Long-term dupilumab efficacy in type 2 asthma regardless of baseline characteristics

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To the Editor:

Several factors have been associated with an increased risk of asthma exacerbations, such as sex, age, obesity, age at asthma onset and asthma control. Additionally, prior exacerbation history is a significant independent predictor of future exacerbation risk for patients with asthma [1].

Type 2 inflammation is characterised by the inflammatory cytokines interleukin (IL)-4, IL-5, and IL-13 [2]. Over 70% of patients with asthma exhibit a type 2 inflammatory phenotype [3], with increased production of IL-4, IL-5 and IL-13 [2], key and central drivers of type 2 inflammation in multiple diseases [4]. Dupilumab, a fully human monoclonal antibody [5, 6], blocks IL-4Rα, the shared receptor component for IL-4 and IL-13, and has proved effective for the treatment of patients with moderate-to-severe asthma. The LIBERTY ASTHMA TRAVERSE study (www.clinicaltrials.gov identifier number NCT02134028) was a single-arm, open-label extension study that evaluated the long-term safety and efficacy of dupilumab added on to standard-of-care therapy in adolescent and adult patients with moderate-to-severe asthma who participated in a previous dupilumab asthma study [7]. Safety findings in TRAVERSE were consistent with the known dupilumab safety profile [7].

In this descriptive analysis, we investigated the efficacy of dupilumab in patients with moderate-to-severe type 2 asthma (defined as blood eosinophil counts ⩾150 cells per µL or exhaled nitric oxide fraction (F_{ENO}) ⩾25 parts per billion (ppb) at baseline) who participated in the parent study QUEST (NCT02414854) and subsequently enrolled in TRAVERSE, and who completed the full 96 weeks (3 years) of study participation, based on subgroups defined by parent study baseline (PSBL) demographics and disease characteristics. The biomarker cut-offs used to define type 2 asthma in this analysis were informed by previous pre-specified subgroup analyses of QUEST, demonstrating greater reductions in exacerbations and greater improvement in lung function in patients with higher baseline blood eosinophil (⩾150 cells per µL) or F_{ENO} (⩾25 ppb) [8].

In the QUEST study, patients were randomised 2:2:1:1 to receive add-on subcutaneous dupilumab 200 mg or 300 mg or matched-volume placebo every 2 weeks for 52 weeks. During TRAVERSE, patients received dupilumab 300 mg every 2 weeks for up to 96 weeks. Comprehensive study designs and methodologies have been previously published for both studies [7, 8].

This *post hoc* analysis included patients from the parent study QUEST with evidence of type 2 inflammation at PSBL, who subsequently enrolled in TRAVERSE, and those who completed 96 weeks (3 years) of study participation. End-points included the unadjusted annualised severe asthma exacerbation rates (AERs) for TRAVERSE weeks 0–96, and the mean change from parent study (QUEST) baseline in pre-bronchodilator (BD) forced expiratory volume in 1 s (FEV_1) (in litres) at TRAVERSE weeks 48 and 96. Efficacy was evaluated descriptively according to demographic and disease characteristics at QUEST baseline, including age, gender, geographical region, body mass index, height, race, ethnicity, age at asthma onset, medication use, pre-BD FEV_1, number of severe asthma exacerbations in the year before QUEST, smoking history, blood eosinophil counts and F_{ENO}.

Severe asthma exacerbations were defined as a deterioration of asthma leading to treatment for ⩾3 days with systemic glucocorticoids or hospitalisation or an emergency department visit leading to treatment with

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The TRAVERSE study demonstrated the long-term efficacy of dupilumab for the treatment of patients with uncontrolled, moderate-to-severe, type 2 asthma across a range of baseline demographics and disease characteristics up to 96 weeks https://bit.ly/3XSwX62

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systemic glucocorticoids. AERs were calculated as the total number of events that occurred during the observational period divided by the total patient-years followed in the observational period. Mean±SE change in pre-BD FEV_1 was calculated as change from parent study (QUEST) baseline to TRAVERSE weeks 48 and 96. No formal statistical analysis was performed in this study because the TRAVERSE open-label study was not designed to assess comparative effectiveness.

Of the patients from QUEST, 1530 enrolled in TRAVERSE (placebo–dupilumab: n=517; dupilumab–dupilumab: n=1013); 1227 of these patients were found to have type 2 asthma (placebo–dupilumab: n=423; dupilumab–dupilumab: n=804); and 185 out of 423 patients in the placebo–dupilumab group and 364 out of 804 patients in the dupilumab–dupilumab group completed 3 years of dupilumab treatment.

At PSBL, the mean number of exacerbations in the past year in the overall population was 2.09. In patients with type 2 asthma who completed 3 years of study participation across all subgroups defined by baseline characteristics, AERs during TRAVERSE weeks 0–96 ranged from 0.045 to 0.438 in patients who received dupilumab during QUEST (dupilumab–dupilumab group) and 0.0 to 0.539 in patients who received placebo during QUEST (figure 1a). Numerically similar results were observed for the overall type 2 population (data not shown).

At PSBL, the mean pre-BD FEV_1 in the overall population was 1.78 L. Change from PSBL in pre-BD FEV_1 at TRAVERSE week 48 in patients with type 2 asthma who completed 3 years of study participation across all subgroups defined by baseline characteristics ranged from −0.11 to 0.89 L (placebo–dupilumab group) and from −0.15 to 1.03 L (dupilumab–dupilumab group) (figure 1b). Mean change from baseline in pre-BD FEV_1 in TRAVERSE at week 96 ranged from −0.38 to 0.74 L for placebo–dupilumab treatment and from −0.02 to 1.1 L for dupilumab–dupilumab treatment, across the subgroups (figure 1c). Numerically similar improvements in lung function were observed for the overall type 2 population (data not shown).

Among patients with type 2 inflammation who completed the TRAVERSE study, reduction in AER and improvement in FEV_1 were numerically similar across subgroups defined by demographic features, biomarkers and asthma-related disease features, although this could not be confirmed statistically due to the design of the study. Previous data demonstrated that patients enrolled in QUEST with type 2 asthma who received dupilumab had significantly lower rates of severe asthma exacerbation and greater improvements in pre-BD FEV_1 than those who received placebo [8]. Consistent with the findings in the overall TRAVERSE population [7], this *post hoc* analysis of the TRAVERSE study demonstrates progressive reduction in exacerbation rate and sustained improvements in pre-BD FEV_1 as observed in the parent study, in patients with type 2 asthma and regardless of a wide range of baseline demographics and disease characteristics. For patients who initiated dupilumab treatment in TRAVERSE, there was a numerically similar onset of response as observed in dupilumab treatment patients in QUEST, once again regardless of a wide range of baseline demographics and disease characteristics.

The AER remained low and lung function was sustained for up to 96 weeks, supporting long-term efficacy across multiple baseline features. The efficacy of dupilumab was mostly numerically similar across subgroups. One exception was specific categories regarding race; however, the low number of patients recorded in the categories black/African descent (n=7) and other (n=2) limits interpretation within these subgroups. Future studies with greater patient population diversity are needed to better evaluate efficacy in these groups.

One potential limitation of this study was the possibility of survivorship bias. Not all patients completed the study period and it is possible that those who did not complete the study experienced less clinical benefit than those who remained. An additional limitation was that the study was not designed or powered to perform statistical comparisons between groups or *versus* baseline; therefore, all results presented are entirely descriptive.

In summary, this descriptive analysis of the TRAVERSE study demonstrated long-term efficacy of dupilumab up to 96 weeks in patients with uncontrolled, moderate-to-severe, type 2 asthma across a range of baseline demographics and disease characteristics. This analysis is limited in the ability to assess efficacy across race, due to low representation of patients from the black/African descent category, underlining the need to improve diversity in future studies. Nonetheless, these findings significantly add to the body of knowledge guiding treatment decisions for patients with moderate-to-severe asthma.

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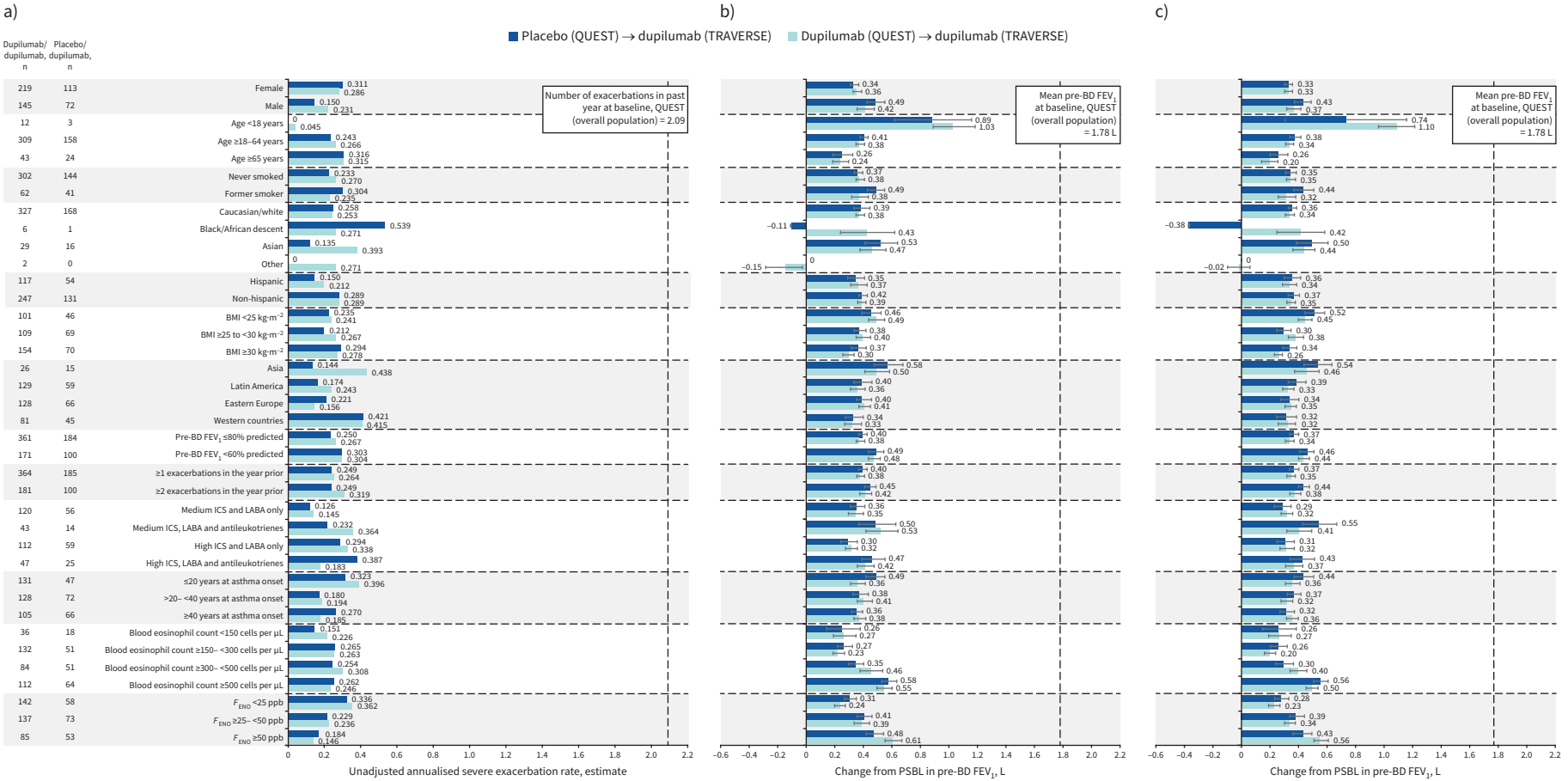

FIGURE 1 a) Unadjusted annualised severe exacerbation rates at TRAVERSE weeks 0–96, and change from parent study baseline (PBSL) in pre-bronchodilator (BD) forced expiratory volume in 1 s (FEV_1) at TRAVERSE b) week 48 and c) week 96 in patients with moderate-to-severe type 2 asthma and who completed 3 years of study, stratified by baseline demographic and disease characteristics. Type 2 asthma defined as blood eosinophil counts ⩾150 cells per µL or exhaled nitric oxide fraction (F_{ENO}) ⩾25 parts per billion (ppb). Error bars in b) and c) represent standard errors. BMI: body mass index; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist.

Michael E. Wechsler[1], Linda Rogers[2], G. Walter Canonica[3,4], Arnaud Bourdin[5], Arman Altincatal[6], Megan Hardin[6], Xavier Soler[7], Paul J. Rowe[8], Yamo Deniz[7], Harry Sacks[7] and Juby A. Jacob-Nara[8]

[1]Department of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, CO, USA. [2]Icahn School of Medicine at Mount Sinai, New York, NY, USA. [3]Department of Biomedical Sciences, Humanitas University, Milan, Italy. [4]Asthma and Allergy Unit, IRCCS Humanitas Research Hospital, Milan, Italy. [5]Department of Respiratory Diseases, University of Montpellier, Montpellier, France. [6]Sanofi, Cambridge, MA, USA. [7]Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA. [8]Sanofi, Bridgewater, NJ, USA.

Corresponding author: Michael Wechsler (mikewechsler@gmail.com)

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Ethics statement: The TRAVERSE study was performed in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Written informed consent (or assent, where appropriate) was obtained from all patients (or their parents or legal guardians) before enrolment in the study. The protocol and informed consent or assent forms were approved by independent ethics committees and institutional review boards at the study sites.

Author contributions: M. Hardin, X. Soler, P.J. Rowe, Y. Deniz, H. Sacks and J.A. Jacob-Nara were responsible for conceptualisation of the study. M.E. Wechsler, L. Rogers, G.W. Canonica, A. Bourdin and A. Altincatal performed data curation and analysis. A. Altincatal, M. Hardin, X. Soler, P.J. Rowe, Y. Deniz, H. Sacks and J.A. Jacob-Nara were responsible for methodology. All authors were responsible for writing, drafting, reviewing and editing the manuscript and all authors read and approved the final manuscript.

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Conflict of interest: M.E. Weschler reported personal fees from AstraZeneca, Boehringer Ingelheim, Equillium, Gala Therapeutics, Genentech, Genzyme, Mylan, Novartis, Pulmatrix, Regeneron Pharmaceuticals Inc., resTORbio, Sentien Biotechnologies and Teva; and grants and personal fees from GSK and Sanofi. L. Rogers reported research support from American Lung Association, NIH and Sanofi; consultancy for AstraZeneca, Genentech, Novartis and Sanofi; and payments for organising educational events from AstraZeneca and Genentech. G.W. Canonica reported speaker fees from ALK, AstraZeneca, Boehringer Ingelheim, GSK, HAL Allergy, Menarini, Mundipharma, Novartis, Regeneron Pharmaceuticals Inc., Sanofi, Stallergenes Greer and Uriach; and advisory board membership for ALK, AstraZeneca, Boehringer Ingelheim, GSK, HAL Allergy, Menarini, Mundipharma, Novartis, Regeneron Pharmaceuticals Inc., Sanofi, Stallergenes Greer and Uriach. A. Bourdin reported nonfinancial support during the conduct of the study from GSK; other support from Acceleron Pharma, Actelion, Galapagos, Merck Sharp & Dohme, Nuvaira, Pulmonx, United Therapeutics and Vertex Pharmaceuticals; grants and personal fees from Boehringer Ingelheim; and personal fees from AstraZeneca, Chiesi, GSK, Regeneron Pharmaceuticals Inc. and Sanofi. A. Altincatal, M. Hardin, P.J. Rowe and J.A. Jacob-Nara are employees of Sanofi, and may hold stock and/or stock options in the company. X. Soler and Y. Deniz are employees and shareholders of Regeneron Pharmaceuticals Inc. H. Sacks is an employee of Regeneron Pharmaceuticals Inc. and a shareholder in Optinose.

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