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Received: 28 September 2022 | Revised: 6 April 2023 | Accepted: 7 April 2023

DOI: 10.1111/all.15747

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Asthma and Lower Airway Disease

Dupilumab improves long-term outcomes in patients with uncontrolled, moderate-to-severe GINA-based type 2 asthma, irrespective of allergic status

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Funding information
Regeneron Pharmaceuticals Inc.; Sanofi

Abstract

Background: Previous research has shown greater efficacy of dupilumab in patients with uncontrolled asthma and type 2 inflammation. We analyzed dupilumab's efficacy in patients from the TRAVERSE study with or without evidence of allergic asthma and type 2 inflammation per current GINA guidelines (≥150 eosinophils/μL or FeNO ≥20 ppb).

Methods: All patients aged ≥12 years who rolled over from the placebo-controlled QUEST study (NCT02414854) to TRAVERSE (NCT02134028) received add-on dupilumab 300 mg every 2 weeks for up to 96 weeks. We assessed annualized severe asthma exacerbation rates (AERs) and changes from parent-study baseline (PSBL) in pre-bronchodilator FEV_1 and 5-item asthma control questionnaire (ACQ-5) score in patients with moderate-to-severe type 2 asthma with and without evidence of allergic asthma at PSBL.

Results: In TRAVERSE, dupilumab consistently reduced AER across all subgroups. By Week 96, dupilumab increased pre-bronchodilator FEV_1 from PSBL by 0.35–0.41 L in patients receiving placebo during QUEST (placebo/dupilumab) and 0.34–0.44 L in those receiving dupilumab during QUEST (dupilumab/dupilumab) with an allergic phenotype at baseline. In patients without evidence of allergic asthma, pre-bronchodilator FEV_1 improved by 0.38–0.41 L and 0.33–0.37 L, respectively. By Week 48, ACQ-5 scores decreased from PSBL by 1.63–1.69 (placebo/dupilumab) and 1.74–1.81 (dupilumab/dupilumab) points across subgroups with allergic asthma, and 1.75–1.83 (placebo/dupilumab) and 1.78–1.86 (dupilumab/dupilumab) in those without.

Conclusions: Long-term treatment with dupilumab reduced exacerbation rates and improved lung function and asthma control in patients with asthma with type 2 inflammation as per current GINA guidance and irrespective of evidence of allergic asthma.

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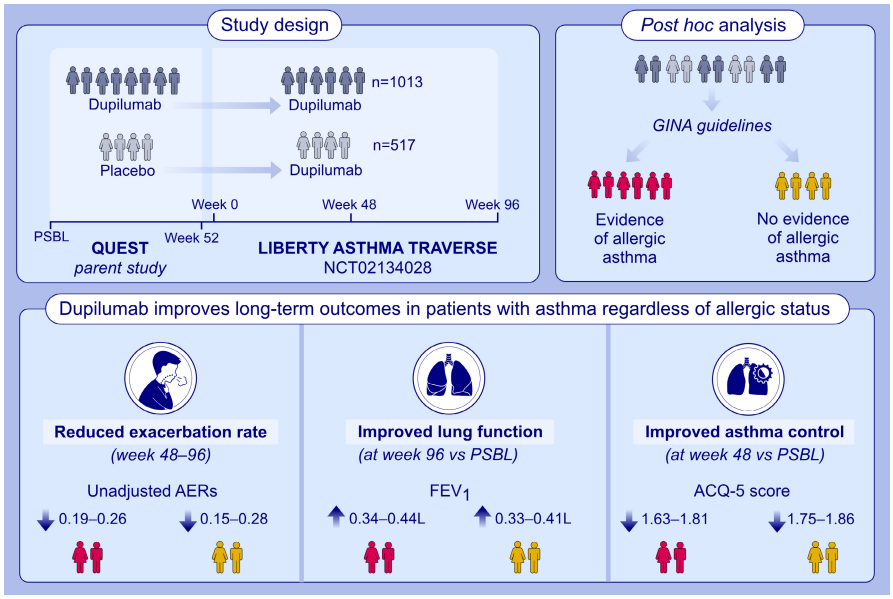

GRAPHICAL ABSTRACT

This post hoc analysis included patients from QUEST who enrolled in TRAVERSE. Patients were stratified per baseline levels of blood eosinophils and FeNO per current GINA definitions, and evidence of allergic asthma. Dupilumab reduced exacerbation rates and improved lung function and asthma control in patients with asthma with type 2 inflammation, irrespective of evidence of allergic asthma.
Abbreviations: ACQ-5, 5-item asthma control questionnaire; AERs, annualized severe asthma exacerbation rates; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; LIBERTY ASTHMA TRAVERSE, Long-Term Safety Evaluation of Dupilumab in Patients With Asthma; NCT, national clinical trial; PSBL, parent study baseline; QUEST, Evaluation of Dupilumab in Patients With Persistent Asthma

1 | INTRODUCTION

Type 2 inflammation, present in most patients with severe asthma, is characterized by one or more of the following biomarkers, according to Global Initiative for Asthma (GINA) guidelines: blood eosinophil count ≥150 cells/μL, fractional exhaled nitric oxide (FeNO) ≥ 20 parts per billion (ppb), sputum eosinophils ≥2%, and/or clinically allergen-driven asthma.[1] At the molecular level, type 2 inflammation features an upregulation of interleukin (IL)-4, IL-5, and IL-13, which are responsible for orchestrating immune responses in allergic diseases and other inflammatory disorders such as asthma.[2,3]

Dupilumab, a fully human monoclonal antibody,[4,5] blocks the shared receptor component for IL-4 and IL-13, key and central drivers in many type 2 inflammatory diseases, including allergic diseases such as asthma and atopic dermatitis,[6] thus inhibiting their signaling. In the phase 3 LIBERTY ASTHMA QUEST study (QUEST; NCT02414854), add-on dupilumab 200 and 300 mg every 2 weeks, vs placebo, significantly reduced severe asthma exacerbations and improved pre-bronchodilator forced expiratory volume in 1 second (FEV_1) in the overall population of patients with uncontrolled, moderate-to-severe asthma. Treatment effects were greater with elevated type 2 biomarkers at baseline, defined as blood eosinophils ≥150 cells/μL or FeNO ≥25 ppb.[7] Results of the primary analysis of the phase 3, open-label extension LIBERTY ASTHMA TRAVERSE study (TRAVERSE; NCT02134028) provided additional evidence of the safety and efficacy profiles of dupilumab in patients with asthma for up to 2 years, including analyses of patients with high type 2 biomarkers as defined in the primary analysis of QUEST (parent study).[8] Safety during TRAVERSE was consistent with the known dupilumab safety profile and has been reported in the primary publication.[8]

Several biologic therapies are available for the treatment of asthma.[7,9–12] Among them, omalizumab, an anti-IgE antibody, and dupilumab, an anti-IL-4Rα antibody, are most likely to target allergic inflammation, due to their modes of action and pleiotropic effects on allergic inflammation.[13] Current GINA guidelines recommend the use of an anti-IgE monoclonal antibody (omalizumab) in patients with allergic asthma.[1] It is worth noting that, in previous analyses of dupilumab asthma studies, including QUEST, dupilumab reduced the rate of severe exacerbations, improved lung function, and improved asthma control in patients with non-OCS-dependent, moderate-to-severe asthma with or without evidence of allergic asthma.[14–16] Dupilumab efficacy was also shown in patients with OCS-dependent, severe asthma, regardless of their allergic phenotype.[16] In a recent analysis comparing the effectiveness of omalizumab, mepolizumab, and dupilumab in adolescents and adults with asthma and with baseline IgE levels of 30–700 IU/mL and blood eosinophil counts of ≥150 cells/μL, using electronic health records from a large US-based academic health care system, it was shown that dupilumab was associated with greater improvements in exacerbation rates and FEV_1 compared with both omalizumab and mepolizumab.[17] In this post hoc analysis, we examined the long-term efficacy of dupilumab in the TRAVERSE study population enrolled from QUEST with or without evidence of an allergic asthma phenotype who presented with type 2 inflammation characteristics per current GINA guidelines.

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2 | METHODS

2.1 | Study design and patients

Details of the TRAVERSE study design and protocol have been previously published.[8] In short, TRAVERSE was a multinational, single-arm, open-label extension study to evaluate the long-term safety and tolerability of dupilumab in adult and adolescent patients with asthma who participated in a previous dupilumab asthma clinical study. The study was conducted according to the Declaration of Helsinki and the Good Clinical Practice principles. Prior to enrolment, all patients or their parents or legal guardians provided written informed consent or assent. Such informed consent/assent forms, together with the study protocol, were reviewed and approved by independent ethics committees and institutional review boards.

This post hoc analysis included patients from QUEST who enrolled in TRAVERSE. In QUEST, patients aged ≥12 years with uncontrolled, moderate-to-severe asthma (defined per GINA 2014 guidelines[18]) treated with medium–to–high-dose inhaled corticosteroids (ICS) and up to 2 additional inhalers were randomized 2:2:1:1 to receive add-on 200 mg or 300 mg dupilumab or volume-matched placebo subcutaneously every 2 weeks for 52 weeks.[7] During TRAVERSE, all patients maintained their background asthma medication and received 300 mg dupilumab subcutaneously every 2 weeks for either 96 or 48 weeks after treatment duration was shortened (protocol amendment) due to accumulating clinical trial safety data on dupilumab.[8] Treatment arms are referred to as "dupilumab/dupilumab" or "placebo/dupilumab" for patients who received dupilumab (200 or 300 mg groups) or placebo (volume-matched groups), respectively, during QUEST.

In TRAVERSE, inclusion criteria required patients to have completed a previous dupilumab asthma study and to receive their background dose of medium- or high-dose ICS, in combination with up to 2 additional controllers, as done during the parent study.[8] Full eligibility criteria of QUEST and TRAVERSE are available in their respective primary publications.[7,8]

2.2 | Outcomes

Full details of the QUEST and TRAVERSE study procedures have been published previously.[7,8] In this analysis, we investigated asthma exacerbations, lung function, and asthma control by assessing three endpoints: the annualized severe exacerbation rate (AER), change from parent study baseline (PSBL) in pre-bronchodilator FEV_1, and change from PSBL in ACQ-5 score throughout TRAVERSE.

2.3 | Statistical analyses

This post hoc analysis is descriptive only; no formal statistical hypotheses were formulated. Analyses were performed on the exposed population, defined as all patients who received ≥1 full or partial dose of study treatment. SAS® software, version 9.4 or higher, was used for statistical analyses.

Patients were stratified according to the presence of allergic asthma and their levels of type 2 inflammation biomarkers at PSBL. Evidence of an allergic asthma phenotype was defined as total serum IgE ≥ 30 IU/mL and ≥1 perennial aeroallergen-specific IgE ≥ 0.35 IU/mL at PSBL, as previously described by Corren et al.[14] Patients who did not meet this criterion were classified as having no evidence of allergic asthma. The following perennial aeroallergens were considered: *Aspergillus fumigatus*, *Alternaria tenuis/alternata*, *Cladosporium herbarium/hormodendrum*, cat dander, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, dog dander, German cockroach, and Oriental cockroach. Furthermore, patients were categorized into 4 subgroups depending on their levels of type 2 inflammation markers at PSBL: ≥150 eosinophils/μL; FeNO ≥20 ppb; ≥150 eosinophils/μL or FeNO ≥20 ppb; and <150 eosinophils/μL and FeNO <20 ppb regardless of their allergic status. These biomarker cutoffs were selected as per the latest GINA guidelines.[1]

The unadjusted AERs were calculated as the total number of events during the observational period divided by the total exposure in patient-years in the observational period. Continuous endpoints (change in FEV_1 and ACQ-5 score over time) were calculated as means with SE or SD.

3 | RESULTS

3.1 | Patient disposition

A total of 1530 patients who completed the QUEST study enrolled in the TRAVERSE open-label extension study. Of these, 517 placebo/dupilumab- and 1013 dupilumab/dupilumab-treated patients were included in this analysis. The number of patients with or without an allergic phenotype who were included in each subgroup according to their baseline levels of type 2 inflammatory markers is presented in Figure S1, and their demographic and disease characteristics at PSBL are included in Table S1. PSBL characteristics were similar across treatment arms and subgroups, except for levels of total IgE, which were lower in patients without evidence of allergic asthma, as expected.

3.2 | Dupilumab treatment reduced annualized severe asthma exacerbation rates in patients with elevated type 2 biomarkers

During TRAVERSE, patients in the dupilumab/dupilumab- and placebo/dupilumab-treated groups with type 2 inflammation showed comparable reductions in AERs, which were sustained throughout the treatment period, regardless of their allergic phenotype. AER results were comparable across all type 2 subgroups (Figure 1).

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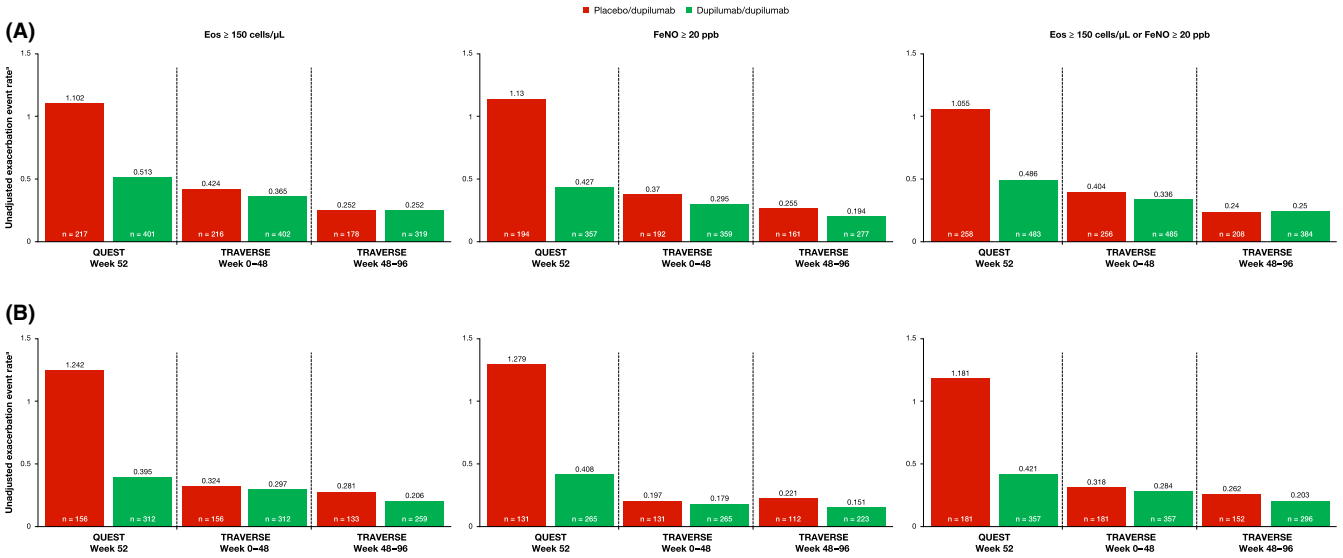

FIGURE 1 Unadjusted annualized severe exacerbation rates in patients (A) with and (B) without evidence of an allergic asthma phenotype, according to their baseline levels of blood eosinophils and FeNO. [a]Calculated as the total number of events that occurred during the treatment period divided by the total number of patient-years followed in the treatment period. Eos, eosinophils; FeNO, fractional exhaled nitric oxide; ppb, parts per billion.

3.3 | Dupilumab improved lung function in patients with elevated type 2 biomarkers

Throughout TRAVERSE, the change from PSBL in pre-bronchodilator FEV_1 followed a similar pattern across all groups of patients with characteristics of type 2 inflammation, irrespective of their allergic phenotype (Figure 2). During the parent study, dupilumab-treated patients showed greater improvements in pre-bronchodilator FEV_1 than did patients who received placebo. At the start of TRAVERSE, patients who had received placebo in the parent study and switched to dupilumab rapidly achieved improvements in pre-bronchodilator FEV_1 similar to those observed in patients in the dupilumab/dupilumab group, and both treatment arms sustained such improvements throughout TRAVERSE.

At Week 96, the mean (SD) change from PSBL in pre-bronchodilator FEV_1 in placebo/dupilumab- vs dupilumab/dupilumab-treated patients with an allergic phenotype was 0.37 (0.44) L vs 0.34 (0.52) L in those with blood eosinophils ≥ 150 cells/μL; 0.41 (0.46) L vs 0.44 (0.54) L in those with FeNO ≥20 ppb; and 0.35 (0.44) L vs 0.35 (0.51) L in those with blood eosinophils ≥ 150 cells/μL or FeNO ≥20 ppb. Improvements for those without an allergic phenotype were 0.39 (0.44) L vs 0.37 (0.42) L in those with ≥150 eosinophils/μL; 0.41 (0.43) L vs 0.35 (0.42) L in those with FeNO ≥20 ppb; and 0.38 (0.43) L vs 0.33 (0.42) L in those with ≥150 eosinophils/μL or FeNO ≥20 ppb.

3.4 | Dupilumab treatment improved asthma control in patients with elevated type 2 biomarkers

In the patients who received dupilumab during QUEST, the reductions obtained during the parent study were sustained up to 48 weeks throughout TRAVERSE. Furthermore, among patients who received placebo during the parent study and initiated dupilumab at the start of TRAVERSE, ACQ-5 scores were reduced and, by Week 24 of TRAVERSE, were similar to those in the dupilumab/dupilumab arm; these reductions were maintained until Week 48. At that time, the mean (SD) change from PSBL in ACQ-5 score in placebo/dupilumab- vs dupilumab/dupilumab-treated patients with an allergic phenotype was −1.65 (1.08) vs −1.74 (1.07) in those with ≥150 eosinophils/μL; −1.69 (1.08) vs −1.81 (1.04) in those with FeNO ≥20 ppb; and −1.63 (1.07) vs −1.75 (1.05) in those with ≥150 eosinophils/μL or FeNO ≥20 ppb. Values for those without an allergic phenotype were −1.75 (1.10) vs −1.86 (1.09) in those with ≥150 eosinophils/μL; −1.83 (1.03) vs −1.83 (1.04) in those with FeNO ≥20 ppb; and −1.76 (1.08) vs −1.78 (1.10) in those with ≥150 eosinophils/μL or FeNO ≥20 ppb at PSBL (Figure 3).

Similar to the observed improvements in lung function, dupilumab improved asthma control across all subgroups of patients with type 2 inflammation, irrespective of the presence of an allergic phenotype.

3.5 | Dupilumab efficacy in patients without type 2 inflammation

In patients without type 2 inflammation and an allergic phenotype at PSBL, AERs during TRAVERSE were similar in the dupilumab/dupilumab arm and placebo/dupilumab arm (Figure 4A). Interestingly, for all study periods examined, in patients without an allergic phenotype, AER in the dupilumab/dupilumab group appears to be somewhat higher compared with the placebo/dupilumab group. Overall, dupilumab maintained reductions in AER observed in the parent study throughout TRAVERSE, regardless of allergic phenotype.

In the subgroup of patients without type 2 inflammation, regardless of evidence of an allergic phenotype, dupilumab maintained lung function throughout TRAVERSE, with the exception

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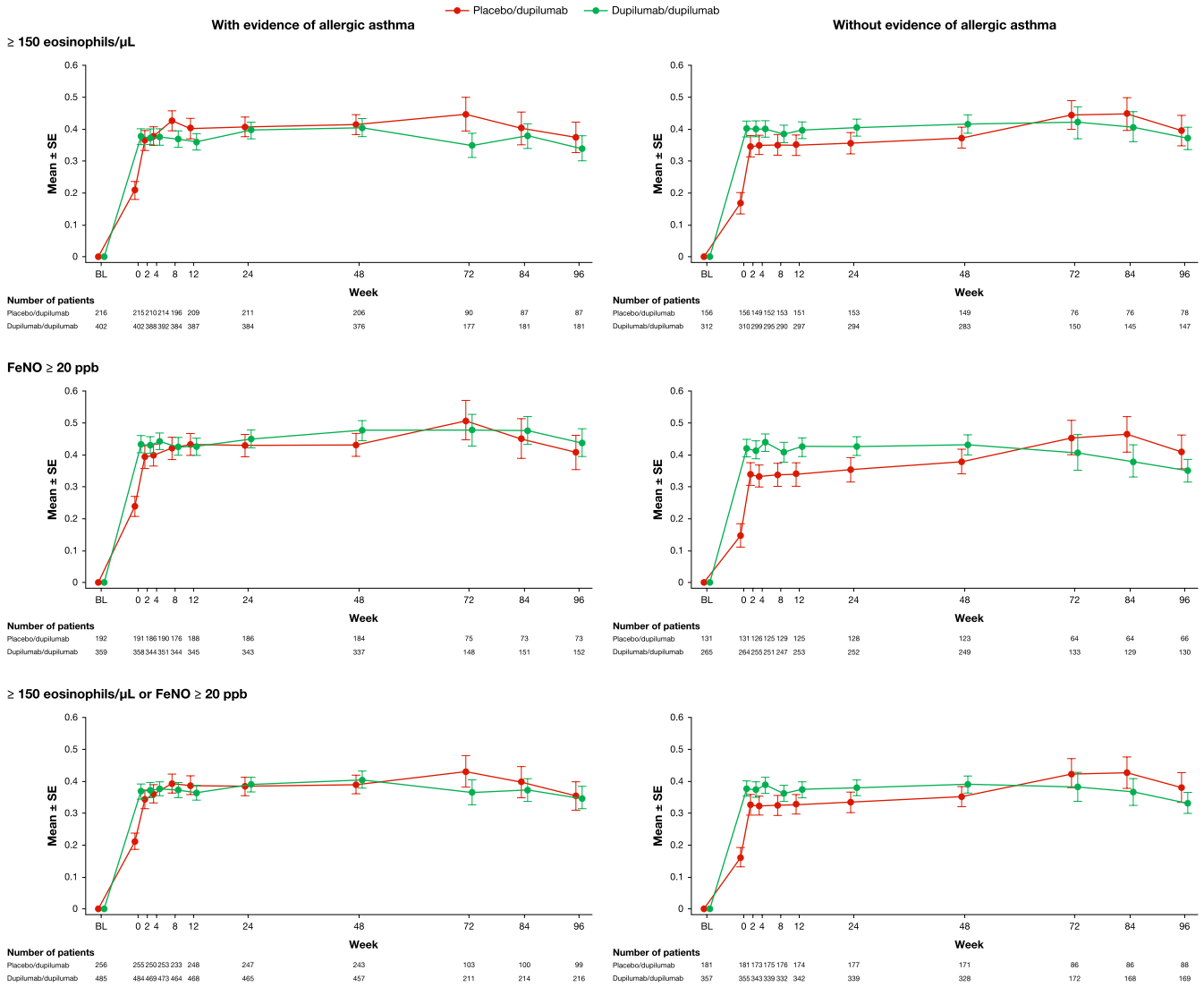

FIGURE 2 Change from PSBL in pre-bronchodilator FEV_1 in patients with and without evidence of an allergic asthma phenotype, according to their baseline levels of blood eosinophils and FeNO. FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ppb, parts per billion; PSBL, parent study baseline; SE, standard error.

of the subgroup without allergic phenotype, where—after small improvements early on—a small decline in lung function may have been observed in the dupilumab/dupilumab group after Week 48 of TRAVERSE (Figure 4B). However, due to the small patient numbers in these groups, further studies are needed to confirm these data.

In the subgroup of patients with <150 eosinophils/µL and FeNO <20 ppb, no noticeable differences in change from PSBL in ACQ-5 scores were observed throughout TRAVERSE between placebo/dupilumab and dupilumab/dupilumab arms, in both patients with and without allergic phenotypes (Figure 4C).

3.6 | Effect of dupilumab treatment In blood eosinophil levels in patients with and without type 2 inflammation

Treatment with dupilumab led to reduced blood eosinophil counts in all subgroups of patients with elevated type 2 biomarkers at PSBL. By the end of the study, patients from the placebo/dupilumab arm reached similar reductions in eosinophil count as the dupilumab/dupilumab subgroup (Figure S2). In patients with <150 eosinophils/µL and FeNO <20 ppb at PSBL, blood eosinophil levels increased slightly during TRAVERSE, but were back to around baseline values by end of the study (Figure S2).

4 | DISCUSSION

For the primary analysis of the QUEST study, patients were stratified by blood eosinophils ≥150 cells/µL to <300 cells/µL, and ≥300 cells/µL at baseline and FeNO ≥ 25 to <50 ppb, and ≥ 50 ppb to describe patients with type 2 inflammatory asthma.[7] A post hoc analysis of QUEST patients showed dupilumab efficacy in patients with moderate-to-severe asthma with type 2 inflammation following the criteria outlined in the 2021 GINA guidelines, with and without an allergic phenotype.[15] In this follow-up post hoc analysis, we aimed

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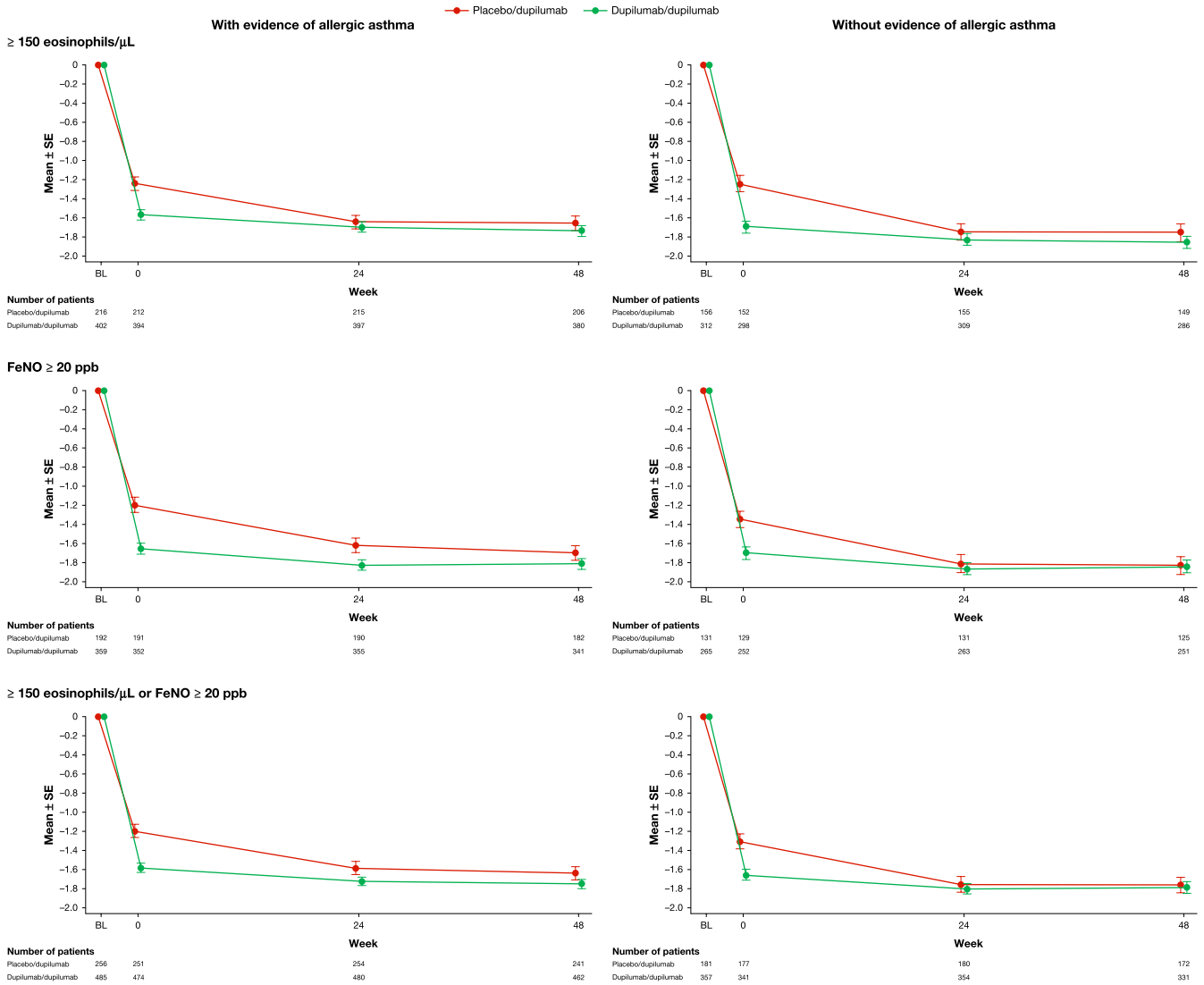

FIGURE 3 Change from PSBL in ACQ-5 score in patients with and without evidence of an allergic asthma phenotype, according to their baseline levels of blood eosinophils and FeNO. ACQ-5, 5-item asthma control questionnaire; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; PSBL, parent study baseline; SE, standard error.

to evaluate the long-term efficacy of dupilumab in these subgroups of patients from QUEST who enrolled in TRAVERSE, for up to an additional 96 weeks. Therefore, patients were stratified by type 2 inflammatory marker into the following subgroups: (i) blood eosinophil counts of ≥150 cells/µL, (ii) FeNO ≥ 20 ppb, (iii) blood eosinophil counts of ≥150 cells/µL or FeNO ≥20 ppb, or (iv) blood eosinophil counts of <150 cells/µL and FeNO <20 ppb at baseline, with and without evidence of allergic asthma as described by Corren et al.[14] It is worth noting that, in the absence of percutaneous allergy skin testing, for this study, allergic reactions were based on the presence of at least one positive allergen-specific IgE at ≥0.35 IU/mL at PSBL; the lack of a clinical diagnosis of allergy or the history of it did not exclude type 2 pathology.

We showed that reductions in AER observed during QUEST in dupilumab-treated patients[15] were sustained throughout TRAVERSE in patients with elevated type 2 biomarkers, (blood eosinophils ≥150 cells/µL or FeNO ≥20 ppb) regardless of their allergic phenotype at PSBL; in the subgroup of patients who initiated dupilumab at the beginning of TRAVERSE, substantial reductions were observed. This adds to the current evidence[7,8,15,19,20] showing that dupilumab reduces the risk of severe exacerbations in patients with asthma with high type 2 biomarkers as per current GINA guidelines[1] and that dupilumab efficacy is sustained long term.[8]

Improvements in lung function and asthma control were also observed in patients with elevated type 2 biomarkers, regardless of allergic phenotype. These improvements were sustained up to 3 years in patients who received dupilumab during the parent study (dupilumab/dupilumab group); in addition, upon switching to dupilumab in TRAVERSE, rapid improvements were observed in patients who had received placebo during the parent study. The observation of sustained lung function in the long term are of great interest and may indicate potential disease-modifying properties of dupilumab. However, more data and further investigation are

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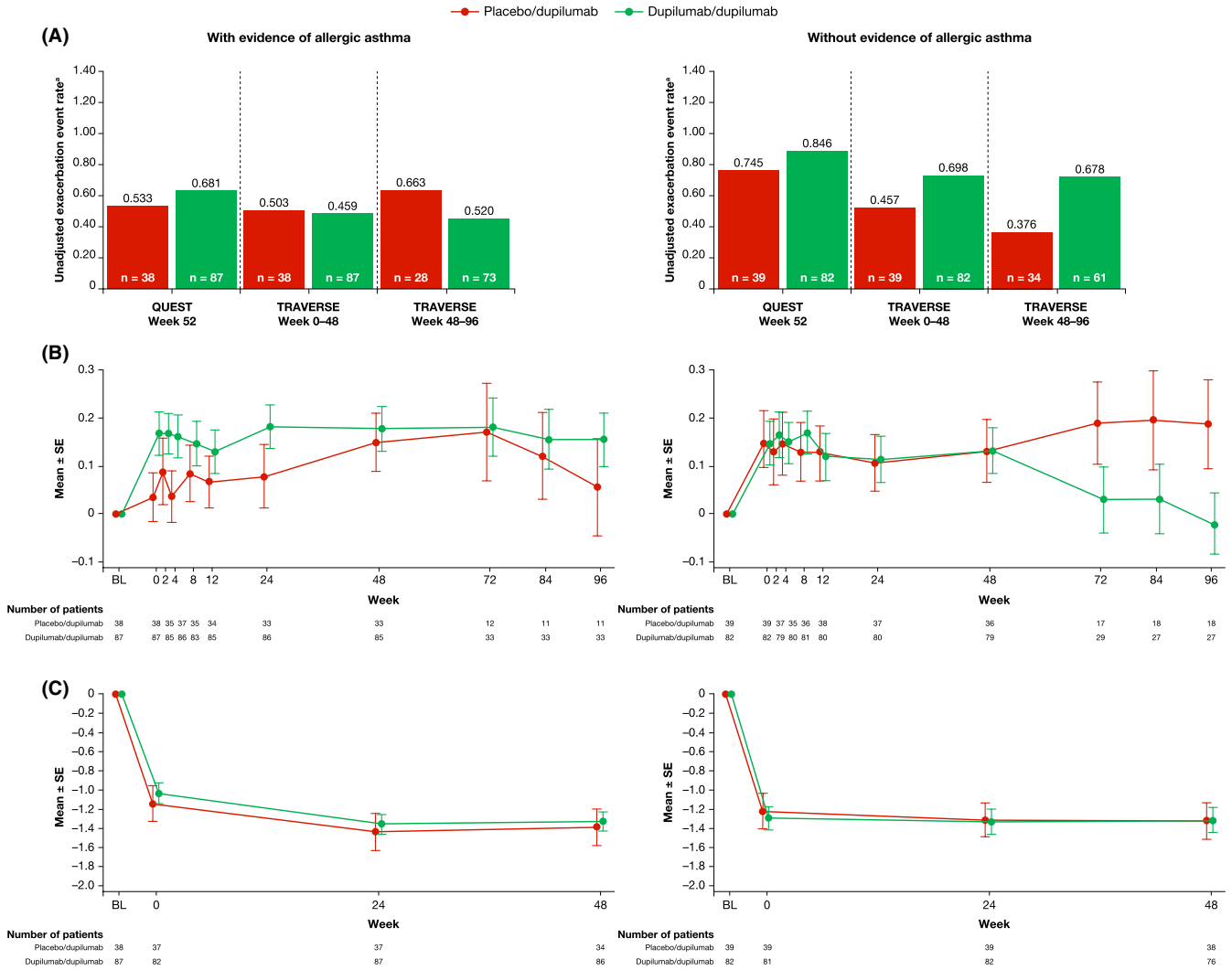

FIGURE 4 Unadjusted annualized severe exacerbation rates (A), change from PSBL in pre-bronchodilator FEV_1 (B), and change from PSBL in ACQ-5 score (C), in patients with baseline levels of <150 eosinophils/μL and FeNO <20 ppb with and without evidence of an allergic asthma phenotype.[a]Calculated as the total number of events that occurred during the treatment period divided by the total number of patient-years followed in the treatment period. ACQ-5, 5-item asthma control questionnaire; Eos, eosinophils; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; FEV_1, forced expiratory volume in 1 second; PSBL, parent study baseline; SE, standard error.

needed to confirm this hypothesis and allude to a potential mechanism of action.

Patients across all subgroups reported clinically meaningful improvements in asthma control as measured by change in ACQ-5 scores ≥0.5[21] during the parent study,[7] which were sustained throughout the open-label extension study.

Dupilumab's effect was not as evident in patients without elevated type 2 biomarkers, regardless of allergic status.

A limitation of this study is the post hoc nature of the analysis and that the study was not powered specifically to examine these subgroups. Also, percutaneous allergy skin testing was not performed during the study and allergic reactions to the panel of aeroallergens were based solely on specific IgE levels at a baseline of ≥0.35 kU/L and the presence of at least one positive allergen-specific IgE, and no pollen or spore counts were performed during the study to assess the amount of allergen present in individual participants' homes and/or geographic area, meaning it is not possible to ascertain the degree to which each sensitized allergen affected each patient. Additionally, patients were allowed to take anti-allergic medications during the study, and their role in influencing the results is unclear. Finally, the definition of allergic asthma did not consider symptoms, and it may be that some patients were sensitized but did not experience allergic symptoms.

In conclusion, this analysis confirmed the results observed in patients with moderate-to-severe asthma with type 2 inflammation with and without evidence of allergic asthma, as seen in the previous QUEST study.[15] The results presented in this paper highlight dupilumab's long-term efficacy in these subgroups of patients. Throughout TRAVERSE, dupilumab further reduced exacerbation rates and improved pre-bronchodilator FEV_1 and asthma control for up to 96 weeks. Furthermore, the greater treatment effect in

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patients with elevated type 2 inflammatory biomarkers at baseline was sustained throughout the TRAVERSE open-label extension study and appeared to be mostly unaffected by the presence of an allergic phenotype.

AUTHOR CONTRIBUTIONS

IDP and GLC acquired data. KFR, RG, NP-A, YD, PJR, JAJ-N, and AR contributed to the conception and design of the study. AA did statistical analyses. All authors participated in the interpretation of the data, provided critical feedback and final approval for submission, and took responsibility for the accuracy, completeness, and protocol adherence of data and analyses. All investigators had confidentiality agreements with the sponsors.

ACKNOWLEDGMENTS

This research was sponsored by Sanofi and Regeneron Pharmaceuticals Inc. ClinicalTrials.gov Identifier: NCT02134028. Medical writing/editorial assistance was provided by Natalia Crespo of Excerpta Medica and was funded by Sanofi and Regeneron Pharmaceuticals Inc., according to the Good Publication Practice guideline. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

Rabe KF: AstraZeneca, Berlin-Chemie, Boehringer Ingelheim, Chiesi, Novartis, Sanofi—consultant, speaker fees. **Pavord ID:** Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Teva—speaker fees; AstraZeneca, Teva—payments for organizing educational events; Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Dey Pharma, Genentech, GSK, Knopp Biosciences, Merck, Merck Sharp & Dohme, Napp Pharmaceuticals, Novartis, Regeneron Pharmaceuticals Inc., RespiVert, Sanofi, Schering-Plough, Teva—consultant fees; AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Napp Pharmaceuticals, Teva—international scientific meeting sponsorship; Chiesi—research grant. **Busse WW:** Regeneron Pharmaceuticals Inc., Sanofi, GSK—consultant and speaker fees. **Chupp GL**: reports personal fees and other fees outside the submitted work (consulting, speaking honoraria, and clinical-trial site) from Amgen, AstraZeneca, Boehringer Ingelheim, Genentech, GSK, RAPT Therapeutics, Regeneron Pharmaceuticals Inc., and Sanofi. **Izuhara, K:** AstraZeneca, Shino-Test, AstraZeneca—research grant. **Altincatal A, Pandit-Abid N, Rowe PJ, Jacob-Nara JA:** Sanofi—employees, may hold stock and/or stock options in the company. **Gall R, Deniz Y, Radwan A:** Regeneron Pharmaceuticals Inc.—employees and shareholders.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Rabe KF, Pavord ID, Busse WW, et al. Dupilumab improves long-term outcomes in patients with uncontrolled, moderate-to-severe GINA-based type 2 asthma, irrespective of allergic status. *Allergy*. 2023;78: 2148-2156. doi:10.1111/all.15747

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