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Long-Term Dupilumab Efficacy on Severe Exacerbations and Lung Function in Patients with Type 2 Asthma

To the Editor:

Exacerbations characteristic of uncontrolled asthma (1–3) are linked to lung function decline (4–8). Airway inflammation and remodeling worsen lung function, which increases the risk for further exacerbations (9–13). Dupilumab, a fully human monoclonal antibody (14, 15), blocks the shared receptor for interleukins-4 and -13, key and central drivers of type 2 inflammation (16, 17). In the QUEST (NCT 02414854) study, dupilumab reduced exacerbations and improved lung function in patients with moderate-to-severe asthma, with greater effects in patients with elevated type 2 biomarkers (18). Patients from QUEST were included in the single-arm, open-label TRAVERSE (NCT 02134028) extension study, showing sustained dupilumab efficacy for up to 3 years (19). This *post hoc* analysis examines the relationship between severe exacerbations and lung function in patients who participated in QUEST and TRAVERSE. Some results of this analysis were previously reported in the form of an abstract (20).

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Data availability: Qualified researchers may request access to patient-level data and related study documents, including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

Clinical trials registered with www.clinicaltrials.gov (NCT 02414854 and NCT 02134028).

Methods

Patients with moderate-to-severe asthma and elevated type 2 biomarkers (blood eosinophils ⩾ 150 cells/μl or fractional exhaled nitric oxide [F_{ENO}] ⩾ 25 ppb) at QUEST baseline included in the QUEST (NCT02414854) (18, 21) and TRAVERSE (NCT02134028) (19, 22) studies were analyzed. In QUEST, patients ⩾12 years old were randomized to dupilumab 200 or 300 mg every 2 weeks or placebo for 52 weeks (18). During TRAVERSE, patients received dupilumab 300 mg every 2 weeks for up to 96 weeks. Full studies have been previously published (18, 19).

Patients with (exacerbators) and without (nonexacerbators) one or more severe exacerbations during QUEST were subdivided into those who received dupilumab during QUEST and TRAVERSE (dupilumab/dupilumab), or placebo during QUEST and dupilumab in TRAVERSE (placebo/dupilumab). Endpoints included the proportion of patients with one or more severe exacerbations, annualized severe exacerbation rate (AER), time from TRAVERSE Week 0 to first severe exacerbation, and absolute mean prebronchodilator percent predicted forced expiratory volume in 1 second (pre-BD ppFEV$_1$). TRAVERSE statistical analyses are descriptive (19). Kaplan-Meier survival curves and hazard ratios (95% confidence interval) were generated to depict time to first exacerbation during TRAVERSE.

Results

A total of 1,227 patients with type 2 asthma from QUEST were included: 580 (47.3%) dupilumab/dupilumab nonexacerbators and 224 (18.3%) exacerbators; 242 (19.7%) placebo/dupilumab nonexacerbators and 181 (14.8%) exacerbators. Patients in exacerbator versus nonexacerbator groups were more likely to receive high-dose inhaled corticosteroids and had higher prior year severe exacerbation rates and lower pre-BD FEV$_1$ (Table 1).

Severe exacerbations. During QUEST, fewer patients in the dupilumab/dupilumab arm had one or more severe exacerbations. During TRAVERSE, in exacerbator groups, substantial reductions in the percentage of patients experiencing severe exacerbations (from 100% during QUEST) were seen in both dupilumab/dupilumab and placebo/dupilumab arms (Figure 1A). Patients in exacerbator versus nonexacerbator groups experienced more exacerbations in the year before QUEST (Figure 1A). In the dupilumab/dupilumab arm, patients in the exacerbator group versus those in the nonexacerbator group had higher AER during QUEST and TRAVERSE; however, substantial reductions from baseline to QUEST to TRAVERSE were seen across both groups. Similar results were observed in the placebo/dupilumab arm (Figure 1A).

Time from TRAVERSE baseline to first severe exacerbation event was longer in nonexacerbator groups than in exacerbator

Table 1. Baseline characteristics by treatment and exacerbation status during QUEST

	Dupilumab/Dupilumab ($n = 804$)		Placebo/Dupilumab ($n = 423$)	
	Nonexacerbators ($n = 580$)	Exacerbators ($n = 224$)	Nonexacerbators ($n = 242$)	Exacerbators ($n = 181$)
At QUEST baseline				
Age, yr	47.0 ± 14.8	48.5 ± 15.8	47.0 ± 15.2	49.4 ± 14.4
Females	341 (58.8)	138 (61.6)	143 (59.1)	119 (65.7)
Body mass index, kg/m^2	28.5 ± 6.1	29.3 ± 7.0	29.4 ± 6.5	29.0 ± 6.3
High-dose inhaled corticosteroid use	279 (48.1)	135 (60.3)	119 (49.2)	113 (62.4)
Fractional exhaled nitric oxide, ppb	42.0 ± 36.7	35.0 ± 26.2	41.0 ± 39.8	42.8 ± 31.4
Exacerbations in past year	1.99 ± 1.65	2.37 ± 2.54	1.90 ± 1.53	2.71 ± 2.33
Prebronchodilator FEV_1, L	1.84 ± 0.63	1.70 ± 0.57	1.84 ± 0.61	1.70 ± 0.54
% predicted	59.2 ± 13.6	56.2 ± 13.1	59.1 ± 13.1	56.9 ± 13.0
FEV_1 reversibility, %	26.8 ± 21.9	24.6 ± 19.2	28.6 ± 20.7	23.4 ± 14.2
Blood eosinophil count, cells/μl	429 ± 386	395 ± 306	388 ± 336	543 ± 463
Total immunoglobulin E, IU/ml	508 ± 873	446 ± 681	445 ± 680	450 ± 719
At TRAVERSE baseline				
Prebronchodilator FEV_1, L	2.26 ± 0.74	1.96 ± 0.71	2.10 ± 0.71	1.80 ± 0.65
% predicted	73.3 ± 15.8	65.0 ± 17.3	68.0 ± 16.0	60.4 ± 16.1
Blood eosinophil count, cells/μl	418 ± 488	379 ± 436	349 ± 289	482 ± 428
Total immunoglobulin E, IU/ml	165 ± 437	115 ± 182	470 ± 816	463 ± 768

Definition of abbreviations: dupilumab/dupilumab = dupilumab during QUEST and TRAVERSE; exacerbators = patients who had one or more severe exacerbations during QUEST; FEV_1 = forced expiratory volume in 1 second; nonexacerbators = patients who had no severe exacerbations during QUEST; placebo/dupilumab = placebo during QUEST and dupilumab during TRAVERSE.
Data are presented as mean ± standard deviation or *n* (%).

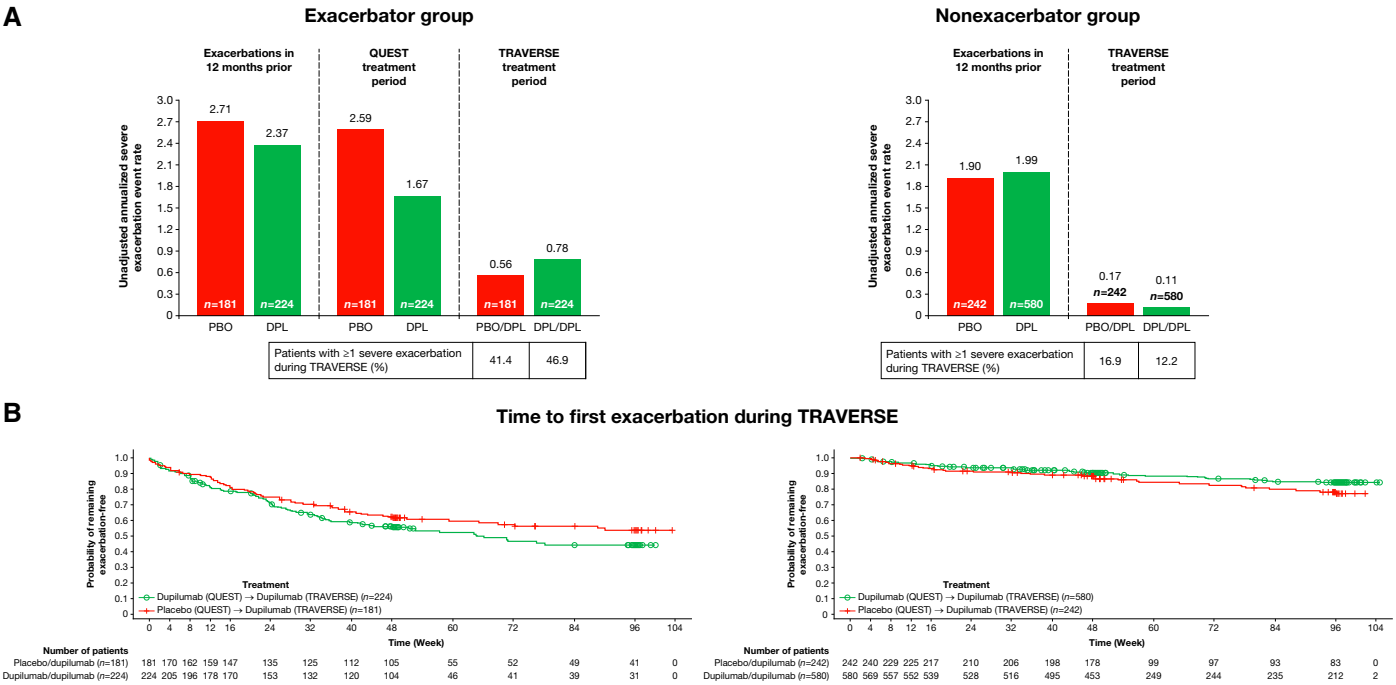

Figure 1. (*A*) Annualized rate of severe asthma exacerbations before QUEST and during QUEST and TRAVERSE, and (*B*) time to first exacerbation during TRAVERSE, in exacerbator group and nonexacerbator group. Unadjusted annualized exacerbation rate is the total number of events that occurred during the treatment period divided by the total number of patient-years followed in the treatment period. Hazard ratios and 95% confidence intervals comparing dupilumab/dupilumab versus placebo/dupilumab among exacerbator and nonexacerbator groups were estimated using Cox models, with the treatment arm as the only covariate in addition to the intercept.
DPL = dupilumab; dupilumab/dupilumab = dupilumab during QUEST and TRAVERSE; exacerbator group = one or more severe exacerbations during QUEST; nonexacerbator group = no severe exacerbations during QUEST; PBO = placebo; placebo/dupilumab = placebo during QUEST and dupilumab during TRAVERSE.

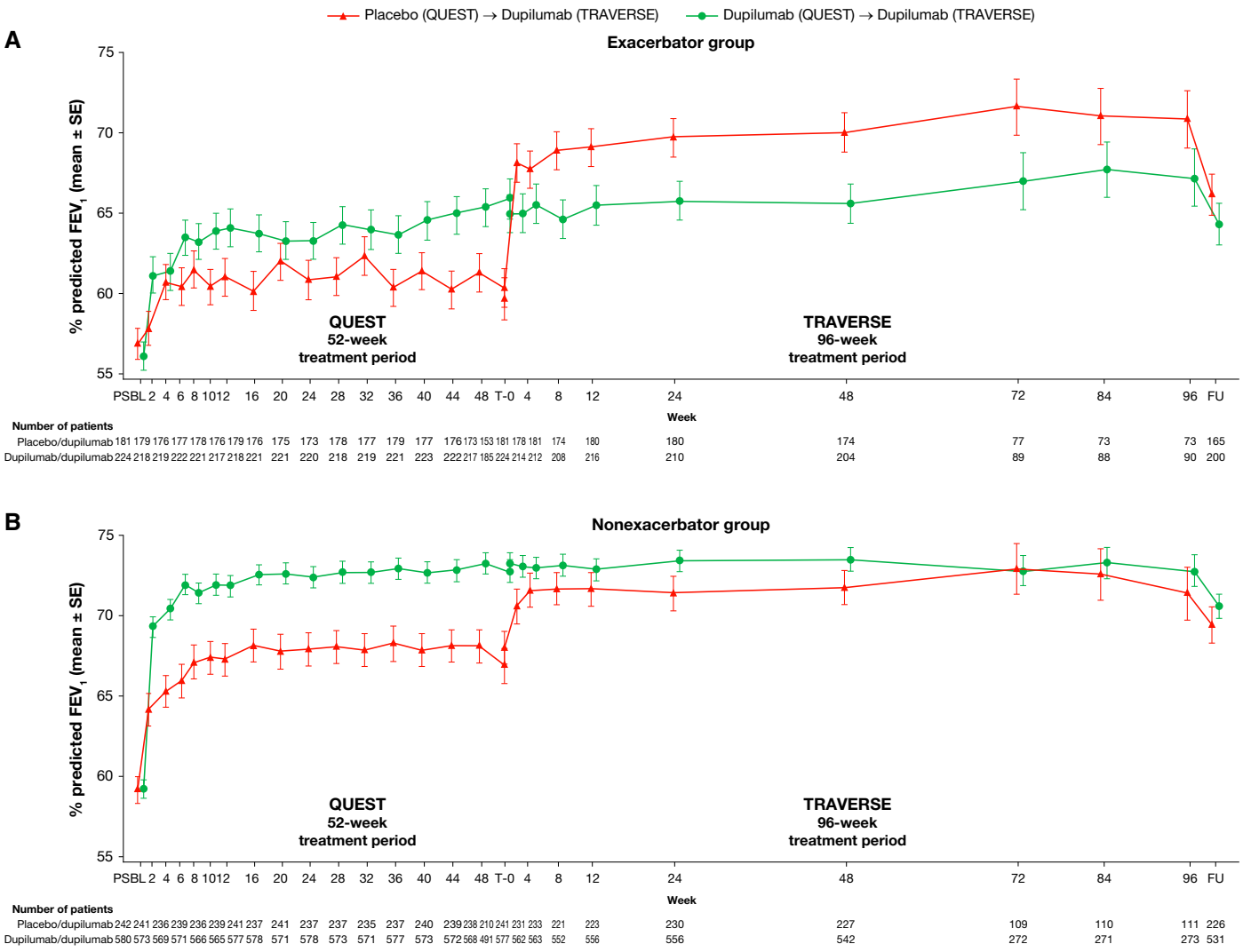

Figure 2. Absolute mean prebronchodilator percent predicted FEV_1 values over time during QUEST and TRAVERSE in (*A*) exacerbator group and (*B*) nonexacerbator group. Five records with values >140 were excluded. The error bars are ±1 standard error. FEV_1 = forced expiratory volume in 1 second; FU = follow-up; PSBL = parent study baseline.

groups overall (Figure 1B). Among the dupilumab/dupilumab exacerbator group, median time to first severe exacerbation during TRAVERSE was 66.1 weeks (~1.3 yr).

Pre-BD ppFEV$_1$. During QUEST, mean absolute values for pre-BD $ppFEV_1$ at Week 52 were 72.8% and 65.9% in the dupilumab/dupilumab nonexacerbator and exacerbator groups, and 66.9% and 59.7% in the placebo/dupilumab nonexacerbator and exacerbator groups, respectively (Figure 2). Improvements in dupilumab/dupilumab nonexacerbator and exacerbator groups during QUEST remained steady through TRAVERSE Week 96 (72.8% and 67.2%, respectively) (Figure 2). Patients in placebo/dupilumab nonexacerbator and exacerbator groups showed large improvements in pre-BD $ppFEV_1$ during TRAVERSE, reaching similar absolute values to those observed in the dupilumab/dupilumab nonexacerbator group (71.4% and 70.8%, respectively, at Week 96).

Discussion

These analyses revealed three key findings in patients who had one or more versus zero severe exacerbations during their first year on dupilumab. First, despite less marked improvements in AER up to 2 years on dupilumab, exacerbators still experienced substantial AER reductions from baseline during QUEST through TRAVERSE. Second, median time to first severe exacerbation after beginning TRAVERSE was >1.3 years. Third, despite lower overall improvements in pre-BD $ppFEV_1$ during their first year on dupilumab, substantial lung function improvements were maintained throughout QUEST and TRAVERSE.

Exacerbators had poorer lung function and more severe exacerbations before starting dupilumab. However, despite also experiencing more severe exacerbations during TRAVERSE, the reduction in AER from 2.37 to 1.67 to 0.78 was substantial,

demonstrating that, even among these patients, dupilumab has highly beneficial effects on AER.

Using suggested cutoffs for pre-BD ppFEV$_1$ values (23), patients in exacerbator and nonexacerbator groups had moderately severe lung function impairment at the QUEST study baseline. In dupilumab/dupilumab patients, this improved to mild impairment in the nonexacerbator group and moderate impairment in the exacerbator group during QUEST, with improvements maintained through TRAVERSE. Despite displaying the lowest pre-BD ppFEV$_1$ values in QUEST, the placebo/dupilumab exacerbator group and the placebo/dupilumab nonexacerbator group improved to mild impairment after dupilumab initiation in TRAVERSE; all groups, regardless of treatment and exacerbation status during QUEST, improved by at least one severity category.

Despite similar mean baseline blood eosinophils and F_{ENO} concentrations between exacerbators and nonexacerbators seen in this analysis, there is growing evidence supporting the clinical value of these biomarkers. Higher F_{ENO} levels predict severe asthma exacerbations, independently or combined with higher eosinophils (24, 25). Additional studies will further clarify the relationship between these biomarkers and treatment outcomes.

Whether exacerbation reduction with dupilumab results in improved lung function, or improved lung function with dupilumab results in fewer exacerbations, or a combination of both, is debatable (4–11), but the long-term benefits of dupilumab among these adults and adolescents with elevated type 2 biomarkers at baseline are evident.

This study has limitations as a *post hoc* analysis and features inherent to study design, including potential for treatment bias (19) and generalizability beyond patients with moderate-to-severe asthma and elevated type 2 biomarkers. As patients were not randomized to study groups, baseline characteristics differed; therefore, between-group comparisons should be interpreted with caution.

Conclusions. In TRAVERSE, dupilumab use was associated with fewer severe exacerbations and an improvement in lung function for up to 3 years, regardless of exacerbation status during QUEST. ■

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Alberto Papi, M.D.*
University of Ferrara, S. Anna University Hospital
Ferrara, Italy

Mario Castro, M.D., M.P.H.
University of Kansas School of Medicine
Kansas City, Kansas

William W. Busse, M.D.
University of Wisconsin School of Medicine and Public Health
Madison, Wisconsin

David Langton, M.B., B.S., M.P.H., Ph.D.
Monash University
Clayton, Victoria, Australia

Stephanie Korn, M.D.
IKF Pneumologie Mainz
Mainz, Germany

and

Thoraxklinik Heidelberg
Heidelberg, Germany

Changming Xia, Ph.D.
Xavier Soler, M.D., Ph.D.
Regeneron Pharmaceuticals Inc.
Tarrytown, New York

Nami Pandit-Abid, Pharm.D.
Sanofi
Bridgewater, New Jersey

Amr Radwan, M.B., B.Chir., F.F.P.M.
Regeneron Pharmaceuticals Inc.
Tarrytown, New York

Juby A. Jacob-Nara, M.D., D.H.Sc., M.P.H., M.B.A.
Paul J. Rowe, M.D.
Sanofi
Bridgewater, New Jersey

Yamo Deniz, M.D.
Regeneron Pharmaceuticals Inc.
Tarrytown, New York

ORCID IDs: 0000-0002-6924-4500 (A.P.); 0000-0001-6328-8994 (M.C.); 0000-0003-2591-4696 (W.W.B.); 0000-0002-1072-2897 (N.P.-A.); 0000-0003-1658-5229 (A.R.); 0000-0002-5372-8762 (J.A.J.-N.).

*Corresponding author (e-mail: ppa@unife.it).

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Missing Pertinent Information Regarding Far-UVC Air Disinfection

To the Editor:

Bueno de Mesquita and colleagues promote far ultraviolet-C (far-UVC) for indoor airborne infection control (1), while omitting its important evidence deficiencies for efficacy and safety. Moreover, they declare that standard, time-tested UVC 254-nm upper-room will be replaced by LED bulbs emitting UVC at 265–270 nm, manufactured, like the far-UVC 222-nm fixtures, by companies from which at least one coauthor previously declared a financial benefit (2) but with no financial conflict disclosures here. They leave unmentioned that UVC 265–270 nm is at least two times riskier to the eyes than UVC 254 nm upon exposure in an indoor occupied space.

It is axiomatic that liquid and air microbe disinfectants be tested in standardized conditions containing extraneous protein "soil" to assess if and how much soil may reduce disinfecting power, because protein soil is part of the real-world conditions in which disinfectants are intended to work. Usually this is accomplished by adding 5–10% fetal calf serum (FCS) or bovine serum albumin to the microbial aerosol. Sometimes "artificial saliva", a nonstandard exploratory approach, is used instead, seeking to mimic exhaled air protein but failing because surfactant, mucin, and other lower-tract proteins in exhaled air are not in saliva or its imitation. Riley and colleagues in 1976, and multiple other classic studies, used Middlebrook 5% bovine serum albumin medium for aerosolizing *Mycobacterium tuberculosis* and measuring UVC 254-nm disinfection. UVC 254 nm was shown to inactivate coronavirus, adenovirus, and bacteriophage BS2 aerosolized in 10% FCS in 2007 (3). The inactivating potency of UVC 254 nm is preserved in protein soil. But far-UVC 222 nm promoters have yet to publish such peer-reviewed efficacy data, while boasting instead of its photons' ability to inactivate proteins (1)—leaving sufficient photons for inactivating the microbial pathogens? One far-UVC 222 nm report describes an experiment bungled because of aerosol foaming with 1% FCS, because the investigators (4) failed to use Antifoam (3).

Far-UVC 222 nm inevitably produces ozone, a safety concern for the 8% of Americans with asthma and others with reactive airway disease. Two hours of 0.4-ppm ozone exposure significantly reduces forced expiratory volume in 1 second and results in neutrophil airway influx, inflammatory cytokines, and other mediators, as well as glucocorticoid resistance (5). These authors trivialize this concern, declaring it minimized by removal via an assumed ventilation system and ozone's rapid reactivity leading to inactivation. But sitting indoors for school, office work, and airplane flights may result in clinically significant exposures; a 70-watt lamp would produce an ambient ozone concentration of 4.7 ppm, according to an online white paper from the International UV Association (6). It would be simple to do crossover experiments with individuals with asthma, normal control participants, and active 222-nm fixtures versus look-alike dummy bulbs. No such results have been forthcoming.

The false impression conveyed of no industry payments to authors is particularly problematic when such devices do not require U.S. Food and Drug Administration review for marketing, and, therefore, unlike drugs and medical devices, do not require disclosure by manufacturers we can view on https://openpaymentsdata.cms.gov/. This places heightened responsibility on authors for ethical disclosure and on editors and reviewers to make sure not merely editors, but also readers, are informed, particularly with a removed paywall for