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Impact of dupilumab across seasons in patients with type 2, uncontrolled, moderate-to-severe asthma

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ABSTRACT

Background: Seasonal variability could influence asthma exacerbations. Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4/IL-13, key and central drivers of type 2 inflammation. In the 52-week QUEST study (NCT02414854), add-on dupilumab every 2 weeks vs placebo significantly reduced exacerbations and improved prebronchodilator forced expiratory volume in 1 second in patients with uncontrolled, moderate-to-severe asthma. TRAVERSE (NCT02134028), the open-label QUEST extension study, enrolled patients with moderate-to-severe asthma to investigate long-term safety and efficacy of dupilumab, including patients who previously received placebo that initiated dupilumab therapy.
Objective: To investigate long-term dupilumab efficacy in reducing exacerbations across yearly seasons in patients with type 2 inflammatory asthma with and without clinical evidence of allergic asthma.
Methods: Unadjusted annualized exacerbation rate and proportions of patients experiencing severe asthma exacerbations are reported by month and season and for both hemispheres.
Results: The proportion of patients with type 2 asthma experiencing 1 or more severe asthma exacerbations during QUEST was 20.8% vs 10.0% in spring, 18.2% vs 7.3% in summer, 22.2% vs 12.6% in autumn, and 26.4% vs 12.0% in winter, for placebo- vs dupilumab-treated patients, respectively; *P* was less than .001 for placebo vs dupilumab in all seasons. Reductions in the proportion of patients experiencing severe exacerbations across seasons in subgroups with and without evidence of allergic asthma were similar to the overall type 2 population. Reductions in severe exacerbations observed during QUEST were sustained during TRAVERSE, up to 96 weeks across both hemispheres.
Conclusion: Dupilumab reduced asthma exacerbations, with no difference in the reduction between seasons, in patients with type 2 inflammation, with and without evidence of allergic asthma.
Trial Registration: ClinicalTrials.gov Identifiers: NCT02414854, NCT02134028.

Introduction

Not all patients with asthma have an equal likelihood of experiencing an exacerbation, with prior exacerbation history being a strong predictor of future exacerbations.[1,2] Factors including low lung function, frequent exacerbation, previous hospitalization, and peripheral eosinophil levels can also predict the response to treatment in terms of reduction of future exacerbations.[3] The risk of asthma exacerbations is also influenced by seasonal changes, usually triggered by exposure to allergens or viruses.[4] The risk of asthma exacerbations in spring and summer can be predicted by dose of inhaled corticosteroids (ICS) required to treat the exacerbation, whereas the risk in autumn and winter is typically driven by viral infection and can be predicted by previous exacerbation history and atopic status.[5]

Dupilumab, a fully human monoclonal antibody,[6,7] blocks the shared receptor component for interleukin (IL)-4 and IL-13, type 2 inflammatory cytokines implicated in numerous allergic diseases

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ranging from asthma to atopic dermatitis,[8] thus inhibiting their signaling. Dupilumab has been approved for asthma in more than 40 countries worldwide, including in the United States for patients aged 6 years or older with moderate-to-severe eosinophilic or oral corticosteroid-dependent asthma.[9-12] Dupilumab is also approved in the United States for the treatment of adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps[13]; inadequately controlled, moderate-to-severe atopic dermatitis in patients 6 months or older[14-16]; eosinophilic esophagitis in patients aged 12 years and older; and prurigo nodularis in adults.[9]

In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab 200 mg or 300 mg every 2 weeks, vs placebo, significantly reduced severe asthma exacerbations, improved prebronchodilator forced expiratory volume in 1 second, and was generally well-tolerated with an acceptable safety profile in the overall population of patients with uncontrolled, moderate-to-severe asthma.[11] Treatment effects were greater with elevated type 2 biomarkers at baseline (blood eosinophils ≥ 150 cells/μL or fractional exhaled nitric oxide ≥ 25 ppb). Treatment effects of dupilumab during QUEST were consistent in patients with and without evidence of allergic asthma.[17] LIBERTY ASTHMA TRAVERSE, a single-arm, open-label, extension study (NCT02134028) in patients with asthma who participated in a previous dupilumab asthma study, including QUEST, evaluated long-term safety and efficacy of add-on dupilumab 300 mg every 2 weeks up to 96 weeks.[18]

We aimed to investigate, in a post hoc analysis, the long-term efficacy of dupilumab in reducing asthma exacerbations across seasons in patients with asthma and type 2 inflammation, with and without an allergic phenotype, from the phase 3 QUEST and TRAVERSE studies.

Methods

Study Design

LIBERTY ASTHMA QUEST (NCT02414854) was a phase 3, randomized, double-blind, placebo-controlled study that assessed the effect of dupilumab in patients aged 12 years or older with uncontrolled, moderate-to-severe asthma. The full study design has been reported previously.[11] Briefly, patients were randomized in a 2:2:1:1 ratio to receive add-on subcutaneous therapy with 200 mg of dupilumab (loading dose: 400 mg), 300 mg of dupilumab (loading dose: 600 mg), or matched placebo. Treatment was administered every 2 weeks for 52 weeks.

LIBERTY ASTHMA TRAVERSE (NCT02134028) was a single-arm, open-label extension study that evaluated the long-term safety and efficacy of dupilumab in patients with asthma who participated in a previous dupilumab asthma study, including QUEST; the full study design has been reported previously.[18]

The Institutional Review Board of both studies was the Copernicus Group which oversaw trial conduct and documentation according to ethics committees at each trial center.

Treatment arms included the combined 200 mg and 300 mg dupilumab arm and combined matched placebo arm from QUEST and dupilumab/dupilumab and placebo/dupilumab arms from TRAVERSE; all patients received dupilumab 300 mg every 2 weeks for 48 or 96 weeks in TRAVERSE.

Study Population

This post hoc analysis included data of patients from QUEST who rolled over to TRAVERSE and who had a type 2 phenotype at QUEST baseline, as indicated by eosinophils 150 cells/μL or higher or fractional exhaled nitric oxide 25 ppb or more. Additional subpopulations included those with and without evidence of an allergic asthma phenotype. Allergic asthma phenotype was defined by baseline total immunoglobulin (IgE) of 30 IU/mL or higher plus 1 or more antigen-specific IgE positive results (≥ 0.35 IU/mL) for perennial allergens, including *Aspergillus fumigatus*, cat dander, dog dander, house dust mites (*Dermatophagoides farina* and *Dermatophagoides pteronyssinus*), German cockroach (*Blatella germanica*), Oriental cockroach (*Blatella orientalis*), *Alternaria tenuis/alternata*, and *Cladosporium herbarum/hormodendrum*.[17] Nonallergic asthma was defined as asthma that did not meet the above mentioned definition of the allergic asthma phenotype.

Study Outcomes

Here, we are reporting the unadjusted annualized rate of severe asthma exacerbation events (number of severe exacerbations per patient-year during the study period) by season and the proportion of patients experiencing 1 or more severe asthma exacerbations by season and by hemisphere, by QUEST baseline exacerbation history (1, 2, ≥ 3 severe asthma exacerbations in the year before QUEST), and by QUEST baseline ICS dose in the overall type 2 population and in subgroups of the type 2 population with and without evidence of an allergic asthma phenotype.

Severe asthma exacerbation was defined as a deterioration of asthma leading to treatment for 3 days or more with systemic glucocorticoids or hospitalization or an emergency department visit requiring treatment with systemic glucocorticoids.

For this analysis, Northern Hemisphere countries include the following: Canada, Colombia, France, Germany, Hungary, Italy, Japan, Korea, Poland, Republic of Mexico, Russian Federation, Spain, Taiwan, Turkey, Ukraine, United Kingdom, and United States. Southern Hemisphere countries include the following: Argentina, Australia, Brazil, Chile, and South Africa.

Seasons by calendar month of the year in the Northern Hemisphere are as follows: winter (December-February), spring (March-May), summer (June-August), and autumn (September-November). Seasons by calendar month of year in the Southern Hemisphere are as follows: winter (June-August), spring (September-November), summer (December-February), and autumn (March-May).

Statistical Analysis

The annualized rate of severe asthma exacerbations during QUEST was analyzed using a negative binomial model with the total number of event onset from randomization up to visit 18 or last contact date (whichever came earlier) and falling under the particular month/season as the response variable during that month/season, with the treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year before the study as covariates and log-transformed standardized observation duration during that season as an offset variable. The proportion of patients with severe asthma exacerbations during QUEST was analyzed using a logistic regression model adjusted for age, geographic region, baseline eosinophil strata, baseline dose of ICS, and number of exacerbations in the previous year as covariates. The Firth method has been applied in cases of quasi-complete separation in the data. For seasonal and monthly exacerbations, all severe asthma exacerbation events during the treatment period were included, independent of whether the patient was on treatment. Patients who discontinued the study before that month or season were not included in the analysis for that month or season. Patients who discontinued in the middle of a month/season who had not experienced an event up until that point were included in the analysis and considered as having no severe asthma exacerbations in that month/season. Data for TRAVERSE were analyzed descriptively in line with the open-label design of the study.

Results

Baseline Demographic and Disease Characteristics

A total of 803 patients on dupilumab and 424 on placebo from QUEST having type 2 asthma enrolled in the TRAVERSE extension study. Demographics at the baseline of QUEST were similar between groups (Table 1). Furthermore, 51% to 55% of the patients across the treatment groups were on high-dose ICS (defined as > 500 μg inhaled fluticasone propionate daily or equipotent equivalent).[11] At baseline, 84% to 85% had an ongoing atopic medical condition. Mean (SD) severe exacerbation rates in the previous year were 2.09 (1.94) for dupilumab and 2.25 (1.95) for placebo, respectively. Most of the patients (74.2%) were in the Northern Hemisphere. Characteristics for patients from the Northern and Southern Hemispheres were generally balanced between the treatment arms (eTable 1).

Asthma Exacerbations in the Overall Type 2 Population

In the type 2 population, the unadjusted rate of severe asthma exacerbations during QUEST ranged from 0.91 to 1.37 for patients receiving placebo and from 0.32 to 0.58 in dupilumab-treated patients (Fig 1A). The proportion of patients with type 2 asthma who experienced 1 or more severe asthma exacerbations during QUEST was significantly higher ($P < .001$) for placebo vs dupilumab across all 4 seasons and ranged from 18.2% to 26.4% in the placebo group and 7.3% to 12.6% in the dupilumab group (Fig 2A).

In the type 2 population, the unadjusted rate of severe asthma exacerbations during the TRAVERSE extension study, in which all patients received dupilumab, varied from 0.25 to 0.45 across seasons in the placebo/dupilumab group and from 0.25 to 0.38 in the dupilumab/dupilumab group (Fig 1A). Across groups and seasons, 5.1% to 8.9% of patients with type 2 asthma experienced 1 or more severe asthma exacerbations during the TRAVERSE 48-week treatment period (Fig 2A). Marginal plots of severe exacerbations per day throughout the year in the type 2 population during QUEST and TRAVERSE are found in eFigure 1.

During QUEST, dupilumab vs placebo reduced the proportion of patients experiencing 1 or more severe asthma exacerbations by hemisphere, reaching statistical significance ($P < .05$) throughout the year in the Northern Hemisphere and during various months in the smaller subgroup of patients in the Southern Hemisphere (eFig 2). Throughout year 1 of TRAVERSE, with all patients receiving dupilumab, numerically lower percentages of patients with 1 or more severe asthma exacerbations were observed in both hemispheres, with further reductions into year 2, for both placebo/dupilumab and dupilumab/dupilumab groups (eFig 2). The polar plot of mean number of days with a severe asthma exacerbation in each week in the type 2 population during QUEST and TRAVERSE by hemisphere is found in Figure 3.

In QUEST, the proportion of patients with type 2 asthma who experienced 1 or more exacerbations varied by hemisphere and across months depending on patient subgrouping by exacerbation history (eFig 3) or ICS dose (eFig 4). Treatment differences between dupilumab and placebo were more apparent in the Northern Hemisphere. In TRAVERSE, the proportion of patients experiencing 1 or more severe exacerbations was similar to or less than that of those observed in the dupilumab group during QUEST, regardless of exacerbation history or QUEST baseline ICS dose, across both hemispheres (eFigs 3 and 4).

Table 1
Baseline Demographic and Disease Characteristics of the Type 2 Asthma Population

Characteristic	Placebo	Dupilumab
N	424	803
Age, mean (SD), y	48.0 (14.9)	47.4 (15.0)
Female, n (%)	262 (61.8)	479 (59.7)
Race, n (%)		
White	367 (86.6)	671 (83.6)
Black/of African descent	10 (2.4)	30 (3.7)
Asian	43 (10.1)	96 (12.0)
Native Hawaiian or other Pacific Islander	0	1 (0.1)
Other	4 (0.9)	5 (0.6)
Hemisphere, n (%)		
Northern	311 (73.3)	599 (74.6)
Southern	113 (26.7)	204 (25.4)
Body mass index, mean (SD), kg/m^2	29.23 (6.38)	28.68 (6.34)
Age at asthma onset, mean (SD), y	27.8 (18.7)	27.1 (19.1)
Asthma exacerbations in the year before QUEST, mean (SD)	2.25 (1.95)	2.09 (1.94)
Number of severe exacerbations experienced in the year before QUEST, n (%)		
1	193 (45.5)	405 (50.4)
2	120 (28.3)	209 (26.0)
3	51 (12.0)	100 (12.5)
≥ 4	60 (14.2)	89 (11.1)
Previous smoker, n (%)	82 (19.3)	145 (18.1)
ICS dose, n (%)		
High	233 (55.0)	413 (51.4)
Medium	190 (44.8)	387 (48.2)
Low	1 (0.2)	3 (0.4)
Ongoing atopic medical condition,[a] n (%)		
Yes	354 (83.5)	680 (84.7)
No	70 (16.5)	123 (15.3)
Blood eosinophils, median (Q1-Q3), cells/μL	360.00 (200.00-570.00)	320.00 (190.00-540.00)
Serum total IgE, median (Q1-Q3), IU/mL	212.00 (79.00-482.00)	191.50 (74.00-522.00)
FeNO, median (Q1-Q3), ppb	32.00 (19.00-53.00)	29.00 (18.00-50.00)

Abbreviations: ICS, inhaled corticosteroid; IgE, immunoglobulin E; FeNO, fractioned exhaled nitric oxide; ppb, parts per billion.
[a]A patient was considered to have an atopic medical condition if the patient had any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis or allergic rhinitis, eosinophilic esophagitis, food allergy, or hives or had baseline (parent study) total IgE of 100 IU/mL or more and at least 1 antigen-specific IgE is positive (≥ 0.35 IU/mL) at baseline.

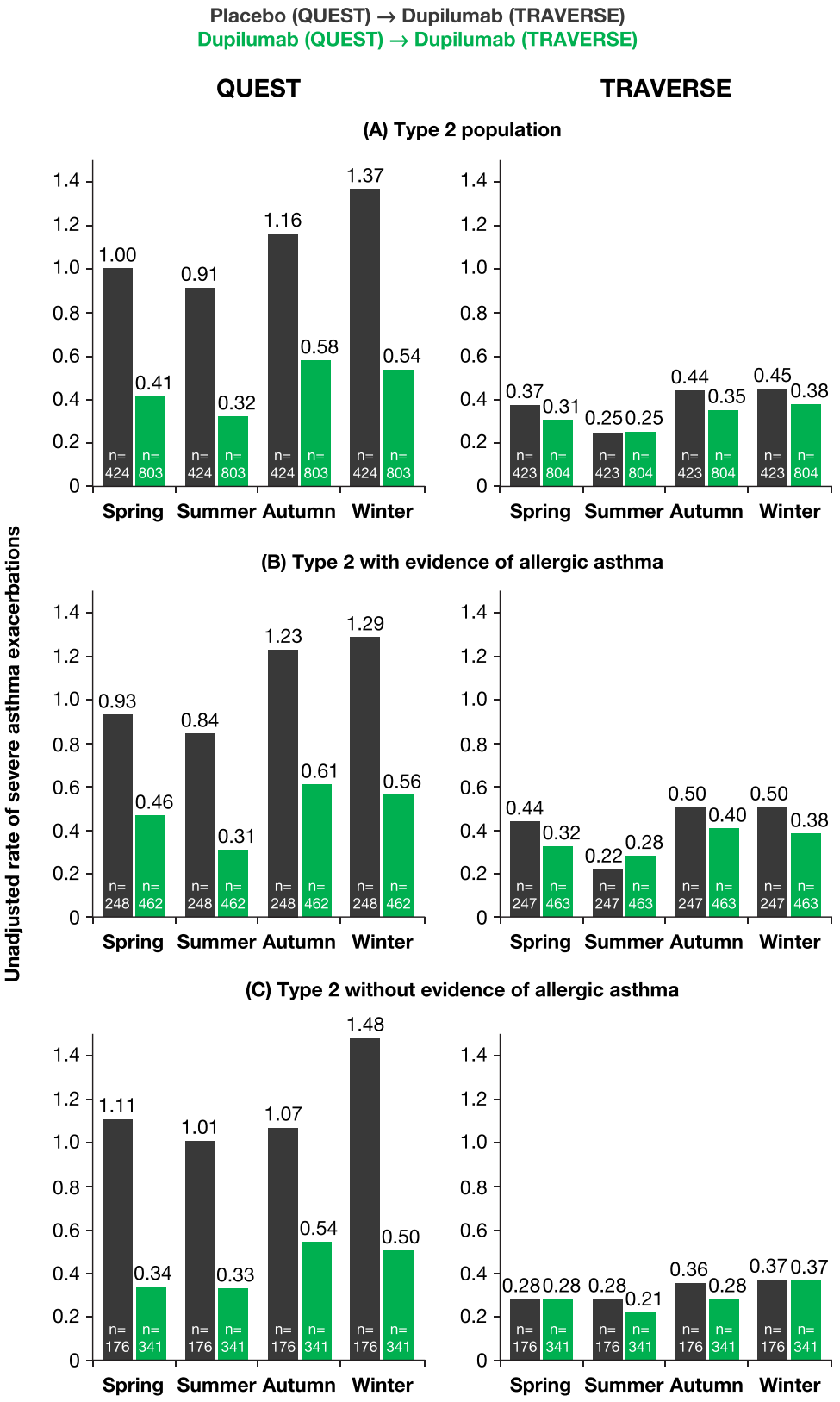

Figure 1. Rate of severe asthma exacerbations for the type 2 worldwide (A) overall, (B) allergic, and (C) nonallergic populations. Overall *P* value for interaction between seasons is greater than .05 for each population during QUEST.

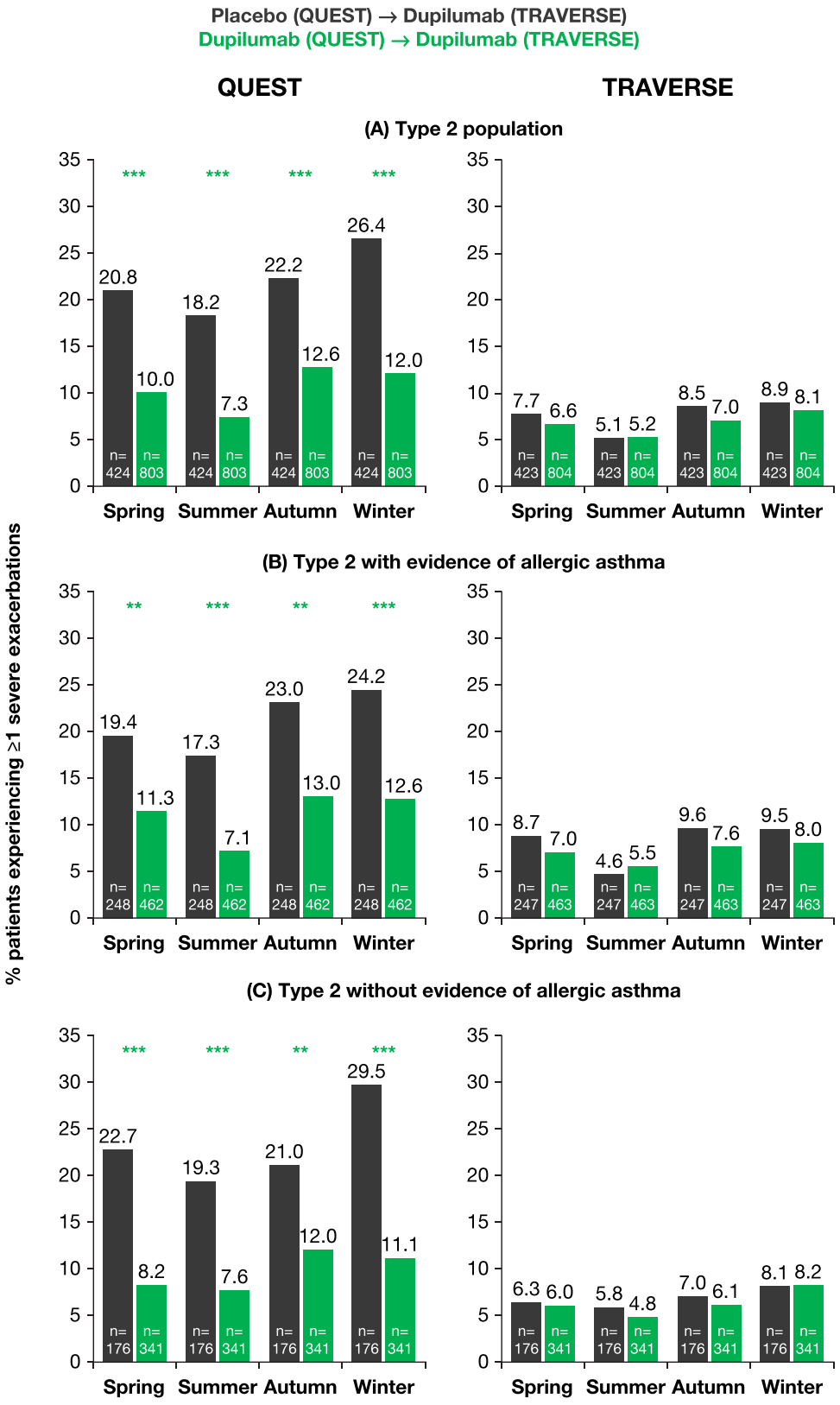

Figure 2. Proportion of patients experiencing 1 or more severe asthma exacerbations by season in the type 2 worldwide (A) overall, (B) allergic, and (C) nonallergic populations. $^{**}P < .01$; $^{***}P < .001$. Overall *P* value for interaction between seasons is greater than .05 for each population during QUEST.

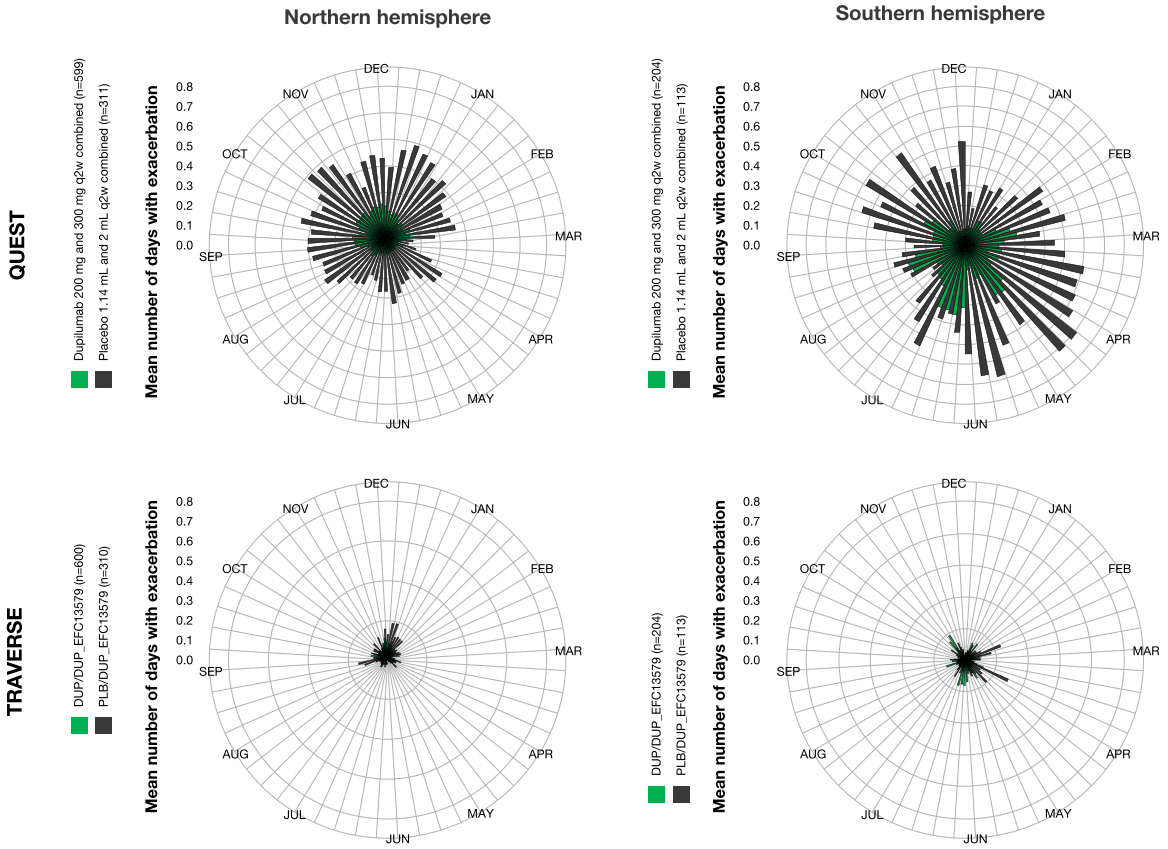

Figure 3. Polar plot of mean number of days with a severe asthma exacerbation in a week in the type 2 population by hemisphere. Northern Hemisphere countries: Canada, Colombia, France, Germany, Hungary, Italy, Japan, Korea, Poland, Republic of Mexico, Russian Federation, Spain, Taiwan, Turkey, Ukraine, United Kingdom, and United States. Southern Hemisphere countries: Argentina, Australia, Brazil, Chile, and South Africa.

Asthma Exacerbations in the Type 2 Population With and Without Evidence of Allergic Asthma Phenotype

In the type 2 population with evidence of an allergic asthma phenotype, the unadjusted rate of severe asthma exacerbations during QUEST varied from 0.84 to 1.29 in the placebo group and from 0.31 to 0.61 in the dupilumab group (Fig 1B). The proportion of patients with type 2 asthma with evidence of an allergic phenotype experiencing 1 or more severe asthma exacerbations during QUEST was significantly higher in the placebo group (17.3% to 24.2% across seasons), compared with dupilumab (7.1% to 13.0%) ($P < .01$) (Fig 2B).

In the type 2 population without evidence of an allergic asthma phenotype, the unadjusted rate of severe asthma exacerbations during QUEST ranged from 1.0 to 1.5 for placebo and 0.3 to 0.5 for dupilumab groups, across seasons (Fig 1C). The proportion of patients with type 2 asthma without evidence of an allergic asthma phenotype experiencing 1 or more severe asthma exacerbations during QUEST was also significantly higher for placebo (19.3% to 29.5%) compared with dupilumab (7.6% to 12.0%) ($P < .01$) (Fig 2C).

No significant treatment-by-season interactions were detected either for the rate of severe exacerbations or for the proportion of patients experiencing 1 or more severe exacerbations in the overall type 2 population ($P = .39$ or $P = .45$, respectively), the type 2 populations with ($P = .71$ or $P = .70$, respectively), or without an allergic phenotype ($P = .35$ or $P = .37$, respectively) (Figs 1 and 2).

Similar to the overall type 2 population, unadjusted severe asthma exacerbation rates and the proportion of patients experiencing 1 or more severe asthma exacerbations were similar between dupilumab and placebo groups during TRAVERSE, for patients with type 2 asthma, both with and without evidence of an allergic phenotype (Figs 1B and C and Figs 2B and C).

When evaluated by hemisphere, in the Northern Hemisphere during QUEST, significant reductions for dupilumab vs placebo in proportions of patients experiencing 1 or more severe asthma exacerbations were observed in patients with type 2 asthma and evidence of an allergic phenotype for all months except January, April, July, November, and December, whereas significant reductions for dupilumab vs placebo were observed for patients with type 2 asthma without evidence of an allergic phenotype for all months except September and October (Fig 4). In the Southern Hemisphere, significant reductions for dupilumab vs placebo were observed in June, November, and December, in patients with type 2 asthma and evidence of an allergic phenotype (Fig 4). Results for years 1 and 2 of TRAVERSE were similar to those of the overall type 2 population in the subgroups with and without evidence of an allergic asthma phenotype (Fig 4). When evaluated by QUEST baseline exacerbation frequency, results were generally similar to those found for the overall population (eFigs 5 and 6). In patients with type 2 allergic asthma, evaluation by ICS dose revealed broadly similar proportion of patients experiencing 1 or more severe asthma exacerbations across treatment groups and hemispheres (eFig 7). In those with nonallergic type 2 asthma, significant differences were found between treatments across multiple months in both ICS dose groups in the Northern Hemisphere, with no significant differences for either ICS dose group in the Southern Hemisphere except in October for high ICS dose (eFig 8).

Discussion

In this post hoc analysis, dupilumab vs placebo significantly reduced severe asthma exacerbations in patients with type 2 asthma during QUEST, independent of seasonality. These reductions were

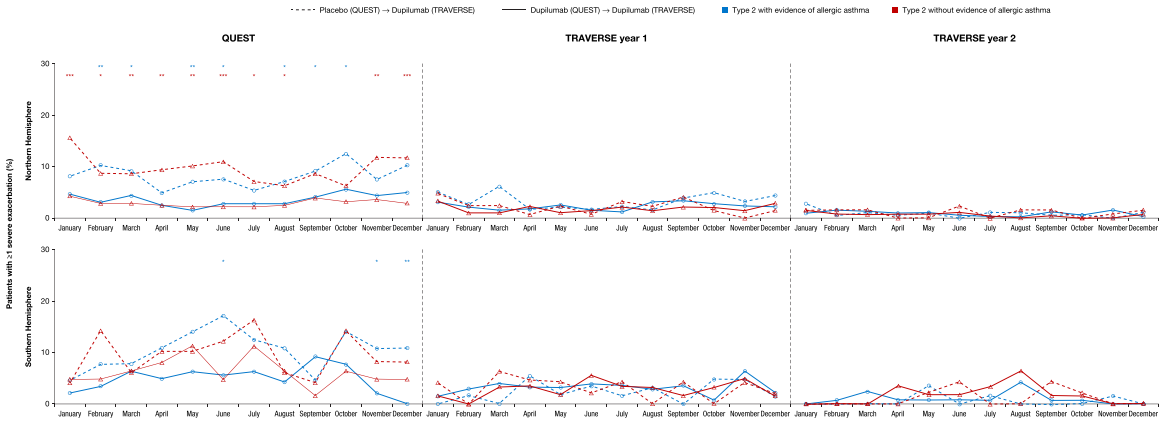

Figure 4. Proportion of patients experiencing 1 or more severe asthma exacerbations by month in the type 2 allergic and type 2 nonallergic populations by hemisphere. $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$. The Firth method has been applied in cases of quasicomplete separation in the data. Patients in QUEST received dupilumab or placebo; on entering TRAVERSE, all patients received dupilumab.

observed regardless of whether severe exacerbation rates were the highest (winter) or the lowest (summer).

The low exacerbation rates across the seasons achieved within the first year of dupilumab treatment during QUEST continued to decline overall across years 2 and 3 of dupilumab treatment in TRAVERSE. A reduction in severe exacerbations in response to dupilumab treatment was observed in both hemispheres during QUEST over the entire year, despite variability in patients receiving placebo, and was sustained with dupilumab for an additional 2 years in TRAVERSE. Importantly, once patients who received placebo in QUEST enrolled in TRAVERSE and switched to dupilumab treatment, they were indistinguishable from patients who received dupilumab in both studies, exhibiting similar trends in exacerbation reduction to years 1 and 2 of TRAVERSE.

To provide additional granularity, we assessed severe exacerbation rates by hemisphere and by month. Although these subgroups were not fully powered to reveal statistical differences, especially in the smaller subgroup of patients from the Southern Hemisphere, we observed similar efficacy with dupilumab treatment during QUEST. The proportion of patients experiencing 1 or more exacerbations declined further during TRAVERSE years 1 and 2, when all patients received dupilumab long term. These patterns were found across subgroups by hemisphere and either exacerbation history, ICS dose, or with or without an allergic phenotype.

Potential mechanisms for this reduction in asthma exacerbations across seasons as a result of dupilumab treatment are suggested in the literature: asthma exacerbations are known to be triggered by seasonal changes, often caused by exposure to allergens or seasonal viral infections.[4] Patients with asthma are predisposed to respiratory infections,[19] in part because of the damage of the airway epithelium by type 2 inflammation, which increases susceptibility to bacteria and viruses[20] and can provoke exacerbations.[21] Importantly, type 2 immune responses are generally not essential for defense against most infections and can potentially impair the effectiveness of type 1 responses.[22,23] For example, when binding to its receptor, IgE activates a cascade that inhibits the order of innate Toll-like receptors to produce type 1 cytokines, including interferon. Blocking of IL-4 has been associated with up-regulation genes associated with type 1 immune responses, resulting in increased circulation of type 1 cytokines, such as interferon gamma.[24] By blocking the shared IL-4/IL-13 receptor, dupilumab treatment progressively decreases circulating total IgE levels,[11] providing a plausible mechanism that may contribute to promoting type 1 responses. The suggestion that reducing type 2 inflammation can treat infection and improve symptoms by altering the equilibrium between type 1 and 2 immunity is further supported by a recent report of a case of disseminated coccidioidomycosis, successfully treated with exogenous interferon, a classic type 1 cytokine, and dupilumab to block type 2 responses.[25] Further support for the effect of dupilumab comes from studies revealing reductions in infections and reduced use of anti-infective medications in clinical trials of dupilumab in atopic dermatitis, chronic rhinosinusitis, and asthma, including QUEST.[26-28] Together, these data support a model, in which blocking signaling of the type 2 cytokines IL-4 and IL-13 by dupilumab may promote type 1 responses to infection, thereby reducing exacerbations caused by seasonal infections, although these effects have not been directly evaluated in vitro or in vivo.

One limitation of this analysis was that specific IgE was only assessed based on perennial and not seasonal allergens in QUEST, and therefore the definition of allergic asthma used for this analysis included only perennial allergens. This means that the nonallergic asthma subgroup reported here might potentially include those with seasonal allergies, such as those to grass, which can trigger asthma exacerbations. The definitions of allergic asthma reported here were therefore independent of allergen exposure or challenge specific to a given season. Although this was a limitation, the data presented here suggested that all patients with allergic asthma could benefit from treatment with dupilumab, regardless of the nature of their allergy (seasonal or perennial). In addition, some seasonal exacerbations are caused by exposure to seasonal viruses, and the benefits of dupilumab would apply equally in these cases to allergic and nonallergic phenotypes.

Another limitation of this analysis was the potential for bias in the selected study population for TRAVERSE. Owing to the nature of this being an open-label extension study, patients entered TRAVERSE on a voluntary basis, and only patients who completed the parent study were eligible for participation. This could have introduced a treatment bias, as those responding to treatment in the parent study were potentially more likely to agree to continue than those on placebo. However, it should be noted that the number of patients from QUEST who chose not to enroll in TRAVERSE was small compared with the total number who completed the study.

An additional limitation of the study was that most patients included (74.6% of patients receiving dupilumab and 73.3% on placebo) were from the Northern Hemisphere, limiting the ability to draw statistically meaningful results from the small number of participants in the Southern Hemisphere. This did not preclude the possibility that dupilumab is effective at reducing exacerbations in patients in the Southern Hemisphere but limited our ability to draw strong conclusions on the seasonal nature of these reductions from the available data. In a subgroup analysis of 530 Latin American patients enrolled in QUEST, dupilumab vs placebo significantly reduced annualized severe asthma exacerbations by more than

50%.[29] A larger future study will be needed to evaluate the seasonal nature of exacerbation reductions in the Southern Hemisphere. In addition, the post hoc nature of this analysis resulted in the inclusion of small numbers of patients when classifying by hemisphere or ICS dose and subsequently by month. These results, provided for completeness, should be interpreted with caution. Moreover, there were more patients with allergic asthma than patients with no evidence of allergic asthma (n = 710 vs n = 517, respectively) and slightly more patients with high ICS dose than with medium ICS dose at baseline (n = 646 vs n = 577, respectively).

In conclusion, dupilumab reduced severe asthma exacerbations, with no difference in the reduction between seasons, during QUEST in patients with type 2 asthma with or without evidence of allergic asthma. Furthermore, the low exacerbation rates observed with dupilumab treatment during QUEST were sustained during years 1 and 2 of TRAVERSE.

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Supplementary Data

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.anai.2023.11.021.

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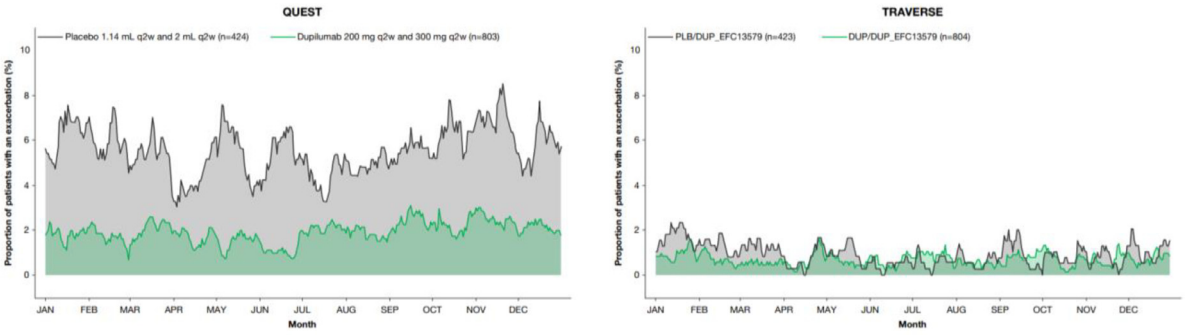
Supplementary Data

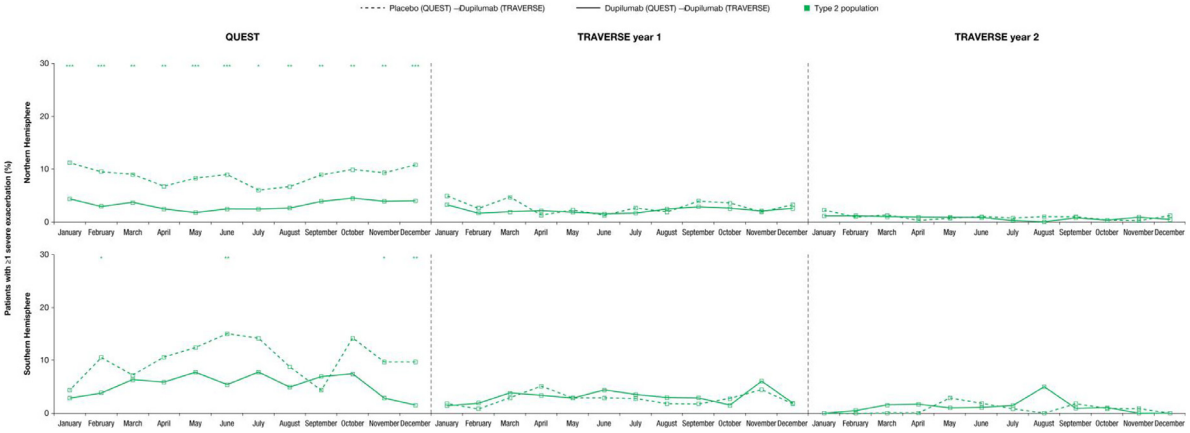
eTable 1
Baseline Demographic and Disease Characteristics of the Type 2 Asthma Population by Hemisphere

	Northern Hemisphere		Southern Hemisphere	
Characteristic	Placebo	Dupilumab	Placebo	Dupilumab
N	311	599	113	204
Age, mean (SD), y	48.8 (14.3)	48.2 (14.5)	45.6 (16.2)	45.1 (16.4)
Female, n (%)	185 (59.5)	348 (58.1)	77 (68.1)	131 (64.2)
Race, n (%)				
White	262 (84.2)	482 (80.5)	105 (92.9)	189 (92.6)
Black/of African descent	7 (2.3)	21 (3.5)	3 (2.7)	9 (4.4)
Asian	42 (13.5)	95 (15.9)	1 (0.9)	1 (0.5)
American Indian or Alaskan Native	0	0	0	0
Native Hawaiian or other Pacific Islander	0	1 (0.2)	0	0
Other	0	0	4 (3.5)	5 (2.5)
Body mass index, mean (SD), kg/m^2	28.72 (6.24)	28.42 (6.25)	30.65 (6.57)	29.45 (6.55)
Age at asthma onset, mean (SD), y	28.9 (18.4)	29.1 (18.8)	24.9 (19.2)	21.0 (18.6)
Asthma exacerbations in the year before QUEST, mean (SD)	2.21 (1.98)	2.10 (1.99)	2.37 (1.88)	2.07 (1.79)
Number of severe exacerbations experienced in the year before QUEST, n (%)				
1	157 (50.5)	321 (53.6)	36 (31.9)	84 (41.2)
2	77 (24.8)	131 (21.9)	43 (38.1)	78 (38.2)
3	31 (10.0)	71 (11.9)	20 (17.7)	29 (14.2)
≥ 4	46 (14.8)	76 (12.7)	14 (12.4)	13 (6.4)
Previous smoker, n (%)	61 (19.6)	105 (17.5)	21 (18.6)	40 (19.6)
ICS dose, n (%)				
High	163 (52.4)	290 (48.4)	70 (61.9)	123 (60.3)
Medium	147 (47.3)	308 (51.4)	43 (38.1)	79 (38.7)
Low	1 (0.3)	1 (0.2)	0	2 (1.0)
Ongoing atopic medical condition,[a] n (%)				
Yes	259 (83.3)	494 (82.5)	95 (84.1)	186 (91.2)
No	52 (16.7)	105 (17.5)	18 (15.9)	18 (8.8)
Blood eosinophils, median (Q1-Q3), cells/μL	370.00 (200.00-580.00)	320.00 (190.00-560.00)	300.00 (200.00-490.00)	310.00 (190.00-505.00)
Serum total IgE, median (Q1-Q3), IU/mL	205.00 (85.00-457.00)	173.00 (67.00-439.00)	240.50 (74.50-576.50)	288.00 (100.00-785.00)
FeNO, median (Q1-Q3), ppb	33.00 (19.00-53.00)	30.00 (18.00-50.00)	30.00 (18.00-50.00)	28.00 (19.00-50.00)

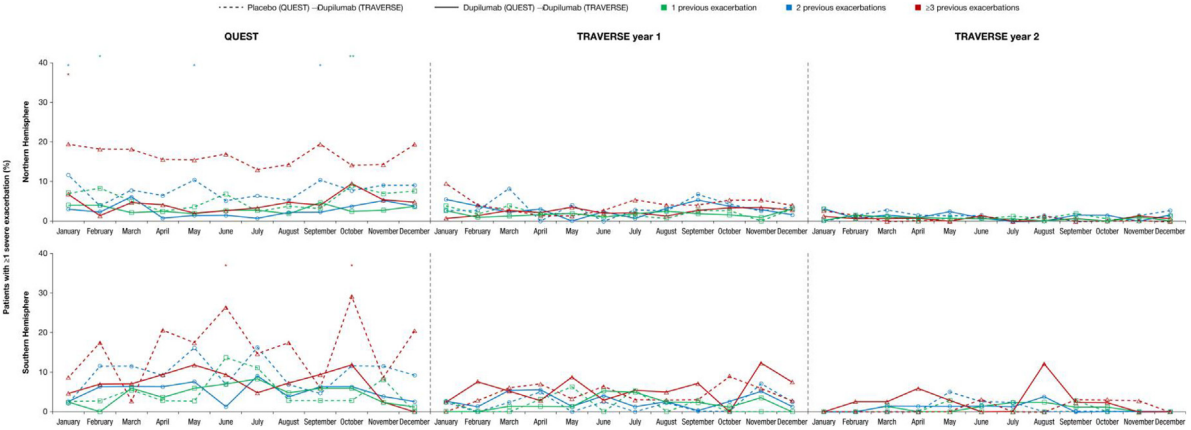
Abbreviations: ICS, inhaled corticosteroid; IgE, immunoglobulin E; FeNO, fractioned exhaled nitric oxide; ppb, parts per billion.
[a]A patient was considered to have an atopic medical condition if the patient had any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis or allergic rhinitis, eosinophilic esophagitis, food allergy, or hives or had baseline (parent study) total IgE of 100 IU/mL or more and at least 1 antigen-specific IgE is positive (≥ 0.35 IU/mL) at baseline. Northern Hemisphere countries: Canada, Colombia, France, Germany, Hungary, Italy, Japan, Korea, Poland, Republic of Mexico, Russian Federation, Spain, Taiwan, Turkey, Ukraine, United Kingdom, and United States. Southern Hemisphere countries: Argentina, Australia, Brazil, Chile, and South Africa.



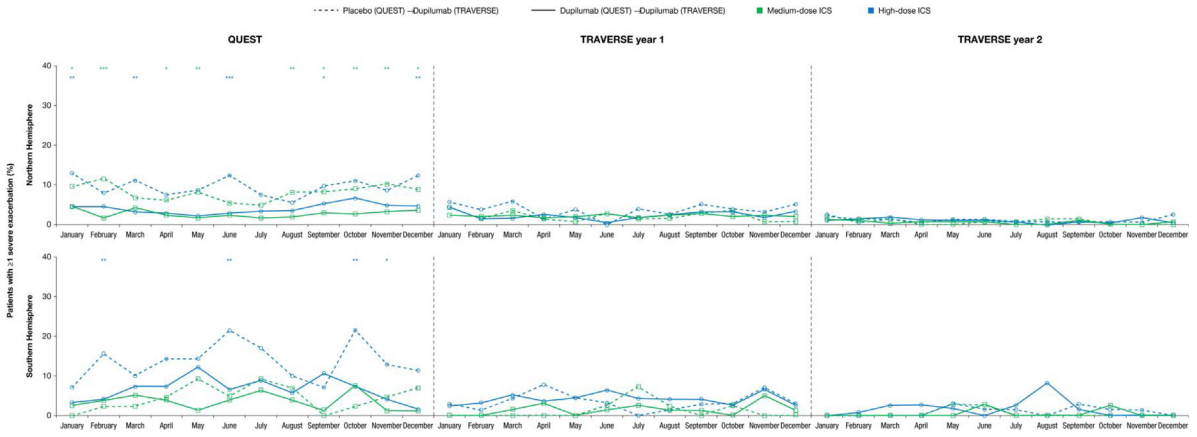
eFigure 1. Marginal plot of exacerbations per day throughout the year in the type 2 population, during QUEST and TRAVERSE.



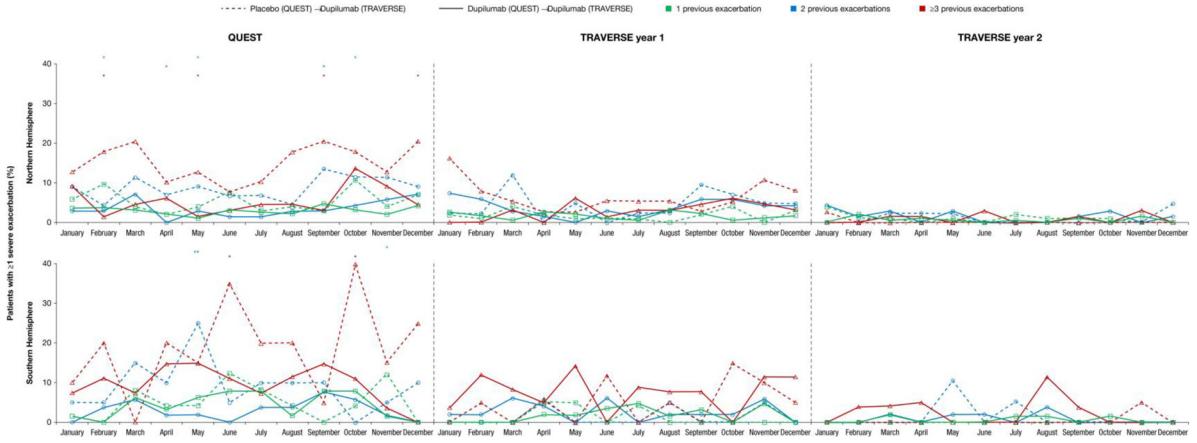
eFigure 2. Proportion of patients experiencing 1 or more severe asthma exacerbations by month in the type 2 population by hemisphere, during QUEST and TRAVERSE. $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$.



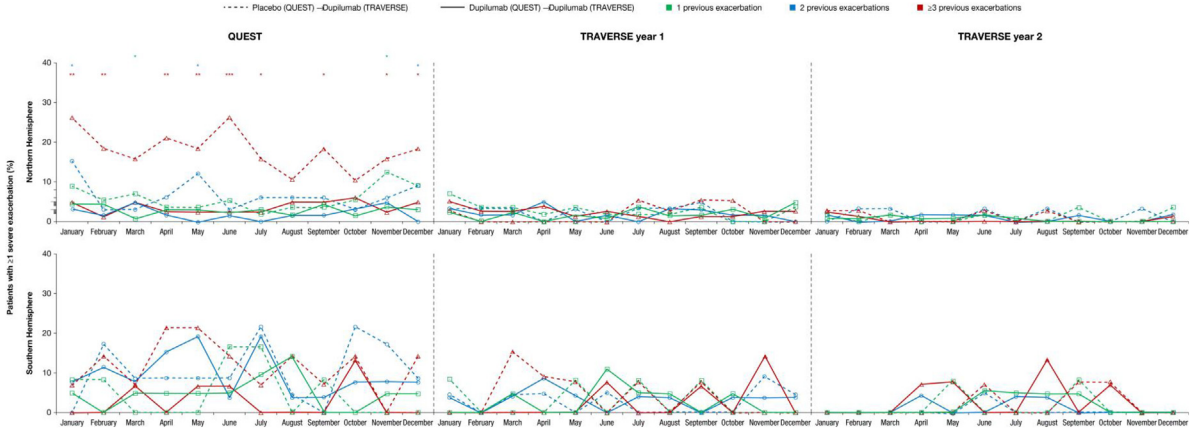
eFigure 3. Proportion of patients experiencing 1 or more severe asthma exacerbations by month in the type 2 population by hemisphere and by exacerbation history during QUEST and TRAVERSE.



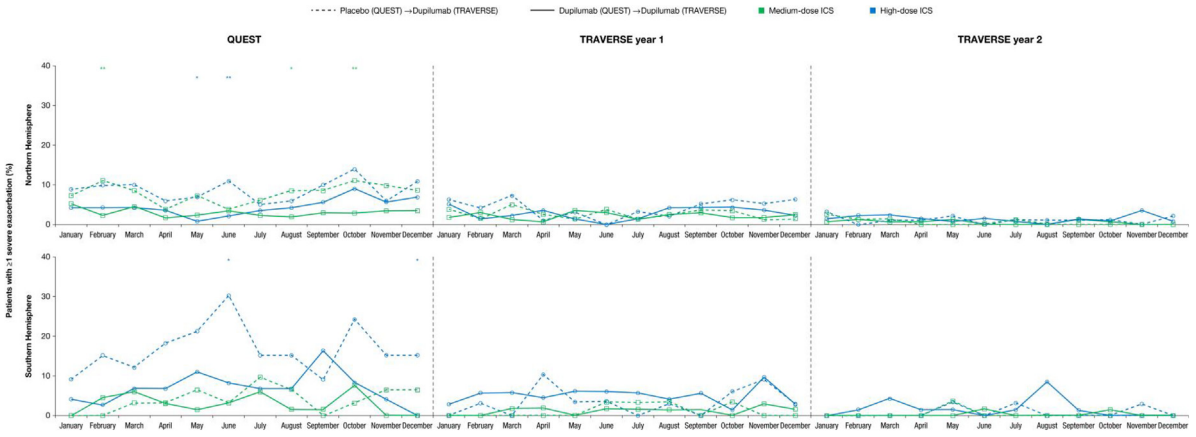
eFigure 4. Proportion of patients experiencing 1 or more severe asthma exacerbations by month in the type 2 population by hemisphere and by ICS dose during QUEST and TRAVERSE. ICS, inhaled corticosteroid.



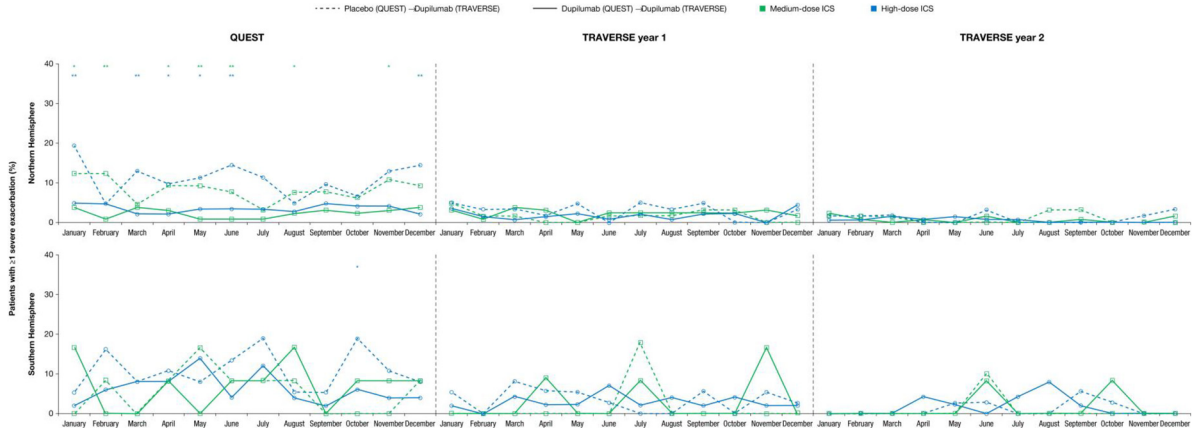
eFigure 5. Proportion of patients experiencing 1 or more severe asthma exacerbations by month in the type 2 allergic population by hemisphere and by exacerbation history during QUEST and TRAVERSE.



eFigure 6. Proportion of patients experiencing 1 or more severe asthma exacerbations by month in the type 2 nonallergic population by hemisphere and by exacerbation history during QUEST and TRAVERSE.



eFigure 7. Proportion of patients experiencing 1 or more severe asthma exacerbations by month in the type 2 allergic population by hemisphere and by ICS dose during QUEST and TRAVERSE. ICS, inhaled corticosteroid.



eFigure 8. Proportion of patients experiencing 1 or more severe asthma exacerbations by month in the type 2 nonallergic population by hemisphere and by ICS dose during QUEST and TRAVERSE.