Dupilumab Improves Asthma and Sinonasal Outcomes in Adults with Moderate to Severe Atopic Dermatitis

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What is already known about this topic? Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with other type 2 inflammatory diseases such as asthma, allergic rhinitis, and other chronic inflammatory conditions of the sinonasal mucosa.

What does this article add to our knowledge? Dupilumab treatment in adult patients with moderate to severe AD and comorbid asthma and/or chronic sinonasal conditions significantly improved AD signs and symptoms as well as asthma and sinonasal disease.

How does this study impact current management guidelines? By inhibiting type 2 inflammation, dupilumab may optimize management of AD, asthma, and chronic sinonasal conditions simultaneously, addressing the systemic immune dysregulation underlying these and other type 2 inflammatory diseases.

*Co-first authors.

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BACKGROUND: Dupilumab has demonstrated efficacy with acceptable safety in clinical trials in patients with moderate to severe atopic dermatitis (AD).

OBJECTIVE: To assess dupilumab’s impact on asthma and sinonasal conditions in adult patients with moderate to severe AD in four randomized, double-blinded, placebo-controlled trials.

METHODS: In LIBERTY AD SOLO 1 (NCT02277743), SOLO 2 (NCT02755649), CHRONOS (NCT02260986), and CAFÉ (NCT02755649), patients received placebo, dupilumab 300 mg every 2 weeks (q2w), or dupilumab 300 mg weekly (qw). In CHRONOS and CAFÉ, patients received concomitant topical corticosteroids. This post hoc analysis assessed Asthma Control Questionnaire-5 (ACQ-5) scores in patients with asthma, Sino-Nasal Outcome Test-22 (SNOT-22) scores in patients with sinonasal conditions, and AD signs and symptoms in all patients.

RESULTS: Of the 2444 patients, 463 had asthma with baseline sinonasal conditions, and AD signs and symptoms in all patients. At week 16, ACQ-5 scores (least squares mean change from baseline [standard error]) improved by 0.27 (0.07), 0.59 (0.08), and 0.56 (0.07) in placebo-, q2w-, and qw- treated patients with asthma, respectively, whereas SNOT-22 improved by 0.27 (19%); 1171 had sinonasal conditions (48%); and 311 had both (13%). At week 16, ACQ-5 scores (least squares mean change from baseline [standard error]) improved by 0.27 (0.07), 0.59 (0.08), and 0.56 (0.07) in placebo-, q2w-, and qw-treated patients with asthma, respectively, whereas SNOT-22 scores improved by 5.1 (0.8), 9.9 (0.9), and 10.8 (0.8) in patients with sinonasal conditions (P < .01 for all dupilumab vs placebo). Improvements in ACQ-5 and SNOT-22 were also seen in patients with both conditions. Dupilumab also significantly improved AD signs and symptoms among all subgroups.

CONCLUSIONS: In this first analysis of patients with comorbid moderate to severe AD, asthma, and/or chronic sinonasal conditions, dupilumab improved all three diseases in a clinically meaningful and statistically significant manner (vs placebo), based on validated outcome measures. © 2021 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/). (J Allergy Clin Immunol Pract 2021;9:1212-23)

Key words: ACQ-5; Allergic rhinitis; Asthma; Atopic dermatitis; Dupilumab; Eczema; Rhinosinusitis; SNOT-22; Type 2 inflammation; Type 2 inflammatory diseases

INTRODUCTION

Atopic dermatitis (AD) is associated with impaired skin barrier function and systemic immune dysregulation, particularly upregulation of the type 2 immune pathway.1-3 The systemic nature of AD is highlighted by the frequent occurrence of comorbid conditions (including most types of asthma, food allergy, eosinophilic esophagitis, and chronic sinonasal conditions such as allergic rhinitis and chronic rhinosinusitis with or without nasal polyps), the pathology of which is characterized by type 2 inflammation.4 Type 2 inflammation is mediated by the induction of T-helper 2 (Th2) lymphocytes and innate lymphoid cells expressing type 2 cytokines interleukin (IL)-4, IL-13, and IL-5, and it has a predominant role in asthma,6-8 and chronic sinonasal conditions.9,10

Current treatment options for AD aim to improve signs and symptoms using a multistep approach and achieve long-term disease control,11,15,16 but the effects of these treatments on comorbid type 2 inflammatory diseases have not been evaluated. In patients with moderate to severe AD, comorbid type 2 inflammatory diseases heighten the already substantial burden of disease associated with primary and secondary AD symptomatology.14 Type 2 inflammatory diseases also increase the complexity of treatment management and thus the burden of treatment and economic burden for these patients.18,19

Dupilumab, a fully human VelocImmune-derived (Regeneron Pharmaceuticals, Inc. Tarrytown, NY) monoclonal antibody, blocks the shared receptor subunit for IL-4 and IL-13, thus inhibiting signaling of both cytokines that are key drivers of type 2 inflammatory diseases.14,22 The efficacy and safety of dupilumab have been established in adult and adolescent patients with moderate to severe AD,23-28 in children with severe AD,25 and in

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Abbreviations used

ACQ-5-5-item Asthma Control Questionnaire
AD-Atopic dermatitis
CRSwNP-Chronic rhinosinusitis with nasal polyps
DLQI-Dermatology Life Quality Index
EASI-ECzema Area and Severity Index
EASI-50-≥50% improvement from baseline in EASI
EASI-75-≥75% improvement from baseline in EASI
IGA-Investigator’s Global Assessment
IL-Interleukin
LS-Least squares
MCID-Minimal clinically important difference
NRS-Numerical Rating Scale
q2w-Every 2 weeks
qw-Weekly
SE-Standard error
SNOT-22-22-item Sino-nasal Outcome Test
TCS-Topical corticosteroids
Th2-T-helper 2

GlaxoSmithKline, Innovaderm, LEO Pharma, Mandal, Menlo, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc, Relaxin, Sanofi, Symbio, Teva, and Vanda Pharmaceuticals; and has received speaker fees from AstraZeneca, GlaxoSmithKline, Optinose, Regeneron Pharmaceuticals, Inc, and Sanofi; and has received consulting fees from AbbVie, Genentech, Regeneron Pharmaceuticals, Inc., and Teva. P. Lio has received grants paid to institution/practice for research and is on advisory boards and speakers’ bureaus of Regeneron Pharmaceuticals, Inc and Sanofi Genzyme. A. B. Rossi is an employee of Sanofi Genzyme and may hold stock and/or stock options in the company. Y. Lu, J. Chao, A. Gadkari, M. Ruddy, N.M.H. Graham, Z. Chen, and M. Ardeleanu are employees and shareholders of Regeneron Pharmaceuticals, Inc. L. Eckert, T. Hultsch, L. P. Mannent, and G. Pirozzi are employees of Sanofi and may hold stock and/or stock options in the company.
other related type 2 inflammatory diseases including asthma and chronic rhinosinusitis with nasal polyps (CRSwNP). Dupilumab versus placebo reduced asthma exacerbations and oral corticosteroid use and improved lung function and quality of life in patients with moderate to severe asthma.\textsuperscript{30,33} It also reduced systemic corticosteroid use, surgery, sinusalitis, and polyp size and improved nasal symptom burden and quality of life in patients with CRSwNP.\textsuperscript{34,35} Dupilumab is approved for patients with diseases driven by type 2 inflammation, specifically AD, asthma, and CRSwNP.\textsuperscript{36}

Although dupilumab independently improves AD, asthma, and CRSwNP as primary conditions, the concurrent efficacy of dupilumab in multiple type 2 inflammatory diseases has not been previously demonstrated. Here, we evaluated the effects of dupilumab on comorbid type 2 inflammatory diseases in patients with AD. We measured asthma improvement using the 5-item Asthma Control Questionnaire (ACQ-5) in patients with co-morbid asthma, and sinonasal condition efficacy improvement using the 22-item Sino-Nasal Outcome Test (SNOT-22) in patients with comorbid chronic sinonasal conditions.

**METHODS**

**Study design**

Designs for the four phase 3, randomized, placebo-controlled trials have been reported in detail previously\textsuperscript{23-25}; details are provided in Figure E1 in this article’s Online Repository at www.jacionline.org. Patients in LIBERTY AD SOLO 1 and 2 received dupilumab monotherapy (300 mg every 2 weeks [q2w] or 300 mg weekly [qw]) or placebo for 16 weeks\textsuperscript{23}; patients in LIBERTY AD CHRONOS received dupilumab (300 mg q2w or 300 mg qw) or placebo for 52 weeks, all with concomitant topical corticosteroids (TCS)\textsuperscript{24}; and patients in LIBERTY AD CAFÉ received dupilumab (300 mg q2w or 300 mg qw) or placebo for 16 weeks with concomitant TCS.\textsuperscript{25} Here, patient groups who received either dupilumab monotherapy or dupilumab with concomitant TCS are referred to as the dupilumab groups; similarly, patient groups who received placebo as monotherapy or placebo with concomitant TCS are referred to as the placebo group. This post hoc analysis used data from trials focused on AD; therefore, analyses of non-AD variables are limited.

**Patient subgroups**

Four subgroups were defined for efficacy analyses: (1) patients with AD and comorbid asthma, with baseline ACQ-5 $\geq 1.0$ (corresponding to uncontrolled asthma)\textsuperscript{36}; (2) patients with AD and comorbid asthma with baseline ACQ-5 $\geq 0.5$ (corresponding to uncontrolled plus partially controlled asthma)\textsuperscript{37}; (3) patients with AD and comorbid sinonasal conditions who completed at least one SNOT-22 assessment; and (4) patients with AD, comorbid asthma requiring treatment and baseline ACQ-5 $\geq 0.5$, and comorbid sinonasal conditions (ie, patients with all three conditions).

Patients with asthma had a documented history of asthma requiring treatment (ie, active at baseline and using at least one medication classified as drugs for obstructive airway diseases by the World Health Organization Drug Dictionary). The ACQ-5 $\geq 0.5$ threshold was selected for analysis of the group with all three comorbid conditions as a compromise between enriching the population for lack of asthma control and maintaining a sufficient subset size for the analysis.

Sinonasal conditions (defined as allergic rhinitis, chronic rhinitis or rhinosinusitis, or nasal polyps) were assessed using the SNOT-22 questionnaire. Sinonasal conditions reported by these patients in the medical history included allergic rhinitis or sinusitis, chronic rhinitis or sinusitis, nasal polyps, including in the context of aspirin-exacerbated respiratory disease, and nasal turbinate hypertrophy.

Because the ACQ-5 and SNOT-22 were prespecified assessments in these studies, to be performed only in trial patients with comorbid asthma and/or sinonasal conditions (as recorded in patients’ medical history and noted as present at baseline), this post hoc analysis is limited to these subsets of patients for whom ACQ-5 and/or SNOT-22 data were collected and met the previously mentioned criteria. The complementary subset of patients with AD who had neither asthma nor chronic sinonasal conditions was used as a comparator.

**End points**

Atopic dermatitis, asthma, and sinonasal outcomes were assessed at baseline and week 16. Signs and symptoms of AD were assessed by the Eczema Area and Severity Index (EASI)\textsuperscript{38,39} and the Peak Pruritus Numerical Rating Scale (NRS)\textsuperscript{40,41} and patients’ quality of life was assessed by the Dermatology Life Quality Index (DLQI).\textsuperscript{42} Separately, for patients with asthma, asthma control was assessed using the ACQ-5\textsuperscript{35}; the total score ranged from 0 to 6 and the minimal clinically important difference (MCID) for ACQ-5 was defined as 0.5.\textsuperscript{43} The SNOT-22 was used to assess chronic sinonasal conditions, with a total score ranging from 0 to 110 and an MCID of 8.9 points.\textsuperscript{44}

End points assessed in this post hoc analysis included ACQ-5 least squares (LS) mean change from baseline at week 16; the proportion of patients with ACQ-5 improvement $\geq 0.5$ at week 16; LS mean change from baseline in EASI at week 16; the proportion of patients with $\geq 75\%$ improvement from baseline in EASI (EASI-75) at week 16; LS mean change in weekly average Peak Pruritus NRS from baseline to week 16; SNOT-22 LS mean change from baseline at week 16; the proportion of patients with SNOT-22 improvement $\geq 8.9$ or an absolute score of 0 at week 16; and for patients with asthma with baseline ACQ-5 $\geq 0.5$ only, the composite of patients achieving $\geq 50\%$ improvement from baseline in EASI (EASI-50), or three or more points reduction in NRS (NRS $\geq 3$), or four or more points reduction in DLQI (DLQI $\geq 4$).

**Statistical analysis**

Data from all four studies were pooled and analyzed by treatment group. Continuous end points were analyzed using an analysis of covariance model with baseline measurement as covariate and treatment arm destination, baseline disease severity strata (Investigator’s Global Assessment [IGA] = 3 vs IGA = 4), and study identifier as fixed factors of the model. Missing values were imputed using the multiple imputation method with censoring after AD rescue treatment use for SNOT-22 and ACQ-5 end points. For categorical end points, $P$ values were derived by Cochran–Mantel–Haenszel test stratified by study identifier and baseline disease severity (IGA = 3 vs IGA = 4), with patients considered nonresponders after rescue treatment use (nonresponder imputation). All statistical analyses were carried out using SAS software (version 9.4, SAS Institute, Cary, NC).

**Ethics**

We conducted SOLO 1, SOLO 2, CHRONOS, and CAFÉ in adherence with the Declaration of Helsinki principles. All patients provided signed written informed consent before performing any study procedures. Institutional review boards and independent ethics committees reviewed and approved the protocol, informed consent form, and patient information before study initiation.
RESULTS

Study population

In total, 2444 patients with AD received either placebo (n = 883), dupilumab 300 mg q2w (n = 670), or dupilumab 300 mg qw (n = 891) across the four studies (Table 1; see Figure E1 in this article’s Online Repository at www.jacionline.org). Overall, among the 2444 study patients, 83.4% reported having one or more type 2 inflammatory diseases in addition to AD, including 39.6% with asthma and 47.9% with allergic rhinitis (see Table E1 in this article’s Online Repository at www.jacionline.org). Among these patients, 463 (18.9%) had comorbid asthma that was uncontrolled or partially controlled (ACQ-5 ≥ 0.5); 350 (14.3%) had uncontrolled asthma (ACQ-5 ≥ 1.0; Table E2 in this article’s Online Repository); 1,171 (47.9%) had comorbid sinonasal conditions (allergic rhinitis, chronic rhinitis or rhinosinusitis, and nasal polyps); and 311 (12.7%) had both asthma (ACQ-5 ≥ 0.5) and sinonasal conditions. Table I presents the number of patients reporting using medication for obstructive airway disease. Baseline characteristics were generally similar across patient subgroups (Table II) and between patients with AD with type 2 inflammatory diseases and the complementary subset without these comorbidities (see Figure E2 in this article’s Online Repository at www.jacionline.org). However, patients with AD, asthma, and chronic sinonasal conditions had significantly higher baseline SNOT-22 scores than did patients with AD plus chronic sinonasal conditions (Table II). Table E3 in this article’s Online Repository (at www.jacionline.org) contains the 95% confidence intervals for data presented in Figures 1 through 6.

Efficacy

Among the two subgroups of patients with comorbid asthma (baseline ACQ-5 ≥ 0.5 and ACQ-5 ≥ 1.0), there was a significantly greater improvement from baseline in ACQ-5 score (Figure 1, A) and a greater proportion of patients with ≥0.5-point (MCID) improvement from baseline in ACQ-5 scores (Figure 1, B) with either dupilumab dose regimen versus placebo at week 16. Atopic dermatitis signs were also improved with either dupilumab dose regimen versus placebo at week 16, with improvements seen in EASI (Figure 2, A) and greater proportion of patients achieving EASI-50 (Figure 2, B). Furthermore, both dupilumab regimens versus placebo led to greater improvement in Peak Pruritus NRS score (Figure 2, C) and greater proportions of patients who achieved at least one meaningful clinical outcome for AD (ie, either EASI-50 or three points or greater improvement in Peak Pruritus NRS score, or four points or greater improvement in DLQI at week 16 (Figure 2, D).

In patients with AD and chronic sinonasal conditions, there was significantly more improvement in SNOT-22 scores and a greater proportion of patients with ≥ 8.9-point improvement in SNOT-22 at week 16 (among patients with baseline SNOT-22 ≥ 8.9) with both dupilumab regimens versus placebo (Figure 3, A and B). Signs and symptoms of AD were significantly improved with both dupilumab dose regimens versus placebo at week 16, including reductions in EASI (Figure 4, A), greater proportion of patients with EASI-75 (Figure 4, B), and greater improvement in Peak Pruritus NRS score (Figure 4, C). The SNOT-22 scores at baseline and week 16 for patients with AD and sinonasal conditions and broken down by sinonasal condition are given in Table E4 in this article’s Online Repository (at www.jacionline.org).

Similarly, patients with all three diseases (AD, asthma with ACQ-5 ≥ 0.5 at baseline, and chronic sinonasal conditions) had significantly greater improvement in ACQ-5 score (Figure 5, A) and more patients had ≥ 0.5 improvement in the ACQ-5 score (Figure 5, B) with either dupilumab dose regimen versus placebo.

<table>
<thead>
<tr>
<th>Selected subgroups</th>
<th>Placebo (n = 883)</th>
<th>Dupilumab 300 mg q2w (n = 670)</th>
<th>Dupilumab 300 mg qw (n = 891)</th>
<th>Total combined studies (N = 2444)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with asthma history, receiving asthma medication, n (%)</td>
<td>281 (31.8)</td>
<td>204 (30.4)</td>
<td>251 (28.2)</td>
<td>736 (30.1)</td>
</tr>
<tr>
<td>Patients with asthma history, receiving asthma medication, and baseline ACQ-5 ≥ 0.5, n/N1 (%)</td>
<td>177/281 (63.0)</td>
<td>137/204 (67.2)</td>
<td>150/251 (59.8)</td>
<td>463/736 (62.9)</td>
</tr>
<tr>
<td>Patients with asthma history, receiving asthma medication, and baseline ACQ-5 ≥ 1.0, n/N1 (%)</td>
<td>137/281 (48.8)</td>
<td>102/204 (50.0)</td>
<td>112/251 (44.6)</td>
<td>350/736 (47.6)</td>
</tr>
<tr>
<td>Patients with chronic sinonasal conditions who completed SNOT-22 assessment, n (%)</td>
<td>389 (44.1)</td>
<td>348 (51.9)</td>
<td>434 (48.7)</td>
<td>1171 (47.9)</td>
</tr>
<tr>
<td>Allergic rhinitis/sinusitis, n/N2 (%)</td>
<td>343/389 (88.2)</td>
<td>294/348 (84.5)</td>
<td>364/434 (83.9)</td>
<td>1001/1171 (85.5)</td>
</tr>
<tr>
<td>Chronic rhinitis/sinusitis, n/N2 (%)</td>
<td>63/389 (16.2)</td>
<td>41/348 (11.8)</td>
<td>54/434 (12.4)</td>
<td>158/1171 (13.5)</td>
</tr>
<tr>
<td>Nasal polyps, n/N2 (%)</td>
<td>29/389 (7.5)</td>
<td>24/348 (6.9)</td>
<td>44/434 (10.1)</td>
<td>97/1171 (8.3)</td>
</tr>
<tr>
<td>Aspirin-exasparated respiratory disease, n/N2 (%)</td>
<td>0/389 (0)</td>
<td>0/348 (0)</td>
<td>1/434 (0.2)</td>
<td>1/1171 (0.1)</td>
</tr>
<tr>
<td>Nasal turbinate hypertrophy, n/N2 (%)</td>
<td>0/389 (0)</td>
<td>3/348 (0.9)</td>
<td>0/434 (0)</td>
<td>3/1171 (0.3)</td>
</tr>
</tbody>
</table>

ACQ-5, 5-item Asthma Control Questionnaire; AD, atopic dermatitis; N1, number of patients with AD and asthma history currently receiving drugs for obstructive airway diseases; N2, number of patients with AD and chronic sinonasal conditions; qw, every 2 weeks; qw, weekly; SNOT-22, 22-item Sinonasal Outcome Test.

*Patient data were pooled from SOLO 1 and 2, CAFÉ, and CHRONOS.

†Patients in CHRONOS and CAFÉ also received concomitant topical corticosteroids.
Baseline patient characteristics

**Table II.** AD plus asthma (ACQ-5 ≥ 0.5)

<table>
<thead>
<tr>
<th>Condition</th>
<th>ACQ-5 (0.5)</th>
<th>ACQ-5 (1.0)</th>
<th>DPL 300 mg qw</th>
<th>PBO</th>
<th>ACQ-5 score (0-6)</th>
<th>22-item Sinonasal Outcome Test score (0-110)</th>
<th>Severity Index (0-72)</th>
<th>Rating Scale (0-10)</th>
<th>Quality Index (0-30)</th>
<th><em>P</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Patient Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age, y</strong></td>
<td>37.8 (13.6)</td>
<td>38.5 (13.3)</td>
<td>37.8 (13.3)</td>
<td></td>
<td>NA</td>
<td></td>
<td>33.4 (14.5)</td>
<td>33.0 (14.5)</td>
<td>33.7 (14.5)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>AD duration, y</strong></td>
<td>28.4 (14.4)</td>
<td>28.5 (15.3)</td>
<td>28.3 (15.3)</td>
<td></td>
<td>34.9 (14.4)</td>
<td></td>
<td>33.4 (14.5)</td>
<td>33.0 (14.5)</td>
<td>33.7 (14.5)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Eczema Area and Severity Index</strong></td>
<td>32.7 (12.8)</td>
<td>32.4 (12.9)</td>
<td>32.4 (12.9)</td>
<td></td>
<td>34.9 (14.4)</td>
<td></td>
<td>33.4 (14.5)</td>
<td>33.0 (14.5)</td>
<td>33.7 (14.5)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Peak Pruritus NRS</strong></td>
<td>7.2 (3.8)</td>
<td>7.2 (3.8)</td>
<td>7.2 (3.8)</td>
<td></td>
<td>7.7 (3.4)</td>
<td></td>
<td>7.3 (3.8)</td>
<td>7.3 (3.8)</td>
<td>7.3 (3.8)</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Rating Scale (0-10)</strong></td>
<td>14.3 (7.5)</td>
<td>14.6 (7.3)</td>
<td>14.7 (7.4)</td>
<td></td>
<td>15.2 (7.1)</td>
<td></td>
<td>16.0 (8.1)</td>
<td>16.0 (8.1)</td>
<td>16.0 (8.1)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Quality Index (0-30)</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>NA</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>ACQ-5 score (0.5)</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>NA</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>ACQ-5 score (1.0)</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>NA</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>22-item Sinonasal Outcome Test score (0-110)</strong></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td></td>
<td>NA</td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>ACQ-5, Asthma Control Questionnaire; AD, atopic dermatitis; DPI, dupilumab; NA, not available; PBO, placebo; qw, every week; q2w, every two weeks.</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DISCUSSION

In this analysis, we demonstrate that dupilumab treatment confers clinical benefits across multiple comorbid diseases, the pathobiology of which is primarily characterized by type 2 inflammation. Dupilumab-treated patients with AD and comorbid asthma and/or chronic sinonasal conditions showed statistically and clinically significant improvement in asthma control (ACQ-5 score) and sinonasal symptoms (SNOT-22 score), in addition to improvements in AD-related outcomes (EASI, Peak Pruritus NRS, and DLQI). Overall, the efficacy of dupilumab in AD outcomes in patient subgroups with comorbid asthma and/or chronic sinonasal conditions was comparable to that of the overall study populations. Furthermore, the safety and efficacy of dupilumab in patients with AD and comorbid asthma and/or chronic sinonasal conditions was similar to those of the overall study populations in the phase 3 trials in moderate to severe AD (data not shown). The positive effects of dupilumab on asthma control and sinonasal symptoms observed in this analysis are supported by previous trials dedicated to evaluating the safety and efficacy of dupilumab in patients with asthma, atopic dermatitis, CRSwNP, and most types of asthma are characterized by type 2 skewing, in which patients with more robust Th2 gene expression are more likely to have severe disease and other comorbid type 2 inflammatory diseases. Comorbid type 2 inflammatory diseases are highly prevalent in patients with moderate to severe AD; over 80% of adult patients in the dupilumab phase 3 trials reported one or more comorbid type 2 inflammatory diseases, among which asthma, allergic rhinitis, and food allergy were most common. These diseases were even more prevalent in trials in adolescent patients. Among the 39% of study patients who reported comorbid asthma, 19% were uncontrolled or only partially controlled (ACQ-5 ≥ 0.5) and 14% were uncontrolled (ACQ-5 ≥ 1.0) despite receiving concomitant asthma medications. Other studies also reported a similar prevalence of comorbid AD and asthma and demonstrated that although it is a heterogeneous disease, most types of asthma are driven by type 2 inflammation.
FIGURE 1. Asthma outcomes at week 16 in patients with atopic dermatitis and asthma. (A) Least squares (LS) mean change (improvement) from baseline in 5-item Asthma Control Questionnaire (ACQ-5) score. (B) Proportion of patients with improvement ≥ 0.5 in ACQ-5. *P < .05, **P < .01, ***P < .001 vs placebo. q2w, every 2 weeks; qw, weekly; SE, standard error.
FIGURE 2. Atopic dermatitis (AD) outcomes at week 16 in patients with AD and asthma. (A) Least squares (LS) mean change (reduction) from baseline in Eczema Area and Severity Index (EASI). (B) Proportion of patients with ≥75% improvement from baseline in EASI (EASI-75). (C) Least squares mean change (reduction) from baseline in weekly average of Peak Pruritus Numerical Rating Scale (NRS) score. (D) Proportion of patients achieving one or more clinically meaningful outcomes in AD: ≥50% improvement from baseline in EASI, or three points or greater improvement in Peak Pruritus NRS, or four points or greater improvement in Dermatology Life Quality Index. ****P < .0001 vs placebo. ACQ-5, 5-item Asthma Control Questionnaire; q2w, every 2 weeks; qw, weekly; SE, standard error.

FIGURE 3. Sinonasal outcomes at week 16 in patients with atopic dermatitis and sinonasal conditions. (A) Least squares (LS) mean change (improvement) from baseline in 22-item Sino-Nasal Outcome Test (SNOT-22) score. (B) Proportion of patients with an improvement of ≥8.9 in SNOT-22 at week 16 (among patients with baseline SNOT-22 ≥ 8.9). ****P < .0001 vs placebo. q2w, every 2 weeks; qw, weekly; SE, standard error.
also been demonstrated that allergic rhinitis and chronic rhinosinusitis, especially with nasal polyps, are predominately driven by type 2 inflammation. Dupilumab’s mechanism of action involves the inhibition of type 2 inflammatory pathways by effectively blocking the signaling of two key cytokines, IL-4 and IL-13. It was developed as a treatment for AD, asthma, and CRSwNP, yet dupilumab has deepened the understanding of pathophysiology in these diseases, particularly the predominance of type 2 inflammation.

Patients with AD and comorbid type 2 inflammatory diseases appear to have an increased disease burden. Among the patients in this analysis, those with both asthma and sinonasal conditions had higher overall SNOT-22 scores than did patients without asthma. However, in these patients, AD-related outcomes in response to dupilumab improved similarly to those of the overall population, whereas dupilumab also conferred significant benefits related to asthma control and sinonasal symptoms in this population. An exploratory analyses showed that generally, more dupilumab-treated patients achieved improvement in both AD and comorbid outcomes than did placebo-treated patients. This offers the possibility of simplifying the treatment approach in these patients by employing a drug that can effectively treat multiple type 2 inflammatory diseases at the same time.

Although this is the first report of comorbidity outcomes among patients with moderate to severe AD, this analysis has limitations. First, it is a post hoc analysis, and some of the subgroups have a small number of patients. Although there were no adjustments for

**FIGURE 4.** Atopic dermatitis (AD) outcomes at week 16 in patients with AD and sinonasal conditions. (A) Least squares (LS) mean change (reduction) from baseline in Eczema Area and Severity Index (EASI). (B) Proportion of patients with ≥75% improvement from baseline in EASI (EASI-75). (C) Least squares mean change (reduction) from baseline in weekly average of Peak Pruritus Numerical Rating Scale (NRS) score. ****P < .0001 vs placebo. q2w, every 2 weeks; qw, weekly; SE, standard error.
multiple analyses, the consistency of results suggests that the findings are real. Second, the presence of comorbid asthma and sinonasal conditions at study entry were documented by the study investigator based on medical records and/or patient reports, and no diagnostic tests, examinations, or investigations were required. Nevertheless, the additional requirements for asthma-related medications and the required thresholds for baseline ACQ-5 scores provided additional assurances that the appropriate patients were included in the asthma subgroups. Third, because clinical trials providing data for this analysis were focused on AD, only one outcome measure was collected for each of the comorbidities analyzed: ACQ-5 for patients with asthma and SNOT-22 for patients with chronic sinonasal conditions, both patient reported. It is possible that the objective improvement in AD led to an overall improvement of well-being resulting in subjective improvements in scores for the other comorbid disorders.

However, ACQ-5 and SNOT-22 are well-validated instruments that have been used extensively in clinical trials and have demonstrated the ability to discern important differences between treatment groups, without a significant influence by external factors. Although SNOT-22 is not validated for all sinonasal conditions included in this analysis (eg, allergic rhinitis), this patient-reported outcome instrument has been validated in chronic rhinosinusitis and contains measures relevant to all of these conditions and overlap with items included in the Rhinitis Quality of Life Questionnaire and the Total Nasal Symptom Score. Finally, ACQ-5 and SNOT-22 were assessed only at baseline and week 16; therefore, no information is available regarding the onset of dupilumab efficacy or the duration of efficacy beyond week 16. However, similar information is available in trials of dupilumab in patients with asthma and chronic sinonasal conditions, which supports the results shown here.

**FIGURE 5.** Asthma and sinonasal outcomes at week 16 in patients with atopic dermatitis, asthma (baseline 5-item Asthma Control Questionnaire 5 (ACQ-5) ≥ 0.5), and sinonasal conditions. (A) Least squares (LS) mean change (improvement) from baseline in ACQ-5 score. (B) Proportion of patients with improvement ≥ 0.5 in ACQ-5. (C) Least squares mean change (improvement) from baseline in 22-item Sino-Nasal Outcome Test (SNOT-22) score. (D) Proportion of patients with an improvement of ≥ 8.9 or score of 0 in SNOT-22. *P < .05, **P < .01, ***P < .001 vs placebo. qw, every 2 weeks; qw, weekly; SE, standard error.
The original validation of ACQ-5 established a threshold of 0.75 for well-controlled asthma; however, for the purpose of this analysis, we applied the threshold of 0.5, suggested by Olaguibel et al. The threshold of 0.5 also enabled us to include a larger sample in the analysis. Our definition of ACQ-5 responder is stringent for this analysis population, whose asthma is overall milder and better controlled (mean baseline ACQ-5 = 1.0) than the populations enrolled in dupilumab asthma trials (mean baseline ACQ-5 = 2.76) or dupilumab CRSwNP trials (mean baseline ACQ-5 = 1.59). Patients with asthma who were enrolled in the AD trials had less room for asthma improvement and less opportunity to reach responder thresholds based on absolute change from baseline. Despite this, a significant treatment effect is observed in the current analysis population with respect to ACQ-5 improvement.

Dupilumab treatment in adult patients with moderate to severe AD and comorbid asthma and/or chronic sinonasal conditions significantly improved AD signs and symptoms as well as asthma and sinonasal disease. These data suggest that by inhibiting type 2 inflammation, dupilumab may help to optimize management of concurrent AD, asthma, and chronic sinonasal conditions. Future research, including real-world studies and registries, will provide additional information to confirm and expand on the findings of this analysis.

**Acknowledgments**

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participation in the studies, their colleagues for their support; Qiuyue Chen and Linda Williams (Regeneron Pharmaceuticals, Inc); and El-Bdaoui Haddad (Sanofi Genzyme); and Heribert Staudinger (Sanofi) for their contributions. Medical writing and editorial assistance were provided by Lola MacRae, PhD, of Excerpta Medica, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc. ClinicalTrials.gov Identifiers: NCT02277743 (SOLO 1), NCT02277769 (SOLO 2), NCT02260986 (CHRONOS), and NCT02755649 (CAFÉ).

Note

For a video abstract of this article, see Video 1, available in this article’s Online Repository at jaci-inpractice.org.

REFERENCES

ONLINE REPOSITORY

Dupilumab phase 3 trials study design

Across studies, eligible patients were aged ≥18 years and had moderate to severe atopic dermatitis with inadequate response to topical treatment. Baseline Eczema Area and Severity Index was ≥16 for patients in LIBERTY AD SOLO 1 and 2 (NCT02277743 and NCT02277769) and LIBERTY AD CHRONOS (NCT02260986) and ≥20 for patients in LIBERTY AD CAFÉ (NCT02755649). In only the CAFÉ trial, eligible patients had inadequate response to cyclosporine A or were intolerant to the drug, or it was otherwise contraindicated Video 1 (available in this article’s Online Repository at www.jaci-inpractice.org.)

FIGURE E1. Study designs of SOLO 1 and 2, CHRONOS, and CAFÉ. *All patients had an inadequate response to topical treatment. EASI, Eczema Area and Severity Index; q2w, every 2 weeks; qw, weekly; R, randomization; TCS, topical corticosteroids.
FIGURE E2. Key baseline parameters for each patient subset and the complementary subset without comorbidities. (A) 5-item Asthma Control Questionnaire (ACQ-5). (B) Eczema Area and Severity Index (EASI). (C) Peak Pruritus Numerical Rating Scale (NRS). (D) Dermatology Life-Quality Index (DLQI). *AD*, atopic dermatitis; *comp*, complementary; *q2w*, every 2 weeks; *qw*, weekly; *SD*, standard deviation.
FIGURE E2. Continued
### TABLE E1. Patients reporting history of type 2 inflammatory disease (in addition to atopic dermatitis)*

<table>
<thead>
<tr>
<th>Medical history subcategory term</th>
<th>Placebo qw (n = 883)</th>
<th>DPL 300 mg q2w (n = 670)</th>
<th>DPL 300 mg qw (n = 891)</th>
<th>Total (N = 2444)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any of the following comorbidities</td>
<td>724 (82.0)</td>
<td>560 (83.6)</td>
<td>755 (84.7)</td>
<td>2039 (83.4)</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>409 (46.3)</td>
<td>332 (49.6)</td>
<td>429 (48.1)</td>
<td>1170 (47.9)</td>
</tr>
<tr>
<td>Asthma</td>
<td>347 (39.3)</td>
<td>280 (41.8)</td>
<td>341 (38.3)</td>
<td>968 (39.6)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>308 (34.9)</td>
<td>260 (38.8)</td>
<td>340 (38.2)</td>
<td>908 (37.2)</td>
</tr>
<tr>
<td>Allergic conjunctivitis</td>
<td>178 (20.2)</td>
<td>165 (24.6)</td>
<td>162 (18.2)</td>
<td>505 (20.7)</td>
</tr>
<tr>
<td>Hives</td>
<td>103 (11.7)</td>
<td>91 (13.6)</td>
<td>113 (12.7)</td>
<td>307 (12.6)</td>
</tr>
<tr>
<td>Allergic conjunctivitis (keratoconjunctivitis)</td>
<td>68 (7.7)</td>
<td>31 (4.6)</td>
<td>73 (8.2)</td>
<td>172 (7.0)</td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>57 (6.5)</td>
<td>37 (5.5)</td>
<td>52 (5.8)</td>
<td>146 (6.0)</td>
</tr>
<tr>
<td>Atopic keratoconjunctivitis</td>
<td>22 (2.5)</td>
<td>28 (4.2)</td>
<td>35 (3.9)</td>
<td>85 (3.5)</td>
</tr>
<tr>
<td>Nasal polyps</td>
<td>20 (2.3)</td>
<td>13 (1.9)</td>
<td>25 (2.8)</td>
<td>58 (2.4)</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>3 (0.3)</td>
<td>7 (1.0)</td>
<td>1 (0.1)</td>
<td>11 (0.5)</td>
</tr>
<tr>
<td>Other allergies†</td>
<td>553 (62.6)</td>
<td>429 (64.0)</td>
<td>584 (65.5)</td>
<td>1566 (64.1)</td>
</tr>
</tbody>
</table>

*DPL, dupilumab; qw, weekly; q2w, every two weeks.
*Data are patient reported, pooled from sponsor trial records.
†Including allergy to animals, medications, metals, etc.

### TABLE E2. Breakdown of patients with atopic dermatitis (AD) plus asthma, by baseline 5-item Asthma Control Questionnaire (ACQ-5) threshold *

<table>
<thead>
<tr>
<th>Patients with AD plus asthma (n = 736)</th>
<th>Total combined studies (N = 2444)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with asthma history, receiving asthma medication, and baseline ACQ-5 ≥ 0.5, n/N (%)</td>
<td>463/2444 (18.9)</td>
</tr>
<tr>
<td>Patients with asthma history, receiving asthma medication, and baseline ACQ-5 ≥ 1.0, n/N (%)</td>
<td>350/2444 (14.3)</td>
</tr>
</tbody>
</table>

*Among patients with AD plus asthma, 62.9% had baseline ACQ-5 of ≥ 0.5 and 47.6% had a baseline ACQ-5 of ≥1.0
### TABLE E3. The 95% confidence intervals for data presented in Figures 1-6

<table>
<thead>
<tr>
<th>End point</th>
<th>Dupilumab 300 mg q2w vs placebo</th>
<th>Dupilumab 300 mg qw vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AD plus asthma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean change from baseline in ACQ-5 score, LS mean difference (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline ACQ-5 ≥ 0.5</td>
<td>−0.32 (−0.53, −0.12)</td>
<td>−0.29 (−0.49, −0.10)</td>
</tr>
<tr>
<td>Baseline ACQ-5 ≥ 1.0</td>
<td>−0.30 (−0.54, −0.05)</td>
<td>−0.27 (−0.51, −0.02)</td>
</tr>
<tr>
<td>Proportion of patients with improvement ≥ 0.5 in ACQ-5, risk difference (95% CI)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline ACQ-5 ≥ 0.5</td>
<td>14.4 (4.1, 24.7)</td>
<td>19.3 (9.2, 29.5)</td>
</tr>
<tr>
<td>Baseline ACQ-5 ≥ 1.0</td>
<td>16.2 (3.8, 28.5)</td>
<td>23.2 (11.2, 35.3)</td>
</tr>
<tr>
<td><strong>LS mean change from baseline in EASI, LS mean difference (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline ACQ-5 ≥ 0.5</td>
<td>−13.89 (−16.62, −11.16)</td>
<td>−13.61 (−16.24, −10.99)</td>
</tr>
<tr>
<td>Baseline ACQ-5 ≥ 1.0</td>
<td>−14.32 (−17.49, −11.15)</td>
<td>−13.95 (−17.04, −10.87)</td>
</tr>
<tr>
<td>Proportion of patients with EASI-75, risk difference (95% CI)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline ACQ-5 ≥ 0.5</td>
<td>37.6 (27.5, 47.7)</td>
<td>36.4 (26.6, 46.2)</td>
</tr>
<tr>
<td>Baseline ACQ-5 ≥ 1.0</td>
<td>41.8 (30.3, 53.3)</td>
<td>37.8 (26.5, 49.1)</td>
</tr>
<tr>
<td><strong>LS mean change from baseline in weekly average of Peak Pruritus NRS score, LS mean difference (95% CI)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline ACQ-5 ≥ 0.5</td>
<td>−2.20 (−2.75, −1.65)</td>
<td>−2.04 (−2.56, −1.51)</td>
</tr>
<tr>
<td>Baseline ACQ-5 ≥ 1.0</td>
<td>−2.20 (−2.82, −1.57)</td>
<td>−2.02 (−2.63, −1.42)</td>
</tr>
<tr>
<td>Proportion of patients achieving ≥1 clinically meaningful outcomes in AD (EASI-50, ≥5-point improvement in Peak Pruritus NRS, or ≥4-point improvement in DLQI), risk difference (95% CI)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline ACQ-5 ≥ 0.5</td>
<td>36.2 (26.3, 46.1)</td>
<td>36.5 (26.8, 46.2)</td>
</tr>
</tbody>
</table>

| **AD plus sinonasal conditions** |                                 |                                 |
| LS mean change from baseline in SNOT-22 score, LS mean difference (95% CI) |                                 |                                 |
| Baseline ACQ-5 ≥ 0.5 | −4.79 (−7.08, −2.50) | −5.74 (−7.82, −3.65) |
| Baseline ACQ-5 ≥ 1.0 | 14.5 (8.2, 20.7) | 17.5 (11.6, 23.4) |
| Proportion of patients with improvement ≥ 8.9 in SNOT-22 at wk 16 (among patients with baseline SNOT-22 ≥ 8.9), risk difference (95% CI)* | 10.92 (−12.67, −9.17) | −11.34 (−13.00, −9.68) |
| LS mean change from baseline in EASI, LS mean difference (95% CI) |                                 |                                 |
| Baseline ACQ-5 ≥ 0.5 | −1.82 (−2.17, −1.47) | −1.91 (−2.24, −1.58) |
| Baseline ACQ-5 ≥ 1.0 | 33.5 (27.0, 40.0) | 35.0 (28.9, 41.0) |
| Proportion of patients with EASI-75, risk difference (95% CI)* |                                 |                                 |
| Baseline ACQ-5 ≥ 0.5 | −1.02 (−1.42, −0.62) | −1.36 (−1.76, −0.96) |
| Baseline ACQ-5 ≥ 1.0 | 9.6 (−2.4, 21.7) | 25.1 (12.8, 37.4) |
| LS mean change from baseline in SNOT-22 score, LS mean difference (95% CI) | −5.80 (−10.28, −1.33) | −6.92 (−11.25, −2.59) |
| The proportion of patients with improvement ≥ 8.9 or score of 0 in SNOT-22, risk difference (95% CI)* | 18.8 (7.2, 30.3) | 28.2 (16.6, 39.8) |
| LS mean change from baseline in EASI, LS mean difference (95% CI) | −12.95 (−16.47, −9.42) | −12.97 (−16.26, −9.67) |
| Proportion of patients with EASI-75, risk difference (95% CI)* | 35.1 (22.9, 47.3) | 33.4 (21.5, 45.4) |
| LS mean change from baseline in weekly average of Peak Pruritus NRS score (95% CI) | −1.70 (−2.39, −1.00) | −2.00 (−2.65, −1.36) |

*ACQ-5, 5-item Asthma Control Questionnaire; AD, atopic dermatitis; CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50, ≥50 % improvement from baseline in EASI; EASI-75, ≥75% improvement from baseline in EASI; LS, least squares; NRS, Numerical Rating Scale; q2w, every 2 weeks; qw, weekly; SNOT-22, 22-item Sino-Nasal Outcome Test.

*Difference is dupilumab minus placebo. Confidence interval was calculated using normal approximation.
### TABLE E4. Baseline and Week 16 22-item Sino-Nasal Outcome Test scores for patients with atopic dermatitis and sinonasal conditions, presented by sinonasal condition*

<table>
<thead>
<tr>
<th>Selected subgroups</th>
<th>Placebo (n = 389)</th>
<th>Dupilumab 300 mg q2w (n = 348)</th>
<th>Dupilumab 300 mg qw (n = 434)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atopic dermatitis plus sinonasal conditions, mean (SE)</td>
<td>31.6 (21.6)</td>
<td>31.3 (19.7)</td>
<td>33.6 (21.8)</td>
</tr>
<tr>
<td>Allergic rhinitis/sinusitis, n1</td>
<td>343</td>
<td>294</td>
<td>364</td>
</tr>
<tr>
<td>Baseline</td>
<td>31.8 (1.2)</td>
<td>32.5 (1.2)</td>
<td>33.7 (1.2)</td>
</tr>
<tr>
<td>Week 16</td>
<td>26.9 (1.2)</td>
<td>22.1 (1.1)</td>
<td>22.6 (1.0)</td>
</tr>
<tr>
<td>Chronic rhinitis/sinusitis, n1</td>
<td>63</td>
<td>41</td>
<td>54</td>
</tr>
<tr>
<td>Baseline</td>
<td>37.6 (2.6)</td>
<td>33.6 (3.7)</td>
<td>41.6 (2.9)</td>
</tr>
<tr>
<td>Week 16</td>
<td>33.1 (2.6)</td>
<td>24.9 (2.4)</td>
<td>25.3 (2.7)</td>
</tr>
<tr>
<td>Nasal polyps, n1</td>
<td>29</td>
<td>24</td>
<td>44</td>
</tr>
<tr>
<td>Baseline</td>
<td>37.3 (4.5)</td>
<td>33.9 (4.4)</td>
<td>43.7 (3.6)</td>
</tr>
<tr>
<td>Week 16</td>
<td>33.8 (4.8)</td>
<td>28.5 (4.8)</td>
<td>30.1 (3.1)</td>
</tr>
<tr>
<td>Aspirin-exacerbated respiratory disease, n1</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Baseline</td>
<td>NA</td>
<td>NA</td>
<td>92.0 (NA)</td>
</tr>
<tr>
<td>Week 16</td>
<td>NA</td>
<td>NA</td>
<td>50.0 (NA)</td>
</tr>
<tr>
<td>Nasal turbinate hypertrophy, n1</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Baseline</td>
<td>NA</td>
<td>41.3 (5.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Week 16</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

n1, number of patients with sinonasal condition; NA, not applicable; q2w, every 2 weeks; qw, weekly; SE, standard error.

*Values are mean (SE) unless otherwise stated.

### TABLE E5. Patients achieving clinically meaningful improvement (MCID) in Eczema Area and Severity Index (EASI), Peak Pruritus Numerical Rating Scale (NRS), 5-item Asthma Control Questionnaire (ACQ-5), or 22-Item Sino-Nasal Outcome Test (SNOT-22) scores at week 16 (patients with atopic dermatitis plus asthma plus sinonasal conditions)*

<table>
<thead>
<tr>
<th>Patients achieving, n1 (%)</th>
<th>Placebo (n = 86)</th>
<th>Dupilumab 300 mg q2w (n = 79)</th>
<th>Dupilumab 300 mg qw (n = 87)</th>
<th>Total (N = 252)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients achieving MCID in only one measure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EASI</td>
<td>15 (17.4)</td>
<td>16 (20.3)</td>
<td>8 (9.2)</td>
<td>39 (15.5)</td>
</tr>
<tr>
<td>Peak Pruritus NRS</td>
<td>1 (1.2)</td>
<td>0 (0)</td>
<td>1 (1.1)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>ACQ-5</td>
<td>3 (3.5)</td>
<td>1 (1.3)</td>
<td>0</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>SNOT-22</td>
<td>9 (10.5)</td>
<td>2 (2.5)</td>
<td>4 (4.6)</td>
<td>15 (6.0)</td>
</tr>
<tr>
<td>Patients achieving MCID in two measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EASI and Peak Pruritus NRS</td>
<td>6 (7.0)</td>
<td>4 (5.1)</td>
<td>6 (6.9)</td>
<td>16 (6.3)</td>
</tr>
<tr>
<td>Peak Pruritus NRS and ACQ-5</td>
<td>2 (2.3)</td>
<td>0</td>
<td>1 (1.1)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>ACQ-5 and SNOT-22</td>
<td>6 (7.0)</td>
<td>0</td>
<td>1 (1.1)</td>
<td>7 (2.8)</td>
</tr>
<tr>
<td>EASI and ACQ-5</td>
<td>7 (8.1)</td>
<td>5 (6.3)</td>
<td>4 (4.6)</td>
<td>16 (6.3)</td>
</tr>
<tr>
<td>Peak Pruritus NRS and SNOT-22</td>
<td>2 (2.3)</td>
<td>0</td>
<td>0</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>EASI and SNOT-22</td>
<td>15 (17.4)</td>
<td>13 (16.5)</td>
<td>6 (6.9)</td>
<td>34 (13.5)</td>
</tr>
<tr>
<td>Patients achieving MCID in three measures</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EASI and Peak Pruritus NRS and ACQ-5</td>
<td>3 (3.5)</td>
<td>3 (3.8)</td>
<td>6 (6.9)</td>
<td>12 (4.8)</td>
</tr>
<tr>
<td>Peak Pruritus NRS and ACQ-5 and SNOT-22</td>
<td>1 (1.2)</td>
<td>0</td>
<td>0</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>ACQ-5 and SNOT-22 and EASI</td>
<td>4 (4.7)</td>
<td>8 (10.1)</td>
<td>11 (12.6)</td>
<td>23 (9.1)</td>
</tr>
<tr>
<td>SNOT-22 and EASI and Peak Pruritus NRS</td>
<td>7 (8.1)</td>
<td>11 (13.9)</td>
<td>13 (14.9)</td>
<td>31 (12.3)</td>
</tr>
<tr>
<td>Patients achieving MCID in all four measures</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>EASI and Peak Pruritus NRS and ACQ-5 and SNOT-22</td>
<td>5 (5.8)</td>
<td>16 (20.3)</td>
<td>26 (29.9)</td>
<td>47 (18.7)</td>
</tr>
</tbody>
</table>

n, number of patients with AD plus asthma plus sinonasal conditions, and with baseline ACQ-5 ≥ 0.5; EASI ≥ 6.7; Peak Pruritus NRS score ≥ 3, and SNOT-22 score ≥ 8.9, and achieving improvement in EASI ≥ 6.7 or NRS ≥ 3 or ACQ-5 ≥ 0.5 or SNOT-22 ≥ 8.9; n1, patients achieving specified score; q2w, every 2 weeks; qw, weekly.

*An MCID was ACQ-5 = 0.5; EASI = 6.7; Peak Pruritus NRS = 3; and SNOT-22 = 8.9. Missing EASI were imputed to 72; missing Peak Pruritus NRS scores were imputed to 10; missing ACQ-5 scores were imputed to 6; and missing SNOT-22 scores were imputed to 15.