controller (e.g., LABA, LTRA) for at least 3 months with a stable dose $\geq$ 1 month prior to visit 1

Pre-bronchodilator $FEV_1 \leq 80\%$ of predicted normal for adults and $\leq$ 90% of predicted normal for adolescents at visits
  1 and 2, prior to randomization

ACQ-5 score $\geq$ 1.5 at visits 1 and 2, prior to randomization

Reversibility of at least 12% and 200 mL in FEV_1 after the administration of 200–400 µg albuterol/salbutamol or
  levalbuterol/levosalbutamol before randomization

Must have experienced, within 1 year prior to visit 1, any of the following events:

  Treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once

  Hospitalization or emergency medical care visit for worsening asthma

Key exclusion criteria

Pts < 12 years of age or the minimum legal age for adolescents in the country of the investigative site, whichever is higher

Weight is less than 30 kg

Diagnosis of chronic obstructive pulmonary disease or other lung disease that may impair lung function

Evidence of lung disease(s) other than asthma, either clinical evidence or imaging (e.g., chest X-ray, CT, MRI), within
  12 months of visit 1 as per local standard of care

A severe asthma exacerbation at any time from 1 month before screening up to and including the baseline visit

Current smokers, or smokers who stopped within 6 months before screening or had a previous smoking history
  of > 10 pack-years

Anti-IgE therapy within 130 days before screening or any other biologic therapy/immunosuppressant within 2 months
  (or five half-lives) before screening

Exposure to another investigative antibody within five half-lives or 6 months before screening, or to any other (non-
 antibody) investigative agent within 30 days before screening

Comorbid disease that might interfere with the evaluation of dupilumab

Previous treatment with dupilumab

ACQ-5 Asthma Control Questionnaire 5-question version, *CT* computed tomography, *FEV$_1$* forced expiratory volume in
1 s, *ICS* inhaled corticosteroid, *LABA* long-acting β$_2$-agonist, *LTRA* leukotriene receptor antagonists, *MRI* magnetic
resonance imaging, *pts* patients

period and absolute change from baseline in pre-bronchodilator FEV_1 at week 12. A severe asthma exacerbation was defined as a deterioration of asthma requiring treatment for $\geq$ 3 days with systemic corticosteroids, or hospitalization or an emergency room visit because of asthma, requiring systemic corticosteroids. The key secondary endpoint was the percentage change from baseline to week 12 in pre-bronchodilator FEV_1. Additional lung
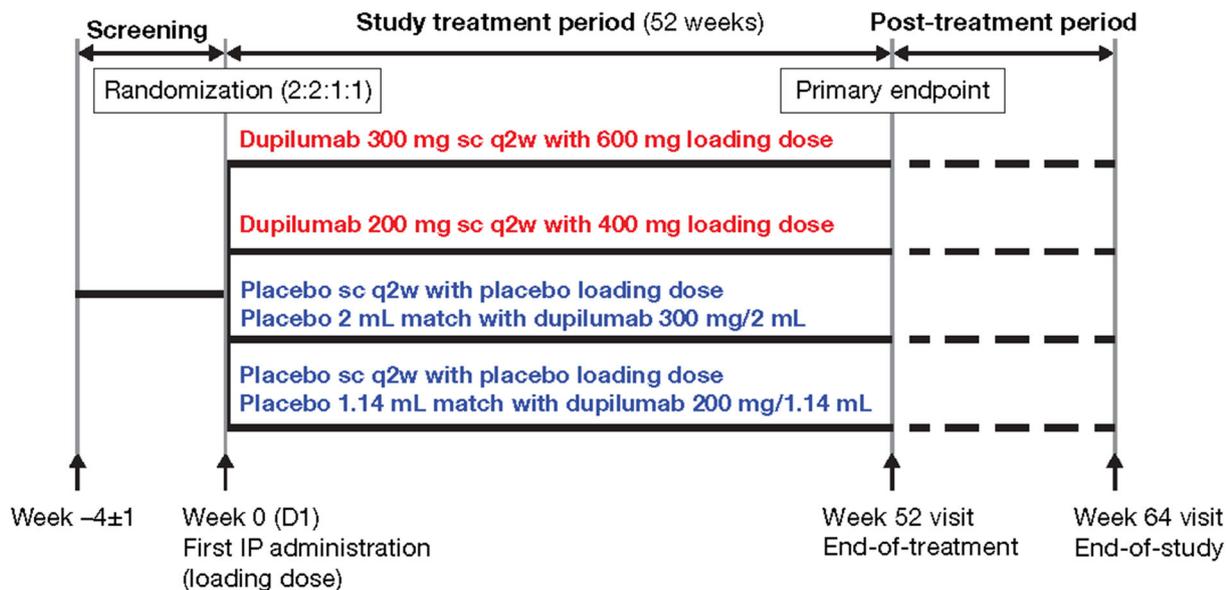
Fig. 1 LIBERTY Asthma QUEST study design. *IP* investigational product, *q2w* every 2 weeks, *sc* subcutaneously

function assessments throughout the study were the percentage predicted FEV_1, morning/evening peak expiratory flow (measured at home using an electronic peak flow meter), forced vital capacity, forced expiratory flow 25–75%, post-bronchodilator FEV_1, and post-bronchodilator slope analysis on FEV_1 to characterize the loss of lung function. Patient-reported outcome measures of asthma control (ACQ-5) and quality of life, including the asthma quality of life questionnaire (AQLQ), were assessed throughout the study period. Safety and tolerability were evaluated by assessing the incidence of adverse events (AEs) and serious AEs, and by examination of vital signs and physical assessment, clinical laboratory testing, and 12-lead electrocardiography (ECG). Blood samples for exploratory genetic analysis of DNA/RNA were also collected and stored for future investigation.

Statistical Considerations

Efficacy analyses were performed on the intention-to-treat (ITT) population (defined as all randomized patients according to the treatment allocated), regardless of whether treatment was received. The annualized rate of severe exacerbation events was analyzed using a negative binomial regression model, with the total number of events occurring during the 52-week treatment period as the response variable, and the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates. Log-transformed observation duration was the offset variable.

Patients who discontinued the study medication were encouraged to return to the clinic for all remaining study visits, and all severe exacerbation events that happened up to week 52 were included in the primary analysis, regardless of whether or not the patient was receiving treatment.

Change from baseline in continuous endpoints such as FEV_1 and patient-reported outcomes were analyzed using a mixed-effects model with repeated measures (MMRM). The model included changes from baseline values as response variables, and treatment, age, baseline eosinophil strata, baseline ICS dose level, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction as covariates. In addition, sex and baseline height were included as covariates only in the models for spirometry parameters. For patients who discontinued the study treatment and stayed in

Table 2 Summary of study outcome measures

Outcome measure	Time frame
Primary efficacy endpoints	
Annualized rate of severe exacerbation events	52 weeks
Absolute change from baseline in pre-bronchodilator FEV_1	Week 12
Secondary efficacy endpoints	
Percentage change from baseline in pre-bronchodilator FEV_1[a]	Week 12
Annualized rate of severe exacerbation events in pts with $\geq$ 300 or $\geq$ 150 eosinophils/μL	Week 12
Absolute change from baseline in pre-bronchodilator FEV_1 in pts with $\geq$ 300 or $\geq$ 150 eosinophils/μL	Week 12
Absolute change from baseline in pre-bronchodilator FEV_1	Weeks 2, 4, 8, 24, 36, 52
Percentage change from baseline in pre-bronchodilator FEV_1	Weeks 2, 4, 8, 24, 36, 52
Annualized rate of severe exacerbation events in pts with $\geq$ 300 eosinophils/μL	52 weeks
Absolute change from baseline in pre-bronchodilator FEV_1 in pts with $\geq$ 300 eosinophils/μL	Week 12
Percentage change from baseline in pre-bronchodilator FEV_1 in pts with $\geq$ 300 eosinophils/μL	Week 12
Annualized rate of severe exacerbation events in pts with $\geq$ 150 eosinophils/μL	52 weeks
Absolute change from baseline in pre-bronchodilator FEV_1 in pts with $\geq$ 150 eosinophils/μL	Week 12
Percentage change from baseline in pre-bronchodilator FEV_1 in pts with $\geq$ 150 eosinophils/μL	Week 12
Annualized rate of severe exacerbation events in pts on high-dose ICS	52 weeks
Absolute change from baseline in pre-bronchodilator FEV_1 in pts on high-dose ICS	Week 12
Percentage change from baseline in pre-bronchodilator FEV_1 in pts on high-dose ICS	Week 12
Change from baseline in other lung function measurements[b]	Weeks 2, 4, 8, 12, 24, 36, 52
Annualized rate of loss of asthma control event	52 weeks
Annualized rate of severe exacerbation events resulting in hospitalization or ER visit	52 weeks
Time to first severe exacerbation event	52 weeks
Time to first loss of asthma control event	52 weeks
Change from baseline in ACQ-5 and ACQ-7 score	Weeks 2, 4, 8, 12, 24, 36, 52
Change from baseline in am/pm asthma symptom score and nocturnal awakenings	Weeks 2, 4, 8, 12, 24, 36, 52
Change from baseline in rescue medication use	Weeks 2, 4, 8, 12, 24, 36, 52
Change from baseline in healthcare resource utilization	Weeks 12, 24, 36, 52
Change from baseline in PROs (AQLQ, EQ-5D-5L, HADS, SNOT-22[c], RQLQ[d])	Weeks 12, 24, 36, 52

Table 2 continued

Outcome measure	Time frame
Other endpoints	
Systemic drug concentration and anti-drug antibodies	Weeks 12, 24, 36, 52
Biomarker assessment (FeNO, blood eosinophils, periostin, TARC, IgE, ECP, eotaxin-3)	Weeks 12, 24, 36, 52
Safety and tolerability (includes AEs, vital signs, physical exam, clinical labs, ECG)	Continuous

ACQ-5 Asthma Control Questionnaire 5-question version, *ACQ-7* Asthma Control Questionnaire 7-question version, *AE* adverse event, *AQLQ (S)* Asthma Quality Of Life Questionnaire with Standardized Activities, *CRS* chronic rhinosinusitis, *CRSwNP* chronic rhinosinusitis with nasal polyposis, *ECG* eletrocardiogram, *ECP* eosinophil cationic protein, *EQ-5D-5L* European Quality of Life Working Group Health Status Measure 5 Dimensions–5 Levels, *ER* emergency room, *FEF* forced expiratory flow, *FeNO* exhaled nitric oxide, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *HADS* Hospital Anxiety and Depression Scale, *ICS* inhaled corticosteroid, *PEF* peak expiratory flow, *PRO* patient-reported outcome, *pts* patients, *RQLQ* Rhinoconjunctivitis Quality of Life Questionnaire, *SNOT-22* 22-item Sino Nasal Outcome Test, *TARC* thymus and activation-regulated chemokine

[a] Key secondary endpoint

[b] Percentage predicted FEV_1, morning/evening PEF, FVC, $FEF_{25-75\%}$, post-bronchodilator FEV_1

[c] Only in pts with CRS/CRSwNP

[d] Only in pts with allergic rhinitis

the study, off-treatment measurements were included in the primary model. An unstructured correlation matrix was used to model within-patient errors, and parameters were estimated using the restricted maximum likelihood method with the Newton–Raphson algorithm.

For subgroups defined in Table 3, treatment-by-subgroup interactions were analyzed using a negative binomial model/MMRM similar to the primary model, with subgroup and treatment-by-subgroup interaction added as covariates in the negative binomial models and subgroup, subgroup-by-treatment interaction, and subgroup-by-treatment-by-visit interaction added as covariates in the MMRM models. Summary statistics were also provided within each subgroup. Planned subgroups for analysis are listed in Table 3, including subgroups defined by baseline blood eosinophil counts, and by baseline FeNO and baseline periostin levels.

Time-to-event endpoints were analyzed using a Cox regression model, with time to event as the dependent variable and treatment, age, number of asthma exacerbation events in the previous year, region (pooled country), baseline eosinophil strata, and baseline ICS dose level as covariates. The Kaplan–Meier method was used to estimate the probability of a patient experiencing an event.

Descriptive statistics were used for demographic and clinical characteristics, pharmacodynamic variables, and for safety variables including AEs, vital signs and findings on physical examination, clinical laboratory testing, and ECG.

Sample Size Estimates

Assuming an annualized exacerbation rate in the placebo group of 0.6, a sample size of approximately 1638 patients was estimated to provide 99% power (two-tailed α level of 0.05) to detect a 55% relative risk reduction (i.e., annualized rate of 0.27 for the dupilumab group) in the annualized rate of severe exacerbations. This sample size was also expected to provide 98% power to the second primary endpoint, capable of detecting a treatment difference of 0.15 L in change of FEV_1 from baseline to week 12. In a population of this size, approximately 84 adolescent patients and 690 (42%) patients with a baseline blood eosinophil count of $\geq$ 300 cells/μL were expected to be randomized.

Table 3 Patient subgroups for analysis

Subgroup	Criteria
Age group (years)	< 18, 18–64, ≥ 65; < 18, ≥ 18
Gender	Male, female
Region	Asia: Japan, South Korea, and Taiwan; Latin America: Argentina, Brazil, Colombia, Chile, and Mexico; East Europe: Hungary, Poland, Russia, Turkey, and Ukraine; Western countries: Australia, Canada, France, Germany, Italy, South Africa, Spain, UK, and USA
Territory	North America: Canada and USA; European Union: France, Germany, Hungary, Italy, Poland, Spain, and UK; Rest of world: Argentina, Australia, Brazil, Colombia, Chile, Japan, Mexico, Russia, South Africa, South Korea, Taiwan, Turkey, and Ukraine
Race/ethnicity	Caucasian/White, Black/of African descent, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other
Baseline blood eosinophil level (cells/μL)	≥ 300, < 300; ≥ 150, < 150
Background ICS dose levels at randomization	Medium, high
Background controller type at randomization	ICS and LABA only, ICS and LABA and anti-leukotrienes only; ICS, LABA, and any third controller, other
Baseline FEV_1 (L)	≤ 1.75, > 1.75
ACQ-5	≤ 2, > 2
Number of severe asthma exacerbations prior to the study	1, > 1
Baseline weight (kg)	< 60, ≥ 60, < 70, ≥ 70, < 90, ≥ 90
Baseline BMI (kg/m^2)	< 25, 25 to < 30, ≥ 30
Smoking history	Former, never
Atopic medical condition	Yes, no
Age at onset of asthma (years)	< 18, 18–40, > 40
Baseline predicted FEV_1 (%)	< 60, 60–90
Baseline periostin (ng/mL)	$<$ Median, $\geq$ median
Baseline FeNO (ppb)	< 25, ≥ 25 to < 50, ≥ 50

ACQ-5 Asthma Control Questionnaire 5-question version, *BMI* body mass index, *FeNO* exhaled nitric oxide, *FEV₁* forced expiratory volume in 1 s, *ICS* inhaled corticosteroids, *LABA* long-acting β₂-agonist

DISCUSSION

Moderate-to-severe asthma patients with persistent symptoms despite ICS plus LABA use represent a population of significant unmet need and one for whom new treatments are required. These patients are at high risk of asthma exacerbations and a substantial proportion has a

history of life-threatening asthma attacks. Patients with severe asthma face an accelerated decline in lung function, which often impairs quality of life and interferes with their work and/or their daily activities. QUEST examined the efficacy of dupilumab in this at-risk patient population, and is the largest placebo-controlled study ever performed in uncontrolled, moderate-to-severe asthma with a biologic agent to date.

Rationale for Endpoint Choice

Annualized rate of severe exacerbation events is one of the most clinically relevant endpoints with which to evaluate asthma controller medications; by capturing this measure over a 52-week treatment period, any impact caused by seasonal variations in exacerbation rates was minimized. Absolute change from baseline in pre-bronchodilator FEV_1 at week 12 was selected as the second primary endpoint; this is a well-accepted parameter to determine the effect of a drug on lung function, and is a predictor of mortality in asthma.

Rationale for Dose and Regimen

In the phase 2b dose-ranging study [9], both the 300 and 200 mg q2w dupilumab dose regimens provided better efficacy compared with the equivalent dupilumab dose regimens administered every 4 weeks on most efficacy endpoints, irrespective of eosinophil count at baseline. Both doses were well tolerated and (with the exception of an increased number of injection site reactions) had tolerability profiles comparable to those observed with placebo. Both regimens were assessed in the current trial to identify and further characterize the optimal dupilumab regimen in this patient population. Matching placebo arms were included to ensure the most robust assessment of the efficacy and safety of the dupilumab regimens.

There are currently limited treatment options for patients with uncontrolled, moderate-to-severe asthma. Add-on long-acting muscarinic receptor antagonists (tiotropium) [10], and anti-IgE (omalizumab) [11] and anti-IL-5 (reslizumab, mepolizumab, and benralizumab)

[12–15] mAbs are all approved, and are added on to standard ICS plus LABA therapy, but are effective only in specific subgroups of patients. Omalizumab is indicated only for persistent asthma patients with a positive skin test or in vitro reactivity to a perennial aeroallergen [16, 17], and anti-IL-5 treatments have shown efficacy only in patients with eosinophilic asthma and are thus indicated for an eosinophilic phenotype [18–20].

Dupilumab is the first biologic to target both IL-4 and IL-13 type 2 cytokines and, as such, targets type 2 inflammation effectively, reducing not only eosinophil levels but also FeNO and periostin, two other type 2-associated biomarkers [9]. The observation that dupilumab was efficacious in patients with baseline eosinophil levels of both < 300 and ≥ 300 cells/µL in the phase 2b study was of particular interest, as prior to this, other biologics (such as the anti-IL-5 agents reslizumab, mepolizumab, and benralizumab) have shown that efficacy is limited to patients with eosinophilic asthma [14, 15, 18–20] and have been more effective in patients with higher baseline eosinophil levels. Such patients are typically associated with more severe asthma [21]. A recently published phase 2 study of tezepelumab, a mAb specific for the epithelial-cell-derived cytokine thymic stromal lymphopoietin, in uncontrolled asthma has also shown efficacy irrespective of baseline eosinophil count [22]. However, QUEST evaluates a biologic therapy for asthma with a trial design that facilitates entry into the study for all patients regardless of baseline eosinophil count, and is the first to assess the primary endpoint in the overall population, rather than a pre-specified eosinophil group. This is important, as it allows the adoption of a "real-world" approach to the treatment of asthma in a large patient population, thus ensuring that data are more representative of clinical practice. In addition, allowing patients the use of a third controller medicine if needed allows for a more accurate reflection of how patients are currently treated in clinical settings.

In terms of limitations of the QUEST study design, some of the subgroup analyses were not adequately powered. As such, any conclusions that may be drawn as a result of these analyses

should be taken with caution until replicated with additional clinical trials.

CONCLUSIONS

QUEST was the largest phase 3 clinical trial to date to assess adults and adolescents (> 12 years of age) with uncontrolled, moderate-to-severe asthma, despite treatment with ICS plus other controller medications, and to enroll patients irrespective of baseline eosinophil levels or any other biomarker requirement. The study aims to confirm earlier findings, and further demonstrate that dupilumab elicits responses in a broad range of patients with uncontrolled, moderate-to-severe asthma, and to provide these patients with improvements in lung function and asthma control, reductions in severe exacerbations, and an improved quality of life.

ACKNOWLEDGEMENTS

Pharmaceuticals, Inc. Jingdong Chao is an employee of and shareholder in Regeneron Pharmaceuticals, Inc. Neil M. H. Graham is an employee of and shareholder in Regeneron Pharmaceuticals, Inc.

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