Original Article

Dupilumab Demonstrates Rapid Onset of Response Across Three Type 2 Inflammatory Diseases

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What is already known about this topic? Dupilumab has demonstrated improvements in clinical outcomes in patients with uncontrolled type 2–driven diseases such as atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyps.

What does this article add to our knowledge? Treatment with dupilumab provides rapid (within 2 weeks), clinically meaningful benefits after treatment initiation that are sustained for the duration of treatment in patients with moderate to severe atopic dermatitis, moderate to severe asthma, or severe chronic rhinosinusitis with nasal polyps.

How does this study impact current management guidelines? Many patients struggle with medication compliance, and clinicians have difficulties adhering to treatment guidelines. We speculate that from both the patient and care provider perspectives, achieving a clinically meaningful response within the first weeks of treatment may result in better adherence and strengthen the relationship between the clinician and patient.

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Abbreviations used
AD- Atopic dermatitis
ANCOV- Analysis of covariance
CRSwNP- Chronic rhinosinusitis with nasal polyps
DLQI- Dermatology Life Quality Index
EASI- Eczema Area and Severity Index
EoE- Eosinophilic esophagitis
IGA- Investigator's global assessment
NRS- Numerical rating scale
UPSIT- University of Pennsylvania Smell Identification Test

BACKGROUND: Type 2 inflammatory diseases often coexist in patients. Dupilumab targets type 2 inflammation and has demonstrated treatment benefits in patients with atopic dermatitis (AD), asthma, and chronic rhinosinusitis with nasal polyps (CRSwNP) with an acceptable safety profile.
OBJECTIVE: This post hoc analysis across five phase 3 studies in patients with moderate to severe AD or asthma, or severe CRSwNP, evaluated time of onset and duration of the treatment response.
METHODS: Patients received subcutaneous dupilumab 200/300 mg or placebo. Assessments included the Eczema Area and Severity Index, Peak Pruritus Numerical Rating Scale, and Dermatology Life Quality Index in AD; pre-bronchodilator FEV_1, daily morning peak expiratory flow, and symptom scores in asthma; and University of Pennsylvania Smell Identification Test, daily nasal congestion, and loss of smell scores in CRSwNP.
RESULTS: At week 2 after the initiation of dupilumab versus placebo, 67.8% versus 36.5% of AD patients achieved a clinically meaningful benefit (Eczema Area and Severity Index: 50% or greater improvement; Peak Pruritus Numerical Rating Scale: 3 point or greater improvement; or Dermatology Life Quality Index: 4 point or greater improvement) ($P < .001$). Moreover, 61.6% versus 39.9% of asthma patients achieved improvements in pre-bronchodilator FEV_1 of 100 mL or greater and 48.8% versus 26.3% achieved 200 mL or greater improvement (both $P < .001$); 33.2% versus 5.6% of CRSwNP patients regained a sense of smell ($P < .001$). Treatment effects further improved or were sustained to the end of treatment.
CONCLUSIONS: Clinically meaningful responses were achieved rapidly after the first dupilumab dose in AD, asthma, or CRSwNP and were sustained throughout treatment (see Video in this article's Online Repository at www.jaci-inpractice.org). **(J Allergy Clin Immunol Pract 2022;10:1515-26)**

Key words: *Anti-IL-4; Anti-IL-13; Asthma; Dupilumab; Rapid onset*

INTRODUCTION

For chronic diseases, the ultimate treatment goal is to achieve long-term control. Therapies with a rapid onset of action may affect the patient or health care provider's choice of therapy earlier in the management process by reducing patient distress and impairment, increasing adherence, and contributing to optimal disease management.[1-3] A survey of allergists involved in the treatment of asthma reported that the rapid onset of drug action was considered an important therapeutic goal.[4]

Dupilumab, a fully human VelocImmune-derived[5,6] monoclonal antibody, blocks the shared receptor component for IL-4 and IL-13 and thus inhibits the signaling pathways of these cytokines, both of which are key and central drivers of type 2 inflammation in multiple diseases.[7,8] Dupilumab is approved for the treatment of certain patients with moderate to severe atopic dermatitis (AD) and moderate to severe asthma, and patients with chronic rhinosinusitis with nasal polyps (CRSwNP) in many countries. In the pivotal LIBERTY phase 3 program, dupilumab treatment demonstrated improvements in symptoms and clinical outcomes, including itch in AD, lung function in asthma, and smell in CRSwNP at the first time point assessed after randomization.[9-12] The current post hoc analysis evaluated clinically meaningful changes in symptoms and clinically relevant outcomes in the first 2 weeks of dupilumab treatment across three type 2 inflammatory diseases based on data from five phase 3 studies of patients with AD, asthma, or CRSwNP.

METHODS

Study designs

These analyses include over 3,000 patients enrolled in five multinational phase 3 dupilumab studies. All studies were conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. CONSORT guidelines were adhered to for all studies included in this analysis, and flow diagrams were previously published in all primary manuscripts, which have been cited throughout. All patients provided written informed consent before participating, and the protocols and consent forms were approved by institutional review boards and local ethics committees prior to patient enrollment. All studies included in this report were registered through ClinicalTrial.gov as follows: phase 3 LIBERTY AD SOLO-1 (NCT02277743), LIBERTY AD SOLO-2 (NCT02277769), LIBERTY ASTHMA QUEST (NCT02414854), LIBERTY NP SINUS-24 (NCT02912468), and LIBERTY NP SINUS-52 (NCT02898454).

LIBERTY AD SOLO-1 (SOLO-1; NCT02277743) and SOLO-2 (SOLO-2; NCT02277769) were identical phase 3, randomized, double-blind, placebo-controlled trials that assessed the efficacy and safety of dupilumab in patients aged 18 years and older with moderate to severe AD whose disease was inadequately controlled by topical treatment.[9,13] A total of 671 patients in SOLO-1 and 708 in SOLO-2 were randomized 1:1:1 to 16 weeks' treatment with dupilumab 300 mg subcutaneously every week or placebo, or dupilumab 300 mg subcutaneously every 2 weeks alternating with placebo. Patients in the active treatment groups received a 600-mg loading dose on day 1.

LIBERTY ASTHMA QUEST (QUEST; NCT02414854) was a phase 3, randomized, double-blind, placebo-controlled study that assessed the effect of dupilumab in patients with uncontrolled moderate to severe asthma.[11] A total of 1,902 patients aged 12 years and older with uncontrolled asthma were randomized 2:2:1:1 to add-on dupilumab 200 mg (400 mg loading dose) or 300 mg (600 mg loading dose) subcutaneously every 2 weeks or matched placebos for 52 weeks.

LIBERTY NP SINUS-24 (SINUS-24; NCT02912468) and LIBERTY NP SINUS-52 (SINUS-52; NCT02898454) were two phase 3, randomized, double-blind, placebo-controlled studies that

TABLE I. Selected baseline disease characteristics

Baseline disease characteristic	Placebo	Dupilumab
Atopic dermatitis patients from SOLO-1 and SOLO-2 pooled, n	460	457
Eczema Area and Severity Index score (median [IQR]) (scale 0-72)*	31.1 (22.2-42.6)	29.7 (21.1-40.5)
Peak pruritus numerical rating scale (median [IQR]) (scale 0-10)*	7.7 (6.4-8.7)	7.7 (6.3-8.8)
Dermatology Life Quality Index score (median [IQR]) (scale 0-30)*	15.0 (9.0-21.0)	14.0 (9.0-20.0)
Asthma patients from QUEST, n	511	987
Prebronchodilator FEV_1 (mean [SD]), L	1.72 (0.55)	1.78 (0.61)
Morning PEF (mean [SD]), L/min	271.40 (110.58)	280.76 (119.88)
Morning asthma symptom score (mean [SD]) (scale 0-4)*	1.17 (0.83)	1.16 (0.87)
Chronic sinusitis with nasal polyps patients from SINUS-24 and SINUS-52 pooled, n	286	438
Smell test (University of Pennsylvania Smell Identification Test) score (mean [SD]) (scale 0-40)*	14.09 (8.30)	13.90 (8.16)
Nasal congestion or obstruction score (mean [SD]) (scale 0-3)*	2.41 (0.54)	2.39 (0.60)
Loss-of-smell score (mean [SD]) (scale 0-3)*	2.72 (0.52)	2.74 (0.54)

For SOLO-1 and -2, regimens presented are dupilumab 300 mg subcutaneously every 2 weeks and placebo. For QUEST, the patient population presented is adult patients (aged 18 years and older) with a type 2 inflammatory phenotype, defined as baseline FeNO of 20 ppb or greater or blood eosinophils of 150 cells/μL or greater. Regimens are combined dupilumab 200 mg subcutaneously every 2 weeks and 300 mg subcutaneously every 2 weeks and combined placebos. For SINUS-24 and -52, regimens are dupilumab 300 mg subcutaneously every 2 weeks and placebo every 2 weeks.
*Higher scores indicate greater disease or symptom severity except for the University of Pennsylvania Smell Identification Test, for which higher scores indicate lower disease severity.

assessed the effects of dupilumab added to standard of care in adults with severe CRSwNP.[12] Patients aged 18 years and older with bilateral CRSwNP and uncontrolled symptoms despite intranasal or systemic corticosteroid use in the past 2 years or sinonasal surgery were eligible for enrollment. In SINUS-24, 276 patients were randomized 1:1 to subcutaneous dupilumab 300 mg or placebo every 2 weeks for 24 weeks; and in SINUS-52, 448 patients were randomized 1:1:1 to subcutaneous dupilumab 300 mg every 2 weeks (600 mg loading dose) for 52 weeks, dupilumab 300 mg every 2 weeks for 24 weeks (600 mg loading dose), and then every 4 weeks for the remaining 28 weeks, or placebo every 2 weeks for 52 weeks.

Details of the study design, patient demographics, and results were previously reported elsewhere for all studies.[9,11-14]

Data sources

This analysis was limited to patient populations that received the approved dosing regimens for AD, asthma, or CRSwNP.[15] In AD, we assessed patients receiving dupilumab 300 mg subcutaneously every 2 weeks or placebo in SOLO-1 and SOLO-2. In asthma, we assessed adult patients (aged 18 years or greater) with a type 2 inflammatory phenotype (baseline FeNO $\geq$20 ppb or blood eosinophils $\geq$150 cells/μL) receiving either dupilumab 200 mg or 300 mg subcutaneously every 2 weeks or matched placebos in QUEST. Although dupilumab is approved for patients aged 12 years or greater with moderate to severe asthma, patients aged 12-18 years were excluded from this analysis for the purpose of comparison across studies. In CRSwNP, we assessed patients receiving dupilumab 300 mg subcutaneously every 2 weeks or placebo in SINUS-24 or SINUS-52. Patients in SINUS-52 assigned to dupilumab every 2 weeks for 24 weeks and then every 4 weeks for the remaining 28 weeks were included in the analysis, because they only received dupilumab every 2 weeks in the time frame assessed (up to week 24).

Assessments

The percent change from baseline in Eczema Area and Severity Index (EASI) score (scale of 0-72; higher scores indicate greater disease severity) at weeks 1 and 2, and in daily peak pruritus as assessed by a numerical rating scale (NRS) (0 = none to 10 = worst imaginable) up to week 2 (day 14) were prespecified end points. The proportion of patients with a clinically meaningful response at weeks 1 and 2 and at the end of treatment (week 16) were analyzed post hoc. A clinically meaningful response was defined as a 50% or greater improvement in EASI score,[16] a 3 point or greater improvement (reduction) in weekly peak pruritus NRS,[17] or a 4 point or greater improvement (reduction) in the Dermatology Life Quality Index (DLQI) (scale of 0-30, with higher scores indicating more impaired quality of life),[18] based on published thresholds.

The change from baseline in prebronchodilator FEV_1 at week 2, change from baseline in daily morning PEF recorded daily by a PEF meter up to week 2 (day 14), and change from baseline in patient-reported morning daily asthma symptom scores (scale of 0-4; higher scores indicate more severe symptoms) up to week 2 (day 14) were assessed post hoc in the type 2 inflammatory phenotype population. The proportion of patients with a clinically meaningful response (defined as a 100 mL or greater or 200 mL or greater improvement from baseline in prebronchodilator FEV_1 based on American Thoracic Society and European Respiratory Society guidelines, respectively, for the treatment of severe asthma)[19] at week 2 and at the end of treatment (week 52) was assessed post hoc.

The University of Pennsylvania Smell Identification Test (UPSIT)[20] score (0-40; lower scores indicate greater impairment) was collected regularly throughout the treatment period, and the daily nasal congestion and obstruction score and daily loss of smell score (for both scales, 0 = no symptoms to 3 = severe symptoms) were recorded daily by patients in an electronic diary up to week 2 (day 14). The proportion of patients with a clinically meaningful improvement in UPSIT score (UPSIT score greater than 18) at week 2 and the end of treatment (week 24), and the change from baseline in daily nasal congestion and obstruction score and daily loss of smell score were assessed post hoc.

Statistical analyses

Least square (LS) mean percentage change from baseline in EASI score was derived from an analysis of covariance (ANCOVA) model with the baseline measurement as covariate and the study identifier, treatment, region, and baseline investigator's global assessment (IGA) strata as fixed factors. The LS mean percent change from

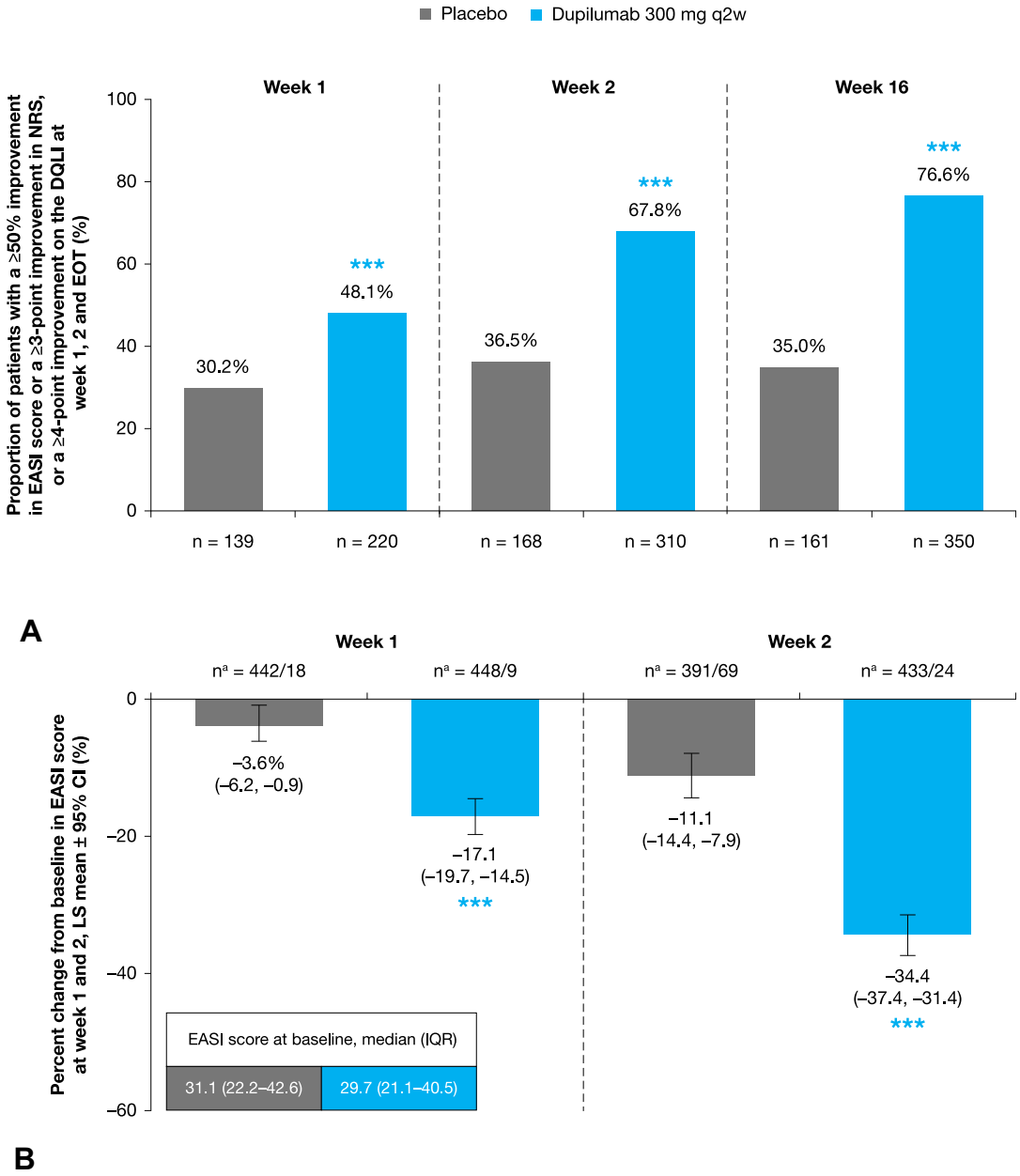

FIGURE 1. (**A**) Proportion of atopic dermatitis (AD) patients from the SOLO-1 and SOLO-2 trials with clinically meaningful improvement. (**B**) Percent change from baseline in Eczema Area and Severity Index (EASI) score at weeks 1 and 2 after the first treatment. (**C**) Percent change from baseline in daily peak pruritus numerical rating scale (NRS) score up to day 14 after the first treatment. For (**A**), values after first rescue treatment used were censored. Patients with missing scores were considered to be nonresponders. For (**B**), values after first rescue treatment used were censored and then imputed using multiple imputations in the EASI score, from which the percent change from baseline was calculated. For (**C**), values after first rescue treatment used were censored and then imputed using the last observation was carried forward. As previously published in the full intent-to-treat population of the SOLO-1 and SOLO-2 studies, least squares (LS) mean percent change from baseline ± SE in the EASI score at week 16 at the end of treatment was −70.0 ± 1.8 for patients treated every 2 weeks (q2w) with dupilumab 300 mg and −34.3 ± 2.3 for placebo-treated patients ($P < .001$).[13] The LS mean percent change from baseline ± SE in daily peak pruritus NRS score in AD patients from the SOLO-1 and SOLO-2 studies at week 16 (the end of treatment) was −47.4 ± 1.7 for patients treated every 2 weeks with dupilumab 300 mg and −20.5 ± 1.9 for placebo-treated patients ($P < .001$).[13] All *P* values are nominal. *CI,* confidence interval*; DLQI*, Dermatology Life Quality Index; *IQR*, interquartile range; *LS*, least squares. *$P < .05$, **$P < .01$, ***$P < .001$ versus placebo. [a]Observed patients/imputed patients.

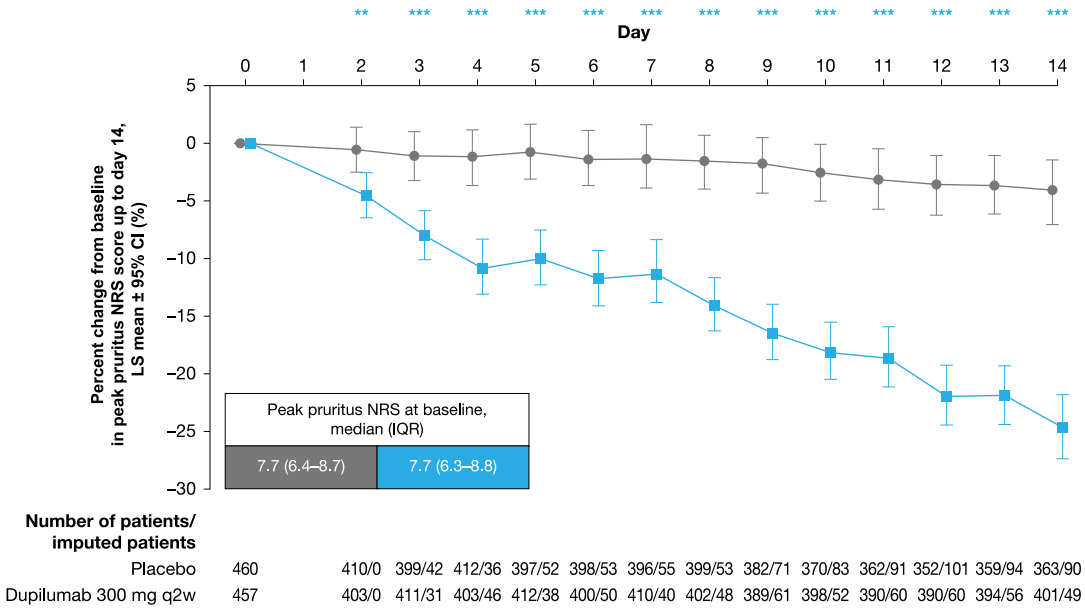

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FIGURE 1. Continued.

baseline in daily peak pruritus NRS score was derived from an ANCOVA model with the baseline measurement as covariate and the treatment, region, and baseline disease severity (IGA = 3 vs IGA = 4) as fixed factors. For both analyses, patients were censored at the time when rescue medication was used, with a multiple imputation method applied to EASI and last observation carried forward for NRS. For the proportion of patients with a clinically meaningful response, EASI, NRS, and DLQI values after first rescue treatment used were censored, and patients with missing values were considered to be nonresponders. *P* values were derived using a Cochran-Mantel-Haenszel test stratified by study identifier, region, and baseline disease severity (IGA = 3 vs IGA = 4).

The LS mean change from baseline in prebronchodilator FEV_1 was derived from an ANCOVA model with change from baseline in prebronchodilator FEV_1 at week 2 as the response variable, and treatment, age, sex, baseline height, region, baseline eosinophil strata, baseline inhaled corticosteroid dose level, and baseline prebronchodilator FEV_1 value as covariates. The LS mean change from baseline in daily morning PEF (L/min) and asthma symptoms was derived from a mixed model with repeated measures, with change from baseline in morning PEF/symptom score values up to day 14 from randomization as the response variable, and treatment, age, sex, baseline height, region, baseline eosinophil strata, baseline inhaled corticosteroid dose level, visit, treatment-by-visit interaction, baseline values, and baseline-by-visit interaction as covariates. The proportion of patients with a clinically meaningful response was analyzed using a logistic regression model adjusted for baseline values. Patients without an improvement of 100 mL or greater or 200 mL or greater from baseline in prebronchodilator FEV_1 at week 2 or week 52, respectively, were considered to be nonresponders.

The LS mean change from baseline in UPSIT score was derived from an ANCOVA model with change from baseline at week 2 as the response variable, and the corresponding baseline value, treatment group, asthma/nonsteroidal anti-inflammatory drug—exacerbated respiratory disease status, surgery history, region, and study indicator as covariates. Data after systemic corticosteroid use or nasal polyp surgery were censored and imputed by worst observation carried forward and multiple imputation. The LS mean change from baseline in daily nasal congestion score and daily loss of smell was derived using the same approach as UPSIT score without imputation. The *P* values for comparing the proportion of patients with UPSIT greater than 18 in dupilumab versus placebo were obtained using χ^2 tests.

We performed analyses post hoc, and all *P* values are nominal.

RESULTS

Table I lists data on patients included in the analyses for each indication and baseline values for all evaluated end points. Full baseline demographics and disease characteristics were reported previously elsewhere.[9,11-13]

Atopic dermatitis

On day 7 after dupilumab initiation, 48.1% of dupilumab-treated AD patients versus 30.2% of placebo-treated patients achieved a statistically significant, clinically meaningful response, defined as 50% improvement or greater in EASI, a 3 point or greater improvement in NRS, or a 4 point or greater improvement on the DLQI (Figure 1, *A*) (risk difference, 17.9 [95% confidence interval (CI), 11.7-24.1; $P < .001$]). At week 2, the proportion of responders in dupilumab-treated patients increased to 67.8% versus 36.5% in placebo-treated patients (risk difference, 31.3 [95% CI, 25.2-37.5]; $P < .001$). By the end of treatment (week 16), this increased to 76.6% of dupilumab-treated patients versus 35.0% of placebo-treated patients (risk difference, 41.6 [95% CI, 35.7-47.4]; $P < .001$).

Atopic dermatitis patients showed a significant decrease in percent change from baseline in EASI score in the dupilumab group compared with placebo at both weeks 1 and 2 (Figure 1, *B*).

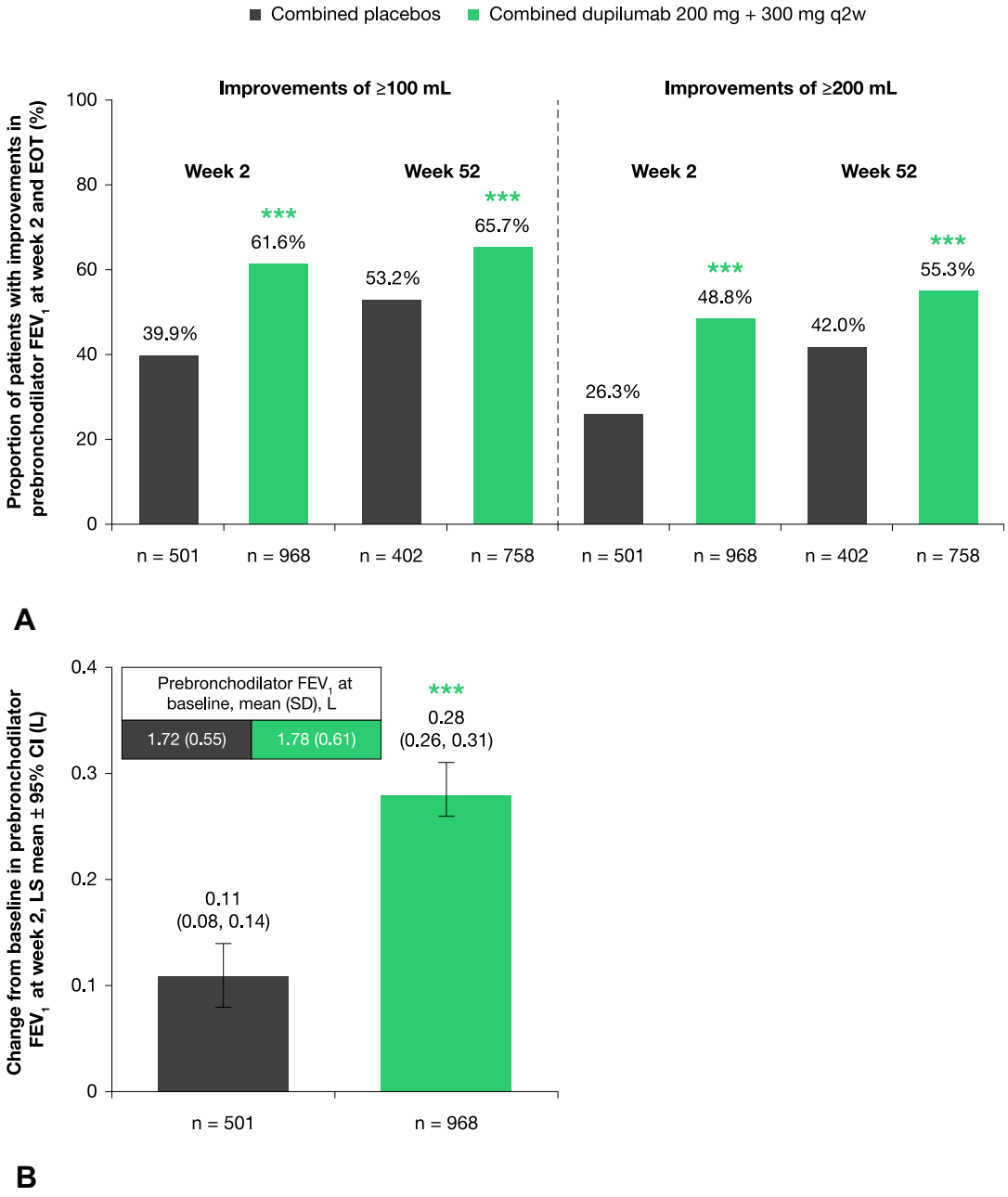

FIGURE 2. (**A**) Proportion of asthma patients from QUEST with clinically meaningful improvements. (**B**) Change from baseline in prebronchodilator FEV_1 at week 2 after the first treatment. (**C**) Change from baseline in morning PEF up to day 14 after the first treatment. (**D**) Change from baseline in morning symptom score up to day 14 after the first treatment. As previously published in the overall intent-to-treat population of asthma patients from the QUEST study, least squares (LS) mean change from baseline ± SE in prebronchodilator FEV_1 (L) at week 52 at the end of treatment was 0.36 ± 0.02 for patients treated every 2 weeks (q2w) with dupilumab 200 mg, 0.35 ± 0.02 for patients treated every 2 weeks with dupilumab 300 mg, and 0.16 ± 0.02 and 0.22 ± 0.02 for matched placebo-treated patients, respectively (both $P < .001$).[11] Least squares mean change from baseline ± SE in the morning PEF in the overall intent-to-treat population of asthma patients from the QUEST study at week 52 at the end of treatment was 28.97 ± 2.82 for patients treated every 2 weeks with dupilumab 200 mg, 26.00 ± 2.82 for patients treated every 2 weeks with dupilumab 300 mg, and 2.35 ± 3.94 and 12.69 ± 3.91 for matched placebo-treated patients, respectively (both $P < .01$).[11] Least squares mean change from baseline ± SE in the morning asthma symptom score in the overall intent-to-treat population of asthma patients from the QUEST study at week 52 at the end of treatment was −0.55 ± 0.03 for patients treated every 2 weeks with dupilumab 200 mg, −0.58 ± 0.03 for patients treated every 2 weeks with dupilumab 300 mg, and −0.40 ± 0.04 and −0.43 ± 0.04 for matched placebo-treated patients, respectively (both $P < .001$).[11] For (**C**) and (**D**), baseline is defined as the average of the morning symptom score or PEF measurement recorded for 7 days before randomization, including the morning diary completed on the randomization day before the first administration of treatment. If less than 4 days' measurement is available during 7 days before randomization, baseline is defined as the average of the four morning symptom score or PEF measurements before and closest to randomization during the whole screening period. All *P* values are nominal. *CI,* confidence interval. $*P < .05$, $**P < .01$, $***P < .001$.

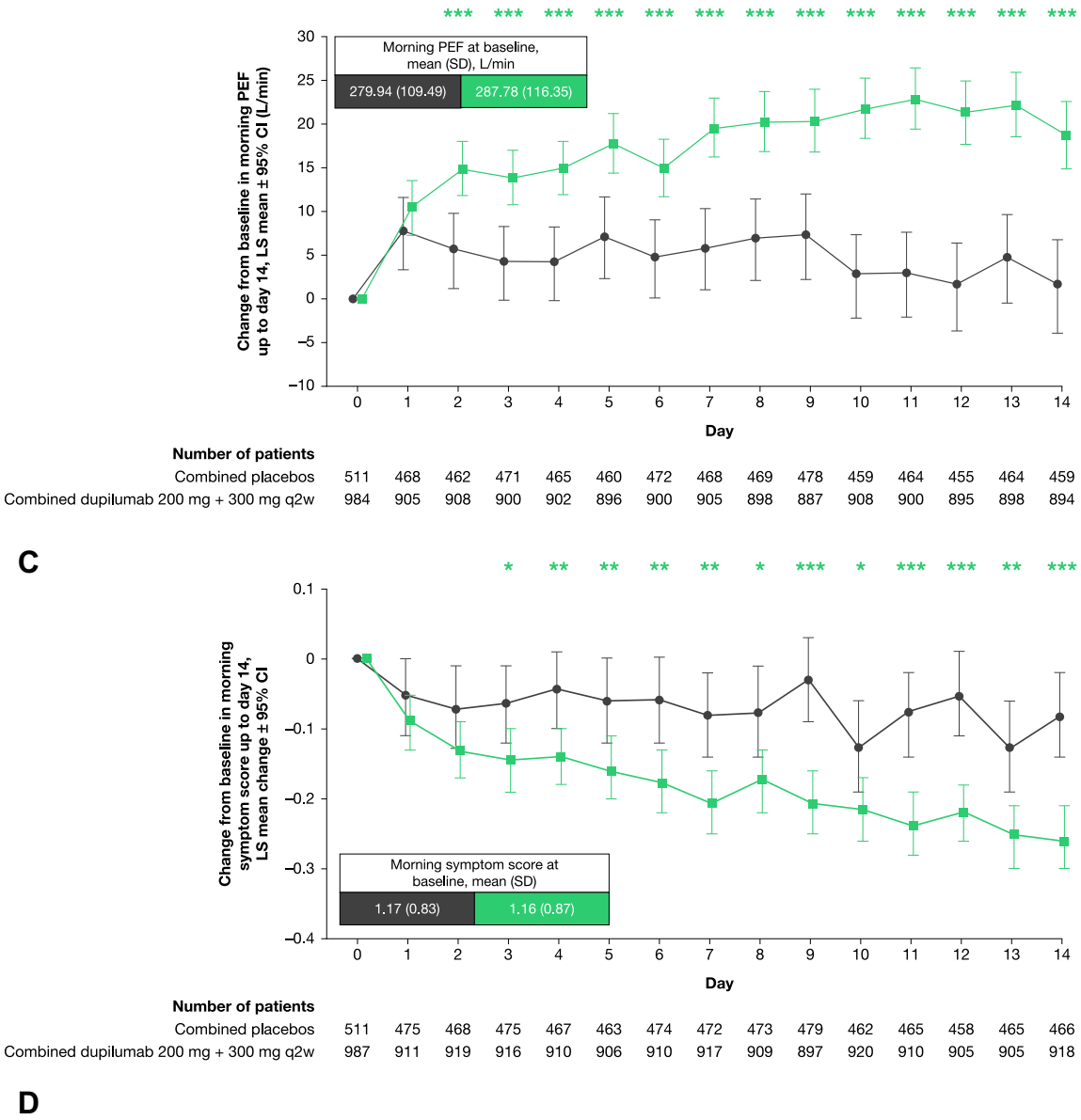

FIGURE 2. Continued.

On day 7, there was a statistically significant LS mean difference between treatments of −13.6% (95% CI, −17.10 to −10.05) in favor of dupilumab ($P < .001$), which increased at week 2 to −23.2% (95% CI, −27.50 to −18.99; $P < .001$).

On day 2, the percent change from baseline in the daily peak pruritus NRS score showed significant improvement for dupilumab compared with placebo, with an LS mean difference of −4.0% (95% CI, −6.63 to −1.33; $P = .003$); this progressively improved up to the end of the first 2 weeks of treatment (LS mean difference, −20.4% [95% CI, −24.17 to −16.56]; $P < .001$) (Figure 1, *C*).

Asthma

At week 2, the proportion of asthma patients who achieved an improvement of 100 mL or greater or 200 mL or greater in prebronchodilator FEV_1 from baseline favored the combined dupilumab group versus placebo; 61.6% of dupilumab patients achieved 100 mL or greater and 48.8% achieved 200 mL or greater (vs 39.9% and 26.3% in placebo, respectively; both $P < .001$) (Figure 2, *A*). This was sustained through the end of treatment (week 52); 65.7% and 55.3% of dupilumab-treated patients versus 53.2% and 42.0% of placebo patients achieved FEV_1 improvements of 100 mL and greater and 200 mL and greater, respectively (both $P < .001$). At week 2, combined dupilumab significantly improved prebronchodilator FEV_1 by LS mean (95% CI) 0.28 L (0.26-0.31), compared with 0.11 L (0.08-0.14) in the combined placebo group ($P < .001$) (Figure 2, *B*). Improvement from baseline in morning PEF was significantly greater for the combined dupilumab group from day 2 (LS mean difference vs placebo [95% CI] of 9.38 L/min [4.22-14.55]; $P < .001$), with an increasing magnitude of effect observed up to day 14 (LS mean difference vs placebo, 17.33

L/min [10.90-23.75]; $P < .001$) (Figure 2, *C*). Rapid improvements were also seen in the morning asthma symptom score; significant LS mean differences versus placebo in change from baseline were observed by day 3 (−0.08 [−0.15 to −0.01]; $P = .023$) (Figure 2, *D*).

Chronic rhinosinusitis with nasal polyps

In CRSwNP patients, at week 2, a significantly higher proportion of patients treated with dupilumab than placebo showed clinically meaningful improvements in sense of smell (55.4% of dupilumab vs 28.0% of placebo patients had an UPSIT score greater than 18 [$P < .001$]) (Figure 3, *A*). By week 24, 72.0% of dupilumab-treated patients versus 22.9% placebo-treated patients had an improved sense of smell, defined as an UPSIT score of greater than 18 ($P < .001$).[20] Overall, dupilumab significantly improved UPSIT scores from baseline by an LS mean (95% CI) of 6.81 (5.90-7.73) versus 1.28 (0.23-2.33) in the placebo group ($P < .001$) at week 2 (Figure 3, *B*). Improvements from baseline in daily nasal congestion or obstruction score were significantly greater for the dupilumab group from day 1 (LS mean difference vs placebo [95% CI] of −0.07 [−0.13 to −0.01]; $P = .016$). Similarly, improvements from baseline in daily loss of smell were significantly greater for dupilumab-treated patients from day 2 (LS mean difference vs placebo [95% CI] of −0.07 [−0.12 to −0.02]; $P = .0047$). The magnitude of improvement continued to increase in dupilumab-treated patients versus placebo for both measures and did not plateau within the first 2 weeks assessed (Figure 3, *C* and *D*).

DISCUSSION

In this analysis of 3,139 patients with AD, asthma, or CRSwNP from five phase 3 studies, dupilumab treatment consistently exhibited clinically meaningful improvements after the first dose, irrespective of the disease studied. Improvements were observed in clinical signs, symptoms, and/or quality of life in AD; lung function and symptoms in asthma; and nasal congestion or obstruction and sense of smell in CRSwNP. By week 2 of dupilumab treatment, 67.8% of AD patients, 61.6% of asthma patients, and 55.4% of CRSwNP patients met clinically meaningful thresholds ahead of the second dupilumab dose. These proportions increased to 66% to 77% by the end of each treatment period. This early onset of effects in patients with high disease burden and difficult-to-treat symptoms, together with sustained improvements and the acceptable safety profile reported previously, confirm that dupilumab offers important benefits across multiple type 2 inflammatory diseases. These results mirror the rapid and sustained suppression of type 2 inflammatory biomarkers previously observed after dupilumab treatment in each disease state.[11,21-24]

Some clinically meaningful improvements were also seen in patients receiving placebo, and treatment benefits were not achieved by week 2 in all dupilumab-treated patients analyzed, which suggests that early improvements may not be fully attributable to dupilumab. Nonetheless, because the proportion of patients achieving clinically meaningful responses with dupilumab progressively increased over the treatment period, physicians may consider continuing treatment even if a suboptimal effect is observed within the first weeks. Furthermore, in both AD trials assessed, the magnitude of improvement from baseline in EASI score and peak pruritus NRS continued at every assessment up to 16 weeks, compared with marginal changes for placebo.[9,13] In the overall QUEST intent-to-treat population, the magnitude of improvement in pre-bronchodilator FEV_1 in dupilumab-treated patients continued to increase up to week 16 and was sustained through week 52.[11] Similarly, in SINUS-24 and SINUS-52, improvements in both nasal polyp score and nasal congestion or obstruction were observed in CRSwNP patients treated with dupilumab at week 4 and continued to the end of the 24- or 52-week treatment period.[12] Longer-term studies added to the body of evidence and suggested that improvements with dupilumab are rapid and continue beyond the first months of treatment. Two open-label extension studies in patients with AD[25] and asthma[26] demonstrated treatment benefits of dupilumab, irrespective of whether the patients were dupilumab-naive (received placebo during the parent study). In dupilumab-naive AD patients, improvements in EASI and peak pruritus NRS were observed at week 4 of the extension and improved progressively and consistently with non−dupilumab-naive patients up to week 76.[25] Similarly, rapid improvements in FEV_1 were observed in dupilumab-naive asthma patients by week 2 of the extension study; they progressed up to week 4 and were sustained up to 2 years. The magnitude of FEV_1 improvements was comparable to that in patients who received dupilumab for 3 years.[26] Recent data from a real-world registry also noted high adherence to long-term dupilumab treatment, with rapid and long-term efficacy.[27] Finally, a case series of patients with AD investigating the use of dupilumab at a tertiary care center in the United States reported that of 112 treated patients, 89% continued to be treated at 800 days.[28]

Rapid response by week 4 was also described for the anti−IL-5 biologic benralizumab in severe eosinophilic asthma patients with comorbid CRSwNP, but response time was longer in asthma patients without CRSwNP.[29-31] Numeric improvements in morning PEF were observed for benralizumab versus placebo in severe eosinophilic asthma patients by day 2, and become clinically meaningful by week 3.[32] A significant response was reported with another anti−IL-5 biologic, mepolizumab, in patients with severe uncontrolled type 2 asthma in 4 months, which the authors considered to be rapid.[33] In AD patients, Janus kinase inhibitors provide rapid relief of pruritis as early as week 1.[34] Treatment with cyclosporine has long been known to offer rapid relief, but effects are short-lived and relapses are common.[35]

Many patients struggle with medication compliance, and clinicians have difficulties adhering to treatment guidelines.[36] We speculate that achieving a clinically meaningful response within the first weeks of treatment may result in better adherence and strengthen the relationship between clinician and patient.[36-38] Type 2 inflammatory comorbidities often overlap, resulting in an increase in overall symptom and disease burden.[39] A drug that can rapidly provide clinical benefits simultaneously for these comorbidities by targeting the underlying and shared type 2 inflammatory process may be a more desirable option for patients. In these studies, 82% of asthma patients had an ongoing atopic or allergic condition at study baseline,[11] and 80% of CRSwNP patients had a history of any type 2 disease, in which 59% of these patients reported a history of asthma.[12] The rapid onset of action, sustained response, and acceptable safety profile suggest that dupilumab may provide a beneficial treatment option for patients across three type 2 inflammatory diseases.

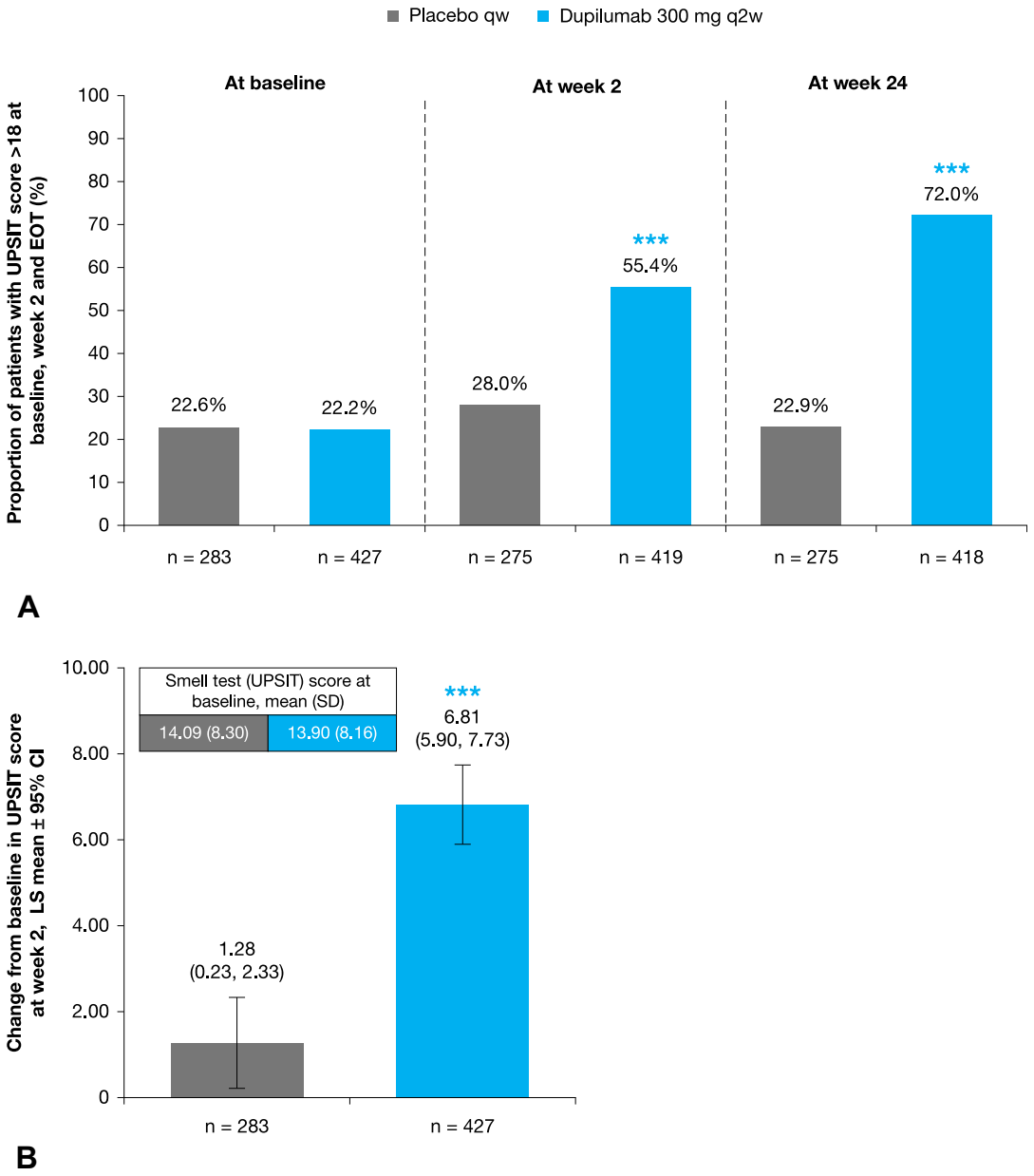

FIGURE 3. (**A**) Proportion of chronic rhinosinusitis with nasal polyps (CRSwNP) patients from SINUS-24 and SINUS-52 with University of Pennsylvania Smell Identification Test (UPSIT) score greater than 18 at baseline and weeks 2 and 24. (**B**) Change from baseline in UPSIT score at week 2. (**C**) Change from baseline in daily nasal congestion or obstruction score up to day 14. (**D**) Change from baseline in daily loss of smell score up to day 14. Anosmia is classified as an UPSIT score less than 19. As previously published, in the overall intent-to-treat population of CRSwNP patients from the SINUS-24 and SINUS-52 studies, least squares (LS) mean change from baseline ± SE in UPSIT score at week 24 was 10.54 ± 0.48 for patients treated every 2 weeks (q2w) with dupilumab 300 mg and −0.03 ± 0.55 for placebo-treated patients ($P < .001$).[12] The LS mean change from baseline ± SE in daily nasal congestion or obstruction score in the overall intent-to-treat population of CRSwNP patients from the SINUS-24 and SINUS-52 studies at week 24 was −1.30 ± 0.05 for patients treated every 2 weeks with dupilumab 300 mg and −0.42 ± 0.06 for placebo-treated patients ($P < .001$). The LS mean change from baseline ± SE in daily loss of smell score in the overall intent-to-treat population of CRSwNP patients from the SINUS-24 and SINUS-52 studies at week 24 was −1.30 ± 0.05 for patients treated every 2 weeks with dupilumab 300 mg and −0.26 ± 0.06 for placebo-treated patients ($P < .001$).[12] For (**C**) and (**D**), baseline is defined as the average of the measurements on or before randomization if there are four or more measurements collected within 7 days on or before randomization. If fewer than four measurements are collected within 7 days on or before randomization, the average of the most recent four measurements on or before randomization is considered to be the baseline. Data collected after treatment discontinuation were included. Data after systemic corticosteroid or nasal polyp surgery have been censored. Twelve patients had systemic corticosteroid or nasal polyp surgery within 15 days of randomization. *CI,* confidence interval. All *P* values are nominal. $*P < .05$, $**P < .01$, $***P < .001$.

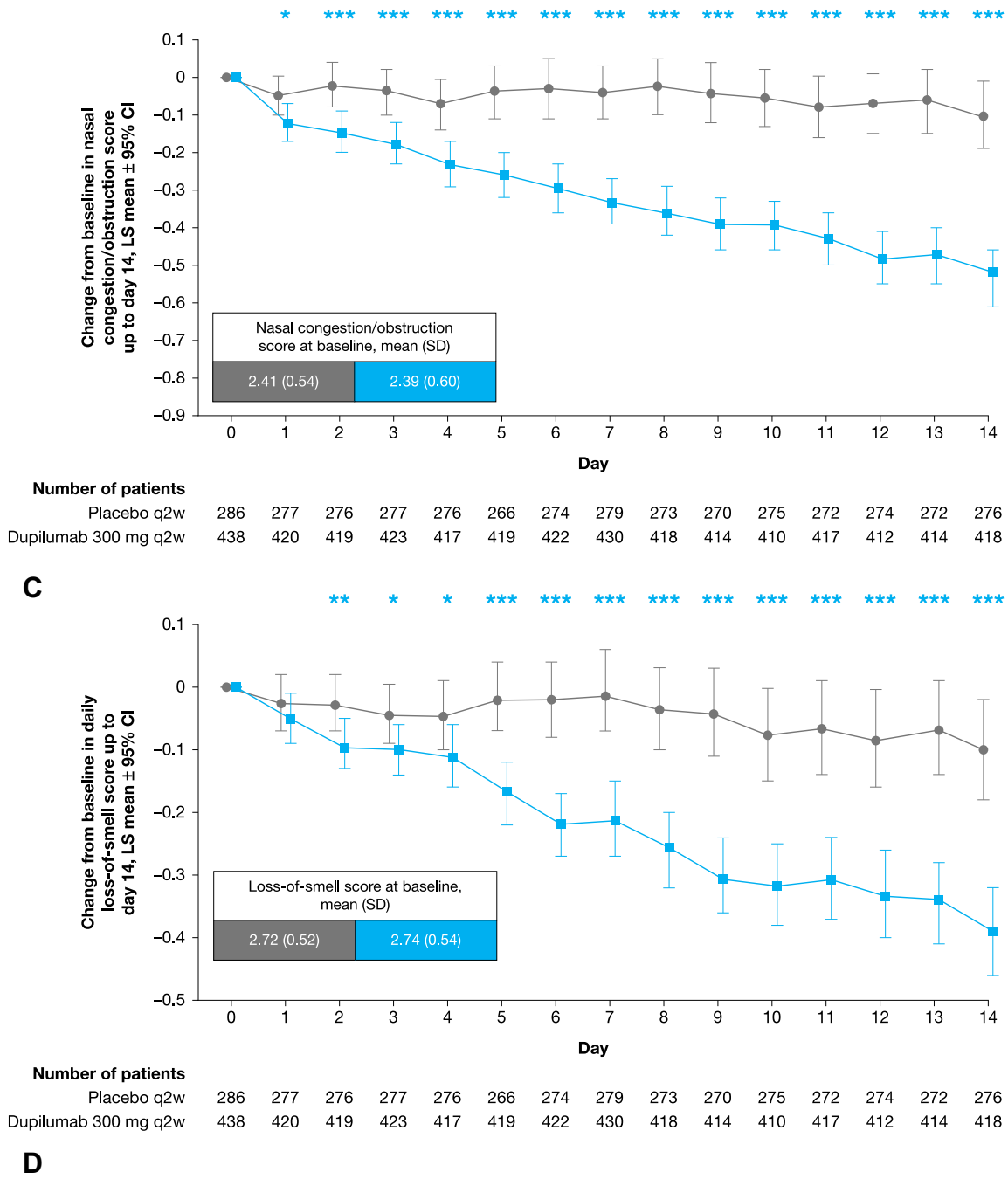

FIGURE 3. Continued.

Despite a common inflammatory pathway, the clinical expression of type 2 inflammatory diseases manifests across a range of anatomic sites. Here, we have shown dupilumab to be efficacious in skin and upper and lower airways. Other organs are affected by type 2 inflammatory conditions, such as the esophagus in eosinophilic esophagitis (EoE). Dupilumab was shown to improve dysphagia and other features of EoE significantly in a recent phase 2 study in adults with active EoE[40]; it is currently under phase 3 investigation.

A major strength of this analysis is the inclusion of five large, randomized, double-blind, placebo-controlled studies across three diseases. This analysis included patients from dupilumab clinical trials receiving treatment regimens that were approved for use and thus available to patients. However, limiting the analysis to these five trials could be considered a limitation. Examination of additional data from other trials and real-world evidence would be interesting and an area of future study. The post hoc nature of the analysis must also be considered; all *P* values are nominal. However, the end points chosen for inclusion in the analysis are important to both clinicians and patients, and included both objective and patient-reported outcome measures. The choice of analysis for the first 2

weeks of treatment was based on time points of data collection during the clinical trials. It would have been highly informative to assess the responses over a shorter period (eg, a few days) if the data had been available. In addition, the rapidity of response may differ across the different type 2 inflammatory diseases, which may also affect the length of time to response that patients and clinicians would classify as rapid. Nevertheless, considering that patients had prolonged histories of illness, we pragmatically considered that 2 weeks would be deemed rapid. Finally, some chosen measures may not be designed to change rapidly, and therefore may not be optimum measures of a rapid response.

CONCLUSIONS

In this analysis across five phase 3 studies in three different type 2 inflammatory diseases, dupilumab consistently exhibited clinically relevant benefits in symptoms, signs, and clinical and patient-reported outcomes after the first dose of dupilumab that were sustained to the end of treatment. Because of the shared underlying pathophysiology, many patients have more than one comorbid type 2 inflammatory disease. Dupilumab inhibits both IL-4 and IL-13, which are key and central in type 2 inflammation, reflecting a rapid onset of action. Thus, it potentially provides a simultaneous beneficial treatment option for multiple type 2 inflammatory diseases.

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