Washington University School of Medicine Digital Commons@Becker

Open Access Publications

1-1-2019

Dupilumab improves symptoms, quality of life, and productivity in uncontrolled persistent asthma

Jonathan Corren University of California, Los Angeles

Mario Castro Washington University School of Medicine in St. Louis

Pascal Chanez Aix-Marseille Université

Leonardo Fabbri University of Modena and Reggio Emilia

Vijay N Joish Regeneron Pharmaceuticals, Inc

See next page for additional authors

Follow this and additional works at: https://digitalcommons.wustl.edu/open_access_pubs

Recommended Citation

Corren, Jonathan; Castro, Mario; Chanez, Pascal; Fabbri, Leonardo; Joish, Vijay N; Amin, Nikhil; Graham, Neil M H; Mastey, Vera; Abbé, Adeline; Taniou, Christine; Mahajan, Puneet; Teper, Ariel; Pirozzi, Gianluca; and Eckert, Laurent, ,"Dupilumab improves symptoms, quality of life, and productivity in uncontrolled persistent asthma." Annals of allergy, asthma & immunology., . . (2019). https://digitalcommons.wustl.edu/open_access_pubs/9048

This Open Access Publication is brought to you for free and open access by Digital Commons@Becker. It has been accepted for inclusion in Open Access Publications by an authorized administrator of Digital Commons@Becker. For more information, please contact engeszer@wustl.edu.

Authors

Jonathan Corren, Mario Castro, Pascal Chanez, Leonardo Fabbri, Vijay N Joish, Nikhil Amin, Neil M H Graham, Vera Mastey, Adeline Abbé, Christine Taniou, Puneet Mahajan, Ariel Teper, Gianluca Pirozzi, and Laurent Eckert



Contents lists available at ScienceDirect



Annals

Contract

Jonathan Corren, MD^{*}; Mario Castro, MD[†]; Pascal Chanez, MD[‡]; Leonardo Fabbri, MD[§]; Vijay N. Joish, PhD[¶]; Nikhil Amin, MD[¶]; Neil M.H. Graham, MD[¶]; Vera Mastey, BPharm, MS[¶]; Adeline Abbé, PhD[¶]; Christine Taniou, MS[#]; Puneet Mahajan, PhD^{**}; Ariel Teper, MD^{**}; Gianluca Pirozzi, MD, PhD^{**}; Laurent Eckert, PhD[¶]

Dupilumab improves symptoms, quality of life, and productivity

Gidilluca PIIOZZI, WID, PIID , Laurent Ecken

in uncontrolled persistent asthma

* David Geffen School of Medicine at UCLA, Los Angeles, California

[†] Washington University School of Medicine, Saint Louis, Missouri

[‡] Aix-Marseille Université, APHM CIC NORD, Marseille, France

[§] University of Modena and Reggio Emilia, Modena, Italy

Regeneron Pharmaceuticals, Inc, Tarrytown, New York

^{II} Sanofi, Chilly-Mazarin, France

Altran Technologies, Vélizy-Villacoublay, France

** Sanofi, Bridgewater, New Jersey

ARTICLE INFO

Article history:

Received for publication April 3, 2018. Received in revised form August 7, 2018. Accepted for publication August 13, 2018.

ABSTRACT

Background: In a pivotal, phase 2b study (NCT01854047) in patients with uncontrolled persistent asthma, despite using medium-to-high-dose inhaled corticosteroids plus long-acting β 2 agonists, dupilumab improved lung function, reduced severe exacerbations, and showed an acceptable safety profile.

Objective: To assess the impact of dupilumab on asthma control, symptoms, quality of life (QoL), and productivity. **Methods:** Data are shown for the intention-to-treat population receiving dupilumab 200/300 mg every 2 weeks (doses being assessed in phase 3; NCT02414854), or placebo. Predefined analyses of total scores were conducted at week 24 for the 5-item Asthma Control Questionnaire (ACQ-5), patient-reported morning/evening (AM/PM) asthma symptoms, Asthma Quality of Life Questionnaire (AQLQ), and asthma-related productivity loss. Responder rate analyses for these measures, subgroup analyses by baseline characteristics, and asthma-related productivity loss analyses were conducted post hoc.

Results: Data from 465 patients were analyzed (158 placebo; 307 dupilumab). Both dupilumab doses significantly improved scores through week 24 (all outcomes, overall population). The proportion of patients meeting or exceeding the minimal clinically important difference for the overall population were significantly greater vs placebo (P < .05) for ACQ-5 (range, 72.6%-76.7% vs 61.4%), for AM/PM asthma symptoms score (48.7%-54.1% vs 34.2% and 52.7%-53.5% vs 34.2%, respectively) and for AQLQ (64.0%-65.0% vs 51.3%). The effect of dupilumab was consistent across most subgroups. Productivity loss was significantly higher in placebo- vs dupilumab-treated patients (P < .0001).

Conclusion: Dupilumab produced significant, clinically meaningful improvements in asthma control, symptoms, QoL, and productivity.

Registration: ClinicalTrials.gov Identifier: NCT01854047.

© 2018 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (http://creativecommons.org/licenses/by-nc-nd/4.0/)

from Almirall, AstraZeneca, Boehringer Ingelheim, Boston Scientific, Centocor, Chiesi, GlaxoSmithKline, Novartis, and Teva. V. N. Joish is a former employee and shareholder of Regeneron Pharmaceuticals, Inc. N. Amin, N. M. H. Graham, and V. Mastey are employees of and shareholders in Regeneron Pharmaceuticals, Inc. A. Abbé is a former employee of Sanofi. P. Mahajan, A. Teper, G. Pirozzi, and L. Eckert are employees of and may hold stock and/or stock options in Sanofi. C. Taniou is an employee of Experis IT.

Funding Sources: This research was sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.

https://doi.org/10.1016/j.anai.2018.08.005

Reprints: Jonathan Corren, MD, David Geffen School of Medicine at UCLA, 10780 Santa Monica Blvd, Suite 280, Los Angeles, CA 90025. E-mail: jcorren@ucla.edu.

Disclosures: J. Corren has received research funding from Sanofi. M. Castro and L. Fabbri have received funding from Sanofi for participation in a dupilumab clinical trial. P. Chanez is a consultant for Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Johnson & Johnson, MSD, Novartis, and Teva, is an advisory board member for Almirall, AstraZeneca, Boehringer Ingelheim, Centocor, Chiesi, GlaxoSmithKline, MSD, Novartis, and Teva, has received honoraria from Almirall, AstraZeneca, Boehringer Ingelheim, Centocor, Chiesi, GlaxoSmithKline, MSD, Novartis, Schering Plough, and Teva, and has received research funding

Introduction

Asthma is a heterogeneous disease consisting of phenotypes defined, in part, by clinical parameters such as age of onset, presence of allergic features, degree of airway obstruction, obesity, sex, and smoking history.¹⁻³ These characteristics may be associated with outcome and treatment response.³ Poor asthma control has been associated with increased risk of asthma exacerbations, asthma-related hospitalization,^{4,5} poor quality of life (QoL),⁶ adverse impact on productivity,^{7,8} and possibly, increased risk of mortality.⁹⁻¹¹

Dupilumab, a fully human monoclonal antibody directed against the interleukin (IL)-4 receptor- α , inhibits signaling of IL-4 and IL-13. These cytokines are key drivers of type 2/Th2 immune responses that occur in asthma, allergic rhinitis, food allergies, and atopic dermatitis (AD). Dupilumab is approved in the European Union, United States, and other countries for the treatment of adults with inadequately controlled moderate-to-severe AD. Dupilumab is under clinical development for the treatment of uncontrolled persistent asthma, chronic rhinosinusitis with nasal polyposis, and eosinophilic esophagitis.

A pivotal, phase 2b, dose-ranging study (ClinicalTrials.gov Identifier: NCT01854047) assessed the efficacy and safety of dupilumab in patients with uncontrolled persistent asthma despite the use of medium-to-high-dose inhaled corticosteroids (ICS) plus a long-acting β_2 -agonist (LABA).¹² Dupilumab significantly reduced severe asthma exacerbation rates and improved pulmonary function in both the overall study population and in subgroups defined by baseline eosinophil count (<300 and \geq 300 cells/ μ L), while also demonstrating an acceptable safety profile.¹² When assessed using standard patient-reported outcome (PRO) questionnaires at baseline, more than half of the patients in the study had at least a moderate degree of impaired physical or emotional functioning.¹³ Secondary outcomes that measured asthma control, asthma symptoms, and disease-specific health-related QoL showed that patients receiving dupilumab had improvements in each of these outcomes, irrespective of baseline eosinophil count.¹²

Although the main goals of asthma treatment include reduction of symptoms, improvement in QoL, and prevention of exacerbations, clinical trials of new treatments have primarily focused on exacerbations and lung function as key endpoints. PROs such as symptom control and QoL are increasingly being recognized as being important in asthma, and regulatory agencies often request inclusion of these outcomes in clinical trials.^{14–16} Furthermore, treatment effects on exacerbations, lung function, and PROs show only modest correlations, making each measure a useful independent assessment.

In this post hoc analysis of the phase 2b study, we aimed to further investigate the effect of dupilumab on PROs by examining individual patient response rates and consistency of effect in specific patient subgroups, defined by baseline characteristics. In addition, we examined whether dupilumab treatment could affect loss of productivity in the workplace attributable to asthma.

Methods

Study design, inclusion and exclusion criteria, and main efficacy and safety outcomes of this randomized, double-blind, placebo-controlled, parallel-group, multicenter, multinational, pivotal, phase 2b clinical trial have been described previously.¹² Main inclusion criteria were: adults; asthma diagnosis¹⁷ for 12 months or longer; treatment with medium-to-high-dose ICS+LABA with a stable dose of ICS+LABA for 1 month or longer before screening; pre-bronchodilator forced expiratory volume in 1 second (FEV₁) 40% to 80% of predicted, with reversibility of at least 12% and at least 200 mL in FEV₁ after 200 to 400 µg salbutamol at screening; 5-item Asthma Control Questionnaire (ACQ-5) total score¹⁸ 1.5 or higher at screening and study baseline; and 1 or more systemic corticosteroid burst therapy, hospital admission, or an emergency or urgent medical care visit that required treatment with systemic steroids for worsening asthma within 1 year before screening. Main exclusion criteria were diagnosis of chronic obstructive pulmonary disease or other lung disease impairing pulmonary function; β -adrenergic receptor blocker use; use of systemic corticosteroids within 28 days of, or during, the screening period; current smoker, more than 10 pack-years smoking history, or cessation of smoking within 6 months of screening.

Patients were randomized (1:1:1:1:1) by a centralized treatment allocation system to receive placebo or 1 of the doses of subcutaneous dupilumab (200 mg or 300 mg) every 2 weeks (q2w) or every 4 weeks (q4w) for 24 weeks, followed by a 16-week follow-up period. Because only the 200 mg and 300 mg every 2 weeks regimens were further evaluated in phase 3 clinical trials, this manuscript reports the findings with these doses. This study was done in accordance with the principles established in the Declaration of Helsinki and the International Conference on Harmonisation guidelines for Good Clinical Practice. All study documents and procedures were approved by the appropriate institutional review board or ethics committee at each study site (e-Appendix 1). All patients provided written informed consent before participation in the study.¹²

Asthma control was assessed as change from baseline to week 24 in ACQ-5 total score and individual items (frequency of waking during the night, asthma morning symptoms, activity limitation, shortness of breath, and wheezing caused by asthma).^{18,19} The ACQ-5 scores range from 0 (excellent asthma control) to 6 (poor asthma control).

Asthma symptoms were assessed as change from baseline to week 24 in asthma symptom scores (range, 0-4), using daily patient self-reported morning (AM) and evening (PM) asthma symptoms recorded using an electronic diary. The AM asthma symptom score is a 1-item question recorded on rising and assesses asthma symptoms occurring at night (0 = no asthma symptoms, slept through night; 4 = bad night, awake most of night because of asthma). The PM asthma symptom score is a 1-item question recorded in the evening, and it assesses asthma symptoms that occurred during the day (0 = very well, no asthma symptoms; 4 = asthma very bad, unable to carry out daily activities as usual). Baseline AM or PM scores are the average of the respective scores recorded for 7 days.

Quality of life was assessed as change from baseline to week 24 in the Asthma Quality of Life Questionnaire (AQLQ), a 32-item questionnaire composed of 4 health-related QoL domains (activity limitation, emotional function, exposure to environmental stimuli, and asthma symptoms) rated on a 7-point Likert-like scale (1 = totally limited, all the time, a very great deal, or severely limited; 7 = not at all limited, none, or no discomfort/distress).²⁰

Productivity loss was measured using a patient-reported health care resource utilization questionnaire that included an assessment of the number of days lost from work, whether a patient experienced at least 1 day of sick leave from work because of a severe exacerbation event during the 24-week treatment period, and calculated the annualized rate of sick leave caused by severe exacerbation events. A severe exacerbation event was defined as the deterioration of asthma requiring use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit because of asthma requiring systemic corticosteroids.

To further explore the effects of dupilumab, analyses were also performed on subgroups of patients with baseline clinical characteristics associated with different asthma phenotypes. Subgroups included: sex, body mass index, age at asthma onset, FEV₁, FEV₁ percentage predicted, postbronchodilator reversibility, number of severe asthma exacerbations in the year before the study, ICS+LABA dose at randomization, eosinophil count, history of atopy (defined as 2 or more positive aeroallergen-specific IgE antibodies at baseline), and smoking history.

Results are reported for all patients randomized to receive placebo dupilumab 200 mg every 2 weeks or 300 mg every 2 weeks (ie, the dupilumab regimens under investigation in phase 3 [ClinicalTrials. gov Identifier: NCT02414854]). Changes from baseline at week 24 for ACQ-5, AM and PM asthma symptom scores, and AQLQ total scores for the intention-to-treat overall population, and by eosinophil count less than 300 and at least 300 cells/ μ L were predefined endpoints in the original study.¹² Post hoc analyses included responder rates at week 24 for ACQ-5, AM/PM asthma symptom scores, AQLQ, and changes from baseline at week 24 for the individual items or domains of the ACQ-5 and AQLQ scores, subgroups, and productivity.

A mixed-effect model with repeated measures was used with changes from baseline scores to week 24 as dependent variables. Factors (fixed effects) for treatment, pooled countries/regions, visit, treatment-by-visit interaction, baseline eosinophil strata, baseline scores, and baseline-by-visit interaction were covariates, with an unstructured correlation matrix. The interactions were obtained using a mixed-effect model with repeated measures with additional terms for the subgroup under consideration, treatment-by-subgroup interaction, and subgroup-by-treatment-by-visit interaction.

Responder rates were defined as the proportions of patients with scores exceeding the threshold of the minimum clinically important difference (MCID). To aid clinical interpretability of the PRO findings, two MCIDs are presented for each questionnaire. The first analysis used an MCID of 0.5 for ACQ-5 and AQLQ^{21.22} and 0.35 for AM/PM asthma symptom score. The ACQ-5 and AQLQ thresholds are based on published literature. The AM/PM MCID was derived using Cohen's rule (ie, scores beyond half the standard deviation [SD] are considered clinically meaningful). The second analysis used more conservative MCID estimates; selected MCIDs were 0.6 for ACQ and AQLQ and 0.4 for AM/PM symptoms. Responder rates were compared between treatment groups using multiple logistic regression models for each specific patient subgroup, with response status as the dependent variable and treatment, pooled countries/regions, and baseline score value as covariates.

Table 1

Baseline Characteristics (ITT Population)

		Dupilumab				
	Placebo (n = 158)	200 mg every 2 weeks (n = 150)	300 mg every 2 weeks (n = 157)			
Demographic characteristics						
Mean age, years (SD)	49.0 (12.7)	51.0 (13.4)	47.5 (12.4)			
Male sex, n (%)	54 (34.2)	54 (36.0)	54 (34.4)			
Race, n (%)	. ,	· · ·	. ,			
White	119(75.3)	114 (76.0)	129 (82.2)			
Black or African American	9(57)	9(60)	5(32)			
Asian	25(158)	25(167)	22(140)			
Other	5(32)	2(13)	1(06)			
Employment status at baseline	0 (0.2)	2(113)	1 (0.0)			
Full-time n (%)	79 (52 3)	65 (45.8)	69 (46 9)			
Part-time n (%)	14 (93)	16(113)	18(12.2)			
Unemployed n (%)	46 (30.5)	43 (30 3)	47 (32 0)			
Retired n(%)	12 (7 9)	18 (12 7)	13 (8 8)			
Missing n	7	8	10			
Clinical characteristics	,	0	10			
$PMI > 20 \ lrg/m^2 \ n (\%)$	60 (28 0)	65 (42.2)	62 (40.1)			
$Divit \ge 50 \text{ kg/m}$, $\Pi(\infty)$ Mean baseline eosinophils/ μI (SD)	342.3 (300.0)	361 1 (352 7)	322.9 (245.1)			
Time since first asthma diagnosis	542.5 (500.0)	501.1 (552.7)	522.5 (245.1)			
Number	150	140	156			
Moan years (SD)	130	149	100			
Mean FFV L (SD)	21.90(10.40)	25.95 (15.75)	20.21 (15.45)			
$\frac{1}{1} \frac{1}{1} \frac{1}$	1.82 (0.55)	1.79(0.52)	1.85 (0.53)			
Mean FEV ₁ , % predicted (SD)	60.96 (10.72)	61.23 (11.00)	60.76 (10.39)			
Number of astrinia exacerbations in past year	150	150	157			
Number of patients	108	100	157			
Mean (SD)	2.27 (2.25)	1.85 (1.43)	2.37 (2.29)			
High-dose ICS+LABA use	455		450			
Patients, n	155	144	153			
n (%)	77 (49.7)	75 (52.1)	79 (51.6)			
Any type 2 related comorbidity, " n (%)	108 (70.1)	106 (71.1)	104 (67.5)			
Atopic dermatitis	16(10.4)	10 (6.7)	16(10.4)			
Allergic rhinitis	102 (66.2)	99 (66.4)	94 (61.0)			
Chronic rhinosinusitis	18 (11.7)	23 (15.4)	32 (20.8)			
Nasal polyposis	18 (11.7)	25 (16.8)	30 (19.5)			
Food allergy	17 (11.0)	18 (12.1)	13 (8.4)			
PROs						
ACQ-5 total score (0 to 6, where 6 is worst)						
Patients, n	158	150	157			
Mean (SD)	2.69 (0.80)	2.73 (0.82)	2.80 (0.83)			
AQLQ total score (1 to 7, where 1 is worst)						
Patients, n	156	148	153			
Mean (SD)	4.12 (1.10)	4.03 (1.15)	3.91 (1.13)			
Mean AM/PM symptom score (0 to 4, where 4 is worst)						
AM score (SD)	1.17 (0.79)	1.24(0.81)	1.25 (0.78)			
PM score (SD)	1.32 (0.81)	1.42 (0.79)	1.47 (0.85)			
Smoking history						
Patients, n	158	150	157			
Former smoker, n (%)	34 (21.5)	32 (21.3)	36 (22.9)			
Pack-year						
Patients, n	34	32	35			
Mean (SD)	4.31 (3.13)	4.33 (3.15)	3.88 (3.42)			

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index; FEV₁, forced expiratory volume (L) in 1 second; ICS, inhaled corticosteroids; ITT, intention to treat; LABA, long-acting β_2 -agonist; PRO, patient-reported outcome; SD, standard deviation. ^aUse of ICS+LABA was recorded in an electronic diary.

baccord loss linited history

^bAssessed by clinical history.

^cChronic rhinosinusitis included patients with and without nasal polyposis.



Figure 1. Effect of dupilumab at week 24 on: A: ACQ-5 total score and individual items; B: AM/PM asthma symptom score; and C: AQLQ total score and related domains. ACQ-5, 5item Asthma Control Questionnaire; AM/PM, patient-reported morning/evening asthma symptoms; AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; LS, least squares; q2w, every 2 weeks; SE, standard error.





Unadjusted rates for productivity loss were derived using total number of days of sick leave during the treatment period (between first dose date and last dose date +14 days) divided by total number of patient-years followed in the treatment period. *P* values were estimated using adjusted analyses; Poisson model with the total number of events onset between first dose date and last dose date +14 days as the response variable; treatment, pooled countries/regions, and number of asthma events prior to the study as covariates; and log-transformed standardized treatment duration as an offset variable.

No type I error adjustments for multiplicity were applied in reporting the results. $P \leq .05$ were considered statistically significant.

Results

Baseline Disease Burden

Seven hundred seventy-six patients were enrolled in the phase 2b trial; this analysis, which examines both predefined and post hoc

Table 2

Proportions of Responders at Week 24^a

endpoints, included 465 patients randomized to either the placebo group (n = 158), or to the dupilumab group (200 mg every 2 weeks or 300 mg every 2 weeks; n = 307). Overall, demographics, clinical characteristics, and PRO scores were generally similar across the treatment groups at baseline (Table 1).

PROs

At week 24, both dupilumab regimens (200 and 300 mg every 2 weeks) resulted in significant improvements in ACQ-5 total score (least squares mean difference vs placebo -0.35 and -0.31, respectively; Fig 1A, eFig 1), AM asthma symptom score (-0.22 and -0.20; Fig 1B, eFig 2), PM asthma symptom score (-0.21 and -0.23; Fig 1B, eFig 3), and AQLQ total score (0.32 and 0.36; Fig 1C, eFig 4) (all P < .01).

Dupilumab 200 mg every 2 weeks significantly improved each individual item of the ACQ-5 vs placebo, whereas dupilumab 300 mg every 2 weeks significantly improved 3 of the 5 items (Fig 1A). With the exception of "environmental stimuli," both doses

		Dupilumab			
		Placebo ($n = 158$)	200 mg q2w (n = 150)	300 mg q2w (n = 157)	
Proportion of patients meeting or exceeding the MCID ^b	ACQ-5 total score	61.4	76.7 ^e	72.6 ^d	
	AM asthma symptom score	34.2	48.7 ^d	54.1 ^e	
	PM asthma symptom score	34.2	52.7 ^e	53.5 ^e	
	AQLQ total score	51.3	64.0 ^d	65.0 ^d	
Proportion of patients meeting or exceeding the MCID ^c	ACQ-5 total score	60.1	76.7 ^e	72.6 ^d	
	AM asthma symptom score	31.0	46.7 ^e	51.0 ^e	
	PM asthma symptom score	31.0	50.0 ^e	51.6 ^e	
	AQLQ total score	47.5	60.7 ^d	63.1 ^e	

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; MCID, minimal clinically important difference; q2w, every 2 weeks. ^aPatients who met the corresponding criterion are considered as responders. Patients who did not meet the criterion or had missing value are considered as non-responders. P-values are derived from a logistic regression model with treatment, region (Asia, Latin America, East Europe, or Western Countries), baseline eosinophil stratum, and baseline score as covariates. ^bFor this analysis, MCIDs are 0.5 for ACQ-5 and AQLQ, and 0.35 for AM/PM asthma symptom scores.

^cFor this analysis, MCIDs are 0.6 for ACQ-5 and AQLQ, and 0.40 for AM/PM asthma symptom scores.

 $^{d}P < 0.05$ vs placebo.

 $^{e}P \leq 0.01$ vs placebo.

Table 3

Effect of Dupilumab on Productivity Loss

		Dupi	lumab
	Placebo (n = 158)	200 mg every 2 weeks (n = 150)	300 mg every 2 weeks (n = 157)
Total number of severe exacerbation events	75	20	23
Total number of patients employed ITT	93 (58.9%)	81 (54.0%)	87 (55.4%)
Number of employed patients with ≥ 1 day of sick leave (work) due to severe exacerbation event			
Yes	11 (11.8%)	4 (4.9%)	5 (5.7%)
No	82 (88.2%)	77 (95.1%)	82 (94.3%)
Total days of sick leave (work) due to severe exacerbation event	92	22	24
Total days of sick leave (work) due to severe exacerbation event/per severe exacerbations	1.23	1.10	1.04
Total patient-years followed	41.1	35.9	38.9
Unadjusted annualized days of sick leave due to severe exacerbation event (days/year) ^a	2.238	0.613 ^b	0.617 ^b

Abbreviation: ITT, intention to treat.

^aThe total number of events during the treatment period (between first dose date and last dose date + 14 days) divided by the total number of patient-years followed in the treatment period.

^bP < .0001 with adjusted analyses; Poisson model with the total number of events onset between first dose date and last dose date + 14 days as the response variable, treatment, pooled countries/regions, and number of asthma events because of the study as covariates, and log-transformed standardized (in years) treatment duration as an offset variable.

of dupilumab significantly improved all AQLQ domains compared with placebo (Fig 1C).

Productivity Loss

PRO MCID Analysis

LS mean change from baseline was higher than the MCID for all treatment cohorts on the ACQ-5 total score, AM and PM asthma symptom score, and total AQLQ overall score (Fig 1). The proportion of patients meeting or exceeding the respective MCIDs for each of the PROs assessed are shown in Table 2. Responder rates were greater for dupilumab-treated patients compared to placebo on the ACQ-5, the AM and PM asthma symptom scores and the AQLQ (P < .05 for the 200 mg q2w and 300 mg q2w dose vs placebo for all tests).

Employment status at baseline (either full- or part-time) was comparable across treatment groups (Table 1). Assessment of productivity loss related to severe exacerbation events revealed a total of 22 and 24 days of sick leave in the dupilumab 200 and 300 mg every 2 weeks groups, respectively, compared with 92 days with placebo (P < .001). These translate to unadjusted annualized rates of sick leave because of severe exacerbations of 0.6 days per patient receiving either dose of dupilumab regimen vs 2.2 days for placebo-treated patients (P < .0001 for either dupilumab dose; Table 3), which amounts to a 73% and 72% reduction in loss of productivity for the dupilumab 200 and 300 mg every 2 weeks regimens vs placebo, respectively.

zh. Aog e Alarysis sy Baseline oovallates Week 24 zooling 42W										
Subgroup, P value for interaction	n placebo/ dupilumab	LS mean change from baseline (± SE)	LS mean difference vs placebo (95% Cl)	P value vs placebo	Subgroup, P value for interaction	n placebo/ dupilumab	LS mean change from baseline (± SE)	LS mean difference vs placebo (95% Cl)	P value vs placebo	
Gender, P = 0.1359					Gender, P = 0.3112					
Male	46/49	-1.35 (0.13)		0.3831	Male	46/49	-1.42 (0.13)		0.1959	
Female	81/85	-1.59 (0.10)		0.0007	Female	81/96	-1.50 (0.10)	——	0.0044	
Baseline BMI (kg/m²), P =	0.5381				Baseline BMI (kg/m²), P =	0.7684				
< 30	80/79	-1.42 (0.10)	_ _	0.0227	< 30	80/85	-1.46 (0.09)	— — —	0.0091	
≥ 30	47/55	-1.63 (0.13)		0.0181	≥ 30	47/60	-1.45 (0.13)	 _	0.1528	
Age of onset of asthma, P	9 = 0.1690				Age of onset of asthma, P	= 0.7670				
< 18	45/41	-1.67 (0.14)		0.0081	< 18	45/48	- 1.48 (0.14)		0.0904	
18-40	48/52	-1.37 (0.12)		0.7573	18-40	48/58	-1.52 (0.12)		0.2249	
> 40	34/40	-1.46 (0.14)		0.025	> 40	34/37	-1.22 (0.15)	_	0.2935	
Baseline FEV, (L), P = 0.12	233				Baseline FEV ₁ (L), P = 0.09	954				
≤ 1.75	62/69	-1.52 (0.11)		0.0008	≤ 1.75	62/74	-1.50 (0.11)		0.0013	
> 1.75	65/65	-1.48 (0.11)		0.2451	> 1.75	65/71	-1.44 (0.11)		0.383	
Baseline predicted FEV1 (%), P = 0.3608	3	-		Baseline predicted FEV1 (%), P = 0.5060)			
< 60	49/59	-1.60 (0.12)		0.0106	< 60	49/63	-1.54 (0.12)		0.0294	
≥ 60	78/75	-1.40 (0.10)		0.0762	≥ 60	78/82	-1.38 (0.10)	———	0.887	
Post bronchodilator rever	sibility (L), P :	= 0.1199	_		Post bronchodilator revers	sibility (L), P =	= 0.4724			
≤ 0.38	60/71	-1.44 (0.11)		0.0011	≤ 0.38	60/69	-1.30 (0.11)		0.0164	
> 0.38	67/63	-1.51 (0.12)		0.255	> 0.38	67/76	-1.59 (0.11)		0.0958	
No. of asthma events prio	r to the study,	P = 0.0039			No. of asthma events prior	r to the study,	P = 0.0007			
≤1	65/80	-1.27 (0.09)		0.6576	≤ 1	65/63	-1.12 (0.10)	-+ -	0.4836	
> 1	62/54	-1.74 (0.14)	_	0.0002	> 1	62/82	- 1.70 (0.11)	— — —	< 0.0001	
ICS+LABA dose at randor	nization, $P = 0$.5639	-		ICS+LABA dose at randon	nization, P = 0	.6299			
Medium	71/62	-1.50 (0.11)		0.0215	Medium	71/67	-1.43 (0.11)		0.0579	
High	53/66	-1.54 (0.12)		0.0035	High	53/75	-1.47 (0.11)		0.01	
Baseline eosinophil count	t (cells/uL). P	= 0.7657			Baseline eosinophil count	(cells/µL), P =	= 0.1129	_		
< 300	75/75	-1.46 (0.10)		0.0201	< 300	75/87	-1.29 (0.10)	- +	0.2259	
≥ 300	52/59	-1.59 (0.12)		0.0171	≥ 300	52/58	-1.72 (0.13)		0.0021	
History of atopy, $P = 0.741$	89		_		History of atopy, $P = 0.586$	5	. ,			
With history of atopy	93/80	-1 47 (0 10)		0.0188	With history of atopy	93/110	-1.41 (0.09)		0.0391	
Without history of atopy	34/50	-1.51 (0.14)	_	0.0681	Without history of atopy	34/32	-1.52 (0.17)		0.0933	
Smoking history, P = 0.35	37		-		Smoking history, P = 0.23	22	. ,			
Former	28/27	-1.48 (0.18)		0.0317	Former	28/34	-1.53 (0.17)		0.016	
Never	99/107	-1.49 (0.09)		0.0187	Never	99/111	-1.43 (0.09)		0.0564	
		,,							_	
		-1.6	1.2 0.8 0.4 0 0.4 0.8	1.2			- 1.6	-1.2 -0.8 -0.4 0 0.4 0.8	1.2	
			Better than placebo Worse than p	lacebo				Better than placebo Worse than placebo	acebo	

Figure 2. ACQ-5, analysis by baseline covariates. A: ACQ-5 analysis by baseline covariates, Week 24 200 mg every 2 weeks; B: ACQ-5 analysis by baseline covariates, Week 24 300 mg every 2 weeks; ACQ-5, 5-item Asthma Control Questionnaire; BMI, body mass index; FEV₁, forced expiratory volume (L) in 1 second; ICS; inhaled corticosteroids; LABA, long-acting β₂-agonist; q2w, every 2 weeks; SE, standard error.

2A. ACQ-5 Analysis by Baseline Covariates Week 24 200mg q2w

2B. ACQ-5 Analysis by Baseline Covariates Week 24 300mg g2w

3A. AM Asthma Symptom Scores Week 24 200mg q2w

3B. AM Asthma Symptom Scores Week 24 300mg q2w

.ue for	n placebo/ dupilumab	LS mean change from baseline (± SE)	LS mean difference vs placebo (95% Cl)	P value vs placebo	Subgroup, P value for interaction	n placebo/ dupilumab	LS mean change from baseline (± SE)	LS mean difference vs plac (95% Cl)	ebo P value v placebo
Gender, P = 0.0489					Gender, P = 0.0726				
Male	48/49	-0.47 (0.08)		0.7392	Male	48/47	-0.47 (0.08)		0.7583
Female	84/87	-0.64 (0.06)		0.0003	Female	84/98	-0.60(0.06)		0.0007
Baseline BMI (kg/m²), P	= 0.1255				Baseline BMI (kg/m²), P =	0.3412			
< 30	84/79	-0.62 (0.06)		0.0005	< 30	84/85	-0.57 (0.06)		0.0028
≥ 30	48/57	-0.50 (0.08)	—•–	0.4718	≥ 30	48/60	-0.54 (0.08)		0.2934
Age of onset of asthma,	, P = 0.2065				Age of onset of asthma, P	= 0.6904			
< 18	47/42	-0.56 (0.09)	—•+	0.1105	< 18	47/48	-0.47 (0.09)		0.4133
18-40	50/53	-0.49 (0.08)		0.4695	18-40	50/59	-0.60 (0.08)		0.0744
> 40	35/40	-0.75 (0.10)		0.0027	> 40	35/36	-0.62 (0.10)		0.0444
Baseline FEV, (L), P = 0	.1684				Baseline FEV, (L), P = 0.15	536			
≤ 1.75	65/71	-0.64 (0.07)		0.0018	≤ 1.75	65/75	-0.63 (0.07)	_ _	0.0026
> 1.75	67/65	-0.51 (0.07)		0.2336	> 1.75	67/70	-0.49 (0.07)		0.315
Baseline predicted FEV	1 (%), P = 0.315	5			Baseline predicted FEV1 (%), P = 0.8804		_	
< 60	53/61	-0.55 (0.08)		0.275	< 60	53/61	-0.63 (0.08)	<mark>_</mark>	0.0773
≥ 60	79/75	-0.60 (0.07)		0.0023	≥ 60	79/84	-0.51 (0.06)		0.0324
Post bronchodilator rev	ersibility (L), P	= 0.0068			Post bronchodilator reven	sibility (L), P =	0.3793		
≤ 38	63/72	-0.67 (0.07)		<.0001	≤ 38	63/71	-0.53 (0.07)		0.0062
> 38	69/64	-0.47 (0.07)	· · · · · · · · · · · · · · · · · · ·	0.1137	> 38	69/74	-0.59 (0.07)	— —	0.1137
No. of asthma events pr	rior to the study	P = 0.3693			No. of asthma events prio	r to the study,	P = 0.1924	_	
≤1	68/80	-0.48 (0.06)		0.0817	≤1	68/64	-0.43 (0.07)	— <mark>—</mark> ——	0.2684
> 1	64/56	-0.67 (0.08)		0.0089	> 1	64/81	-0.67 (0.07)	_ _	0.0038
ICS+LABA dose at rand	lomization, P = 0	0.2878			ICS+LABA dose at random	nization, P = 0	3845		
Medium	70/62	-0.61 (0.07)		0.0014	Medium	70/68	-0.59 (0.07)		0.0027
High	59/68	-0.55 (0.07)		0.0962	High	59/74	-0.55 (0.07)	_ _	0.0902
Baseline eosinophil cou	unt (cells/µL), P	= 0.7335			Baseline eosinophil count	(cells/µL), P =	0.6868		
< 300	77/77	-0.50 (0.07)	_ _ _	0.0305	< 300	77/87	-0.48 (0.06)		0.0444
≥ 300	55/59	-0.69 (0.07)	_ _	0.0212	≥ 300	56/58	-0.68 (0.08)		0.0285
History of atopy, $P = 0.1$	1010	. ,			History of atopy, $P = 0.341$	18	()	_	
With history of atopy	97/83	-0.46 (0.06)		0.1392	With history of atopy	97/111	-0.50 (0.05)		0.0311
Without history of atop	v 35/50	-0.79 (0.10)	_ _	0.0096	Without history of atopy	35/31	-0.73 (0.12)		0.0486
Smoking history, $P = 0$.	1053	. ,			Smoking history, P = 0.53	37	. ,	_	
Former	30/28	-0.75 (0.10)		0.0029	Former	30/33	-0.59 (0.10)		0.00487
Never	102/108	-0.53 (0.06)	· · · · · · · · · · · · · · · · · · ·	0.0409	Never	102/112	-0.55 (0.06)		0.0212
		-·	1.0 -0.8 -0.6 -0.4 -0.2 0 0.2 0.4 0.6 0.8	1.0 1.2			-1	.0-0.8-0.6-0.4-0.2 0 0.2 0.4 0.6	0.8 1.0 1.2
			Better than placebo Worse than placeb	00				Better than placebo Worse than	placebo

Figure 3. Morning asthma symptom scores, analysis by baseline covariates. A: Morning asthma symptom scores, Week 24 200 mg every 2 weeks; B: Morning asthma symptom scores, week 24 300 mg every 2 weeks.

PROs in Patient Subgroups

The effect of dupilumab on ACQ-5 total score, AM/PM asthma symptom scores, and AQLQ total score for each of the subgroups examined is shown in Figures 2 through 5. Significant improvements from baseline to week 24 were observed in many of the subgroups for both dupilumab regimens compared with placebo. Significant treatment-by-subgroup interactions were seen for the following baseline characteristics: sex, number of exacerbations in the previous year, FEV₁, eosinophil count, and postbronchodilator reversibility (Fig. 2-5). The magnitude of the treatment effect varied by subgroup but was consistently favored by dupilumab treatment. ICS/LABA dose level at randomization, history of atopy, and smoking history had nonsignificant treatment-by-subgroup interactions for

4B. PM Asthma Symptom Scores Week 24 300mg q2w

Subgroup, <i>P value for</i> interaction	n placebo/ dupilumab	LS mean change from baseline (± SE)	LS mean difference vs placebo (95% Cl)	P value vs placebo	Subgroup, <i>P value for</i> interaction	n placebo/ dupilumab	LS mean change from baseline (± SE)	LS mean difference vs placebo (95% Cl)	P value vs placebo
Gender, <i>P</i> = 0.2706					Gender, P = 0.4162			_	
Male	48/49	-0.50 (0.10)	_	0.4721	Male	48/47	-0.54 (0.10)	_ +-	0.3094
Female	84/87	-0.66 (0.07)	_ _ _	0.0038	Female	84/98	-0.64 (0.07)		0.0044
Baseline BMI (kg/m ²), P = 0	0.1536				Baseline BMI (kg/m ²), P = 0	0.1747			
< 30	84/79	-0.65 (0.07)	——	0.0025	< 30	84/85	-0.66 (0.07)	——————————————————————————————————————	0.0016
≥ 30	48/57	-0.52 (0.10)	_	0.5907	≥ 30	48/60	-0.56 (0.10)	_	0.428
Age of onset of asthma, P	= 0.5996				Age of onset of asthma, P	= 0.4667			
< 18	48/42	-0.53 (0.10)	—•+	0.2773	< 18	48/48	-0.45 (0.10)		0.6368
18-40	49/53	-0.57 (0.09)		0.2647	18-40	49/59	-0.71 (0.08)		0.0258
≻ 40	35/40	-0.72 (0.11)		0.0224	> 40	35/36	-0.64 (0.11)	_ _	0.0856
Baseline FEV ₁ (L), P = 0.15	61				Baseline FEV ₁ (L), P = 0.07	03			
≤ 1.75	66/71	-0.64 (0.08)	——	0.0039	≤ 1.75	66/75	-0.69 (0.08)	— — —	0.001
> 1.75	66/65	-0.55 (0.08)	————	0.4013	> 1.75	66/70	-0.54 (0.08)		0.4555
Baseline predicted FEV1 (%), P = 0.9829	L			Baseline predicted FEV1 (%), P = 0.1010			
< 60	54/61	-0.61 (0.09)	—• +	0.1312	< 60	54/61	-0.76 (0.09)		0.0086
≥ 60	78/75	-0.60 (0.07)	_ _	0.0269	≥ 60	78/84	-0.50 (0.07)	- - +	0.23
Post bronchodilator revers	sibility (L), <i>P</i> =	0.0189			Post bronchodilator revers	sibility (L), P =	0.2950		
≤ 38	64/72	-0.65 (0.08)		0.0005	≤ 38	64/71	-0.57 (0.08)		0.0056
> 38	68/64	-0.53 (0.08)	· · · · · · · · · · · · · · · · · · ·	0.8238	> 38	68/74	-0.65 (0.08)	—	0.1681
No. of asthma events prior	to the study,	P = 0.2433			No. of asthma events prior	to the study.	P = 0.3508		
≤ 1 · ·	68/80	-0.49 (0.07)		0.2194	 ≤1	68/64	-0.50 (0.08)		0.2087
> 1	64/56	-0.74 (0.10)	_ _	0.0095	> 1	64/81	-0.71 (0.08)	— — —	0.0103
ICS+LABA dose at random	nization, P = 0	.2971			ICS+LABA dose at random	nization. $P = 0$	0961	_	
Medium	69/62	-0.63 (0.08)		0.0051	Medium	69/68	-0.70 (0.08)		0.0005
High	60/68	-0.57 (0.09)		0.1774	High	60/74	-0.54 (0.08)	—— <mark>—</mark> ——	0.2479
Baseline eosinophil count	(cells/uL), P =	= 0.4818			Baseline eosinophil count	(cells/ul.) P =	0.0678		
< 300	76/77	-0.52 (0.08)		0.104	< 300	76/87	-0.46 (0.07)	_ 	0 2733
> 300	56/59	-0.72 (0.09)		0.0209	> 300	56/58	-0.84 (0.09)		0.0014
History of atopy $P = 0.250$	1	0.12 (0.00)	_	0.0200	History of atomy $P = 0.947$	o 30/30	-0.04 (0.03)	-	0.0014
With history of atopy	98/83	-0.53 (0.07)		0 1265	With history of story	00/111	0.61 (0.06)		0.0104
Without history of atopy	34/50	-0.72 (0.11)		0.0426	Without bistony of stopy	24/21	-0.01 (0.00)		0.0104
Smoking history $P = 0.221$	13	-0.72 (0.11)	•	0.0420	Smoking history $P = 0.34$	10	-0.01 (0.13)	-	0.2405
Former	31/28	-0.74 (0.13)		0.0372	Former	31/33	-0.69 (0.12)		0.0637
Never	101/108	-0.56 (0.06)		0.0582	Never	101/112	-0.09 (0.12)		0.0007
Herei	1011100		1.0-0.8-0.6-0.4-0.2 0 0.2 0.4 0.6 0.8 1.	0 1.2	Nevei	101/112	-0.38 (0.00)	1.0-0.8-0.6-0.4-0.2 0 0.2 0.4 0.6 0.8 1.	.0 1.2
			Better than placebo Worse than placebo)				Better than placebo Worse than placebo	b

4A. PM Asthma Symptom Scores Week 24 200mg q2w

Figure 4. Evening asthma symptom scores, analysis by baseline covariates. A: Evening asthma symptom scores, week 24 200 mg every 2 weeks; B: Evening asthma symptom scores, week 24 300 mg every 2 weeks.

5A. AQLQ Analysis by Baseline Covariates Week 24 200mg q2w

5B. AQLQ Analysis by Baseline Covariates Week 24 300mg q2w

Subgroup, P value for interaction	n placebo/ dupilumab	LS mean change from baseline (± SE)	LS mean difference vs placebo (95% Cl)	P value vs placebo	Subgroup, <i>P value for</i> interaction	n placebo/ dupilumab	LS mean change from baseline (± SE)	LS mean difference vs placebo (95% Cl)	P value vs placebo
Gender, P = 0.0376					Gender, P = 0.1064				
Male	45/48	1.02 (0.13)		0.9282	Male	45/47	1.17 (0.13)	<mark>_</mark>	0.4442
Female	82/84	1.31 (0.11)	——	0.0016	Female	82/94	1.30 (0.11)		0.0015
Baseline BMI (kg/m ²), P = 0.	.9051				Baseline BMI (kg/m²), P = 0	0.5797		_	
< 30	46/54	1.29 (0.15)	_ _	0.1242	< 30	46/59	1.24 (0.15)	 _	0.1977
≥ 30	81/78	1.15 (0.11)	_ _	0.0341	≥ 30	81/82	1.26 (0.10)		0.004
Age of onset of asthma, P =	0.1212		-		Age of onset of asthma, P	= 0.7378		_	
< 18	44/39	1.34 (0.17)		0.058	< 18	44/46	1.31 (0.16)	 _	0.0773
18-40	47/52	1.01 (0.13)	· · · · · · · · · · · · · · · · · · ·	0.8104	18-40	47/56	1.26 (0.12)		0.264
> 40	36/40	1.30 (0.16)		0.0112	> 40	36/37	1.11 (0.17)		0.0916
Baseline FEV ₁ (L), P = 0.019	98				Baseline FEV ₁ (L), P = 0.02	60			
≤ 1.75	63/68	1.28 (0.12)	_ 	0.0008	≤ 1.75	63/72	1.31 (0.12)	— <mark>—</mark> —	0.0004
> 1.75	64/64	1.13 (0.12)		0.8711	> 1.75	64/69	1.19 (0.12)		0.5642
Baseline predicted FEV1 (%), P = 0.2923	3			Baseline predicted FEV1 (%	%), P = 0.2639	1		
< 60	49/58	1.25 (0.14)	_	0.0169	< 60	49/62	1.31 (0.13)	— — —	0.0065
≥ 60	78/74	1.13 (0.11)	-++	0.195	≥ 60	78/79	1.17 (0.11)		0.1102
Post bronchodilator reversi	bility (L), P :	= 0.3473			Post bronchodilator revers	sibility (L), P =	0.1706		
≤ 38	61/70	1.24 (0.12)	_ _	0.0141	≤ 38	61/67	1.00 (0.12)	 +-	0.3039
> 38	66/62	1.12 (0.12)	-++	0.2375	> 38	66/74	1.45 (0.11)	I	0.0012
No. of asthma events prior	to the study,	P = 0.0073			No. of asthma events prior	to the study,	P = 0.0008		
≤ 1	66/79	0.99 (0.10)		0.852	≤ 1	66/61	0.92 (0.11)	— — —	0.7555
> 1	61/53	1.43 (0.15)	—• —	0.0014	> 1	61/80	1.51 (0.12)	— — —	<0.0001
ICS+LABA dose at randomi	zation, P = 0	.8582			ICS+LABA dose at random	ization, P = 0	.8273		
Medium	70/61	1.29 (0.12)	_ _	0.0314	Medium	70/65	1.31 (0.12)		0.0199
High	54/65	1.17 (0.13)		0.0709	High	54/73	1.19 (0.12)		0.0483
Baseline eosinophil count (cells/µL), P	= 0.0135			Baseline eosinophil count	(cells/µL), P =	= 0.0053		
< 300	74/74	1.06 (0.11)	_ _	0.74	< 300	74/85	1.07 (0.11)		0.6899
≥ 300	53/58	1.46 (0.13)	_ _	0.0003	≥ 300	53/56	1.57 (0.13)	— — —	< 0.0001
History of atopy, P = 0.2969)				History of atopy, P = 0.460	7			
With history of atopy	94/78	1.14 (0.11)		0.1087	With history of atopy	94/106	1.19 (0.09)		0.0367
Without history of atopy	33/50	1.32 (0.16)	_	0.0435	Without history of atopy	33/32	1.34 (0.20)		0.0606
Smoking history, P = 0.353	7				Smoking history, P = 0.954	11			
Former	100/105	1.21 (0.10)		0.045	Former	100/108	1.29 (0.10)		0.0085
Never	27/27	1.12 (0.19)		0.1349	Never	27/33	1.11 (0.17)		0.1436
		2.5 2.0	0 1.5 1.0 0.5 0 -0.5 -1.0				2.5 2.1	0 1.5 1.0 0.5 0 -0.5 -1.0	
			Better than placebo Worse than pla	acebo				Better than placebo Worse than p	lacebo

Figure 5. AQLQ, analysis by baseline covariates. A: AQLQ analysis by baseline covariates, week 24 200 mg every 2 weeks; B: AQLQ analysis by baseline covariates, week 24 300 mg every 2 weeks. ACQ-5, 5-item Asthma Control Questionnaire; BMI, body mass index; FEV₁, forced expiratory volume (L) in 1 second; ICS; inhaled corticosteroids; LABA, long-acting β₂-agonist; q2w, every 2 weeks; SE, standard error.

ACQ-5, AQLQ, and AM/PM asthma symptom scores. Patients with baseline characteristics usually associated with more severe asthma, including history of more than 1 exacerbation in the prior year or baseline FEV₁ of at least 1.75L, showed a better response to both dupilumab regimens vs placebo in ACQ-5, AM/PM asthma symptom scores, and AQLQ score (P < .05 for all) (Fig. 2-5).

Safety

As reported in detail in the primary manuscript, rates of treatment-emergent adverse events were similar across treatment groups, as were rates of serious treatment-emergent adverse events.¹² Injection-site reactions occurred more often in active treatment groups, and they were dose-related (20% and 26% for dupilumab 200 and 300 mg every 2 weeks, respectively, vs 13% for placebo).¹²

Discussion

Despite receiving medium-to-high-dose ICS+LABA therapy, patients with uncontrolled persistent asthma are characterized by a multidimensional burden of disease, including recurrent exacerbations, reduced lung function, and reduced QoL. In addition, patients with uncontrolled persistent asthma often suffer from other allergic comorbidities such as chronic sinusitis and AD, further complicating the treatment of these patients.

In this pivotal phase 2b trial, dupilumab every 2 weeks dose regimens significantly improved lung function, severe exacerbation rates, and patient-centered outcomes (asthma symptoms, asthma control, and QoL) relative to placebo when added to medium-to-high-dose ICS+LABA therapy in adults with uncontrolled persistent asthma.¹² Significant improvements in all of these endpoints were observed in both the overall population and patients with eosinophil counts of at least 300 cells/µL. Lung function and exacerbation rates were also significantly improved in patients with eosinophil counts less than 300 cells/µL.¹² In this post hoc analysis, we demonstrated that dupilumab significantly improved asthma control, asthma symptoms, QoL, and workplace productivity in the overall population, as well as in a majority of subgroups evaluated; results from the MCID analysis showed that the improvements were clinically meaningful, and consistent with analysis of previously reported mean changes in PROs, where a greater proportion of dupilumab-treated patients benefited from treatment compared to placebo.

Of particular note, significant improvements were observed in patients with a history of more than 1 exacerbation at baseline, or FEV₁ of at least 1.75 L (both dupilumab every 2 weeks dose regimens) at baseline, but not patients with 1 exacerbation or baseline FEV₁ greater than 1.75 L. Although a consistent significant improvement was observed with baseline eosinophil count of at least 300 cells/ μ L for dupilumab vs placebo, patients with less than 300 cells/ μ L only observed an improvement in ACQ-5 with 200 mg every 2 weeks dupilumab vs placebo. These observations suggest that dupilumab may have a greater effect on PROs in patients with more severe asthma and a higher type 2 inflammatory signal at baseline.

Additionally, despite the small sample size (which is an important limitation of this analysis), a significant improvement was observed with dupilumab (200 and 300 mg every 2 weeks) on patient-reported AM asthma symptoms in patient subgroups with eosinophils of at least 300 cells/ μ L and less than 300 cells/ μ L; this is a unique finding compared with those of other studies investigating the use of anti-IL-5 in this patient population. These data are consistent with the overall benefit of dupilumab observed in patients with eosinophils at least 300 cells/ μ L and less than 300 cells/ μ L.¹² Because of the small number of patients with less than 150 eosinophils/ μ L (n = 30 on the 200 mg every 2 weeks and n = 28 on the 300 mg every 2 weeks dupilumab arms), these data were not presented, because no meaningful comparisons could be drawn between the dupilumab and placebo groups. Larger, ongoing phase 3 studies will be needed to confirm these preliminary findings.

Another important finding from this post-hoc analysis is the effect of dupilumab on work productivity improvement. To our knowledge, this is the only double-blind, randomized controlled trial that demonstrates the effects of a biologic (dupilumab) on workplace productivity in patients with uncontrolled persistent asthma. Furthermore, no evidence has been seen of significant improvement in productivity in patients with uncontrolled persistent asthma treated with biologics targeting IL-5.²³

In conclusion, patients with uncontrolled persistent asthma who do not respond to currently available therapies are in need of additional treatment options. This analysis demonstrates that dupilumab every 2 weeks regimens provide significant and clinically meaningful improvements in asthma control, asthma symptoms, and QoL and significantly improve workplace productivity. Furthermore, improvements in these PROs were observed across a range of asthma phenotypes determined by baseline clinical characteristics.

Acknowledgments

Medical writing/editorial assistance provided by Marinella Calle, PhD, of Excerpta Medica, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc. The authors thank Bianca Beghé (University of Modena and Reggio Emilia, Modena, Italy) for her careful review of the manuscript.

Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.anai.2018.08.005.

References

- Ray A, Oriss TB, Wenzel SE. Emerging molecular phenotypes of asthma. Am J Physiol Lung Cell Mol Physiol. 2015;308(2):L130–L140.
- [2] Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. Nat Med. 2012;18(5):716–725.
- [3] Chung KF. Asthma phenotyping: a necessity for improved therapeutic precision and new targeted therapies. J Intern Med. 2016;279(2):192–204.
- [4] Peters SP, Ferguson G, Deniz Y, Reisner C. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respir Med.* 2006; 100(7):1139–1151.
- [5] Colice GL, Ostrom NK, Geller DE, et al. The CHOICE survey: high rates of persistent and uncontrolled asthma in the United States. Ann Allergy Asthma Immunol. 2012;108(3):157–162.

- [6] Chen H, Gould MK, Blanc PD, et al. TENOR Study Group. Asthma control, severity, and quality of life: quantifying the effect of uncontrolled disease. J Allergy Clin Immunol. 2007;120(2):396–402.
- [7] Fletcher M, Jha A, Dunlop W, et al. Patient reported burden of asthma on resource use and productivity across 11 countries in Europe. Adv Ther. 2015;32(4):370–380.
- [8] Chen H, Blanc PD, Hayden ML, et al. Assessing productivity loss and activity impairment in severe or difficult-to-treat asthma. *Value Health*. 2008;11(2): 231–239.
- [9] Bai TR, Vonk JM, Postma DS, Boezen HM. Severe exacerbations predict excess lung function decline in asthma. *Eur Respir J.* 2007;30(3):452–456.
- [10] O'Byrne PM, Pedersen S, Lamm CJ, Tan WC, Busse WW, Investigators Group START. Severe exacerbations and decline in lung function in asthma. *Am J Respir Crit Care Med*. 2009;179(1):19–24.
- [11] Sabin BR, Greenberger PA. Chapter 13: Potentially (near) fatal asthma. Allergy Asthma Proc. 2012;33(Suppl 1):S44–S46.
- [12] Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet.* 2016;388(10039):31–44.
- [13] Corren J, Castro M, Joish V, et al. Burden of persistent asthma in patients treated with medium- to high-dose inhaled corticosteroids: baseline data from a phase 2 clinical trial of dupilumab. CHEST. 2015;148(4):4A.
- [14] US Food and Drug Administration. Guidance for industry. Patient-reported outcome measures: use in medical product development to support labeling claims. December 2009. http://purl.access.gpo.gov/GPO/LPS113413. Accessed March 9, 2018.
- [15] Coons SJ, Kothari S, Monz BU, Burke LB. The patient-reported outcome (PRO) consortium: filling measurement gaps for PRO end points to support labeling claims. *Clin Pharmacol Ther*. 2011;90(5):743–748.
- [16] Sacristán JA. Patient-centered medicine and patient-oriented research: improving health outcomes for individual patients. BMC Med Inform Decis Mak. 2013;13:6.
- [17] Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. 2009. http://www.ginasthma.org. Accessed March 9, 2015.
- [18] Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*, 2005;99(5):553–558.
- [19] Juniper EF. Measurement of Health-Related Quality of Life & Asthma Control. 1999. http://www.qoltech.co.uk/asthma_control_package.html. Accessed March 9, 2018.
- [20] Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax*. 1992;47(2):76–83.
- [21] Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J. 1999;14(4):902–907.
- [22] Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific Quality of Life Questionnaire. J Clin Epidemiol. 1994;47(1):81–87.
- [23] Gunsoy NB, Cockle SM, Albers FC, Doyle S, Cristancho RA. Impact of mepolizumab on work productivity and activity impairment in severe eosinophilic asthma. *Eur Resp J.* 2017;50:PA654.



eFigure 1. Change from baseline in ACQ-5 over time in the overall population.



eFigure 2. Change from baseline in AQLQ over time in the overall population.



eFigure 3. Change from baseline in morning asthma symptom scores over time in the overall population.



eFigure 4. Change from baseline in evening asthma symptom scores over time in the overall population.