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# Dupilumab Significantly Modulates Pain and Discomfort in Patients With Atopic Dermatitis: A Post Hoc Analysis of 5 Randomized Clinical Trials

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**Background:** Pain is a frequent symptom of atopic dermatitis (AD).

**Objectives:** The aims of the study were to evaluate the effects of dupilumab on pain/discomfort in AD and to determine whether pain correlates with other outcomes.

**Methods:** This was a post hoc analysis of 5 randomized, placebo-controlled clinical trials in which adults with chronic AD received placebo or dupilumab 300 mg every 2 weeks or once weekly with and without topical corticosteroids. Proportions of patients with no pain/discomfort on this dimension of the 5-dimension EuroQoL (EQ-5D) at week 16 (all trials) and week 52 (CHRONOS) were compared between placebo and dupilumab. Correlations were evaluated between pain/discomfort and signs and symptoms of AD.

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**Results:** Among 2632 evaluated patients, 72.9% to 83.1% reported at least moderate pain/discomfort at baseline. Higher proportions treated with dupilumab reported no pain/discomfort at week 16 relative to placebo; risk differences ranged from 22.3% (95% confidence interval = 11.5%–33.1%) to 42.2% (95% confidence interval = 26.6%–57.8%, all  $P \leq 0.0001$ ), with similar effects observed at week 52. Correlations at baseline of pain/discomfort with signs and symptoms of AD were low to moderate.

**Conclusions:** Pain/discomfort, present in a substantial proportion of patients with moderate-to-severe AD, was significantly reduced by dupilumab treatment. Given the low-to-moderate correlations with other AD symptoms at baseline, pain likely represents a distinct AD symptom.

**Trial Registration:** ClinicalTrials.gov identifiers NCT01859988, NCT02277743, NCT02277769, NCT02260986, and NCT02755649.

The pathophysiology of atopic dermatitis (AD) is characterized by skin barrier disruption and inflammation mediated by a type 2 immune response.<sup>1–4</sup> Itch (pruritus) is considered the cardinal symptom of AD<sup>5,6</sup> and has a well-recognized impact, affecting sleep, mental health, and health-related quality of life (HRQoL).<sup>7,8</sup> By contrast, pain has not been well characterized in patients with AD, despite being rated as very important by more than 80% of respondents in an international survey of more than 1000 patients with AD.<sup>6</sup> The lack of such information has been identified as an important research gap,<sup>9</sup> and control of pain, as well as other related sensations that may cause discomfort in patients with AD, such as burning and increased sensitivity to touch, remains an unmet need among patients with moderate-to-severe AD.

Emerging data from several studies suggest that pain in patients with AD is an important and potentially independent symptom that contributes to the disease burden.<sup>10–12</sup> Pain is among the top 3 most frequent symptoms associated with AD, which also include itching and sleep difficulties.<sup>5</sup> Pain is one of the most frequent words, identified through text mining analysis, that patients use to describe the impact of AD on their life,<sup>13</sup> and pain is a close second to itch among the AD symptoms that matter to patients when determining the effectiveness of treatment response.<sup>6</sup>

The presence of pain in substantial proportions of patients with AD has consistently been reported,<sup>5,10,11,14,15</sup> and it has been estimated that the prevalence of any pain from AD is 61%, with more than half of these patients (54.5%) reporting pain at least once per week.<sup>15</sup> In a clinic-based study that was specific to pain, somatic pain within the past week was reported by 42.7% of patients with AD regardless of AD severity, of whom 29.2% reported their pain as severe/very severe.<sup>10</sup> Although the reported prevalence of pain in this population was higher in patients with excoriations compared with those without (72.6% vs 57.6%,  $P = 0.02$ ), it should be noted that more than half of the patients without excoriations still reported pain. Another study in patients with AD and chronic itch reported hyperknesis (greater perception of provoked itch) and increased sensitivity to mechanically induced pain at both lesional and nonlesional skin sites,<sup>16</sup> suggesting that the pain may be independent of excoriations, or it might reflect centralization and receptive field recruitment.<sup>17</sup> A study from an international dermatology practice-based survey of patients with AD reported that 78% of patients had concomitant pain and itch, with approximately 15% of the participants reporting pain in both active lesions and nonlesional skin.<sup>11</sup>

Such emerging data on pain/discomfort in patients with AD suggest the need for greater understanding of these symptoms in AD, including their contribution to the disease burden and the effects of therapy on these outcomes. Dupilumab, a fully human monoclonal antibody that targets interleukin-4 receptor alpha (IL-4R $\alpha$ ) and inhibits both IL-4 and IL-13 signaling, has demonstrated significant reductions in itch as well as improvements in clinical and patient-reported outcomes in patients with moderate-to-severe AD in multiple clinical trials.<sup>18–23</sup> The objective of this study was to better understand pain in AD and its relationship to other AD outcomes using the pain/discomfort item of the 3-level version of the 5-dimension EuroQoL (EQ-5D-3L) instrument measured in clinical trials of dupilumab and to determine the effect of dupilumab therapy on this outcome.

## METHODS

### Study Design and Populations

Data included in this report are post hoc analyses from published randomized, double-blind, placebo-controlled trials that evaluated the efficacy and safety of dupilumab for the treatment of adults with moderate-to-severe AD. These studies included a phase 2b clinical trial (Study 1021, NCT01859988)<sup>18</sup> and 4 phase 3 trials: LIBERTY-AD SOLO 1 (NCT02277743) and SOLO 2 (NCT02277769),<sup>19</sup> LIBERTY-AD CHRONOS (NCT02260986),<sup>24</sup> and LIBERTY-AD CAFÉ (NCT02755649).<sup>22</sup> Although the study designs for these trials have previously been reported, brief summaries of relevant methods are provided hereinafter. The current analysis presents data for the placebo and dupilumab 300 mg weekly (qw) and every 2-week (q2w) treatment groups from each of the trials, although the phase 2b study also included other dose regimens.

For inclusion in all trials, patients were required to be adults (18 years or older) with chronic AD for 3 years or more before screening and to meet the following criteria at baseline: an Investigator's Global Assessment score of 3 or higher (on a 0- to 4-point Investigator's Global Assessment scale), corresponding to at least moderate disease; body surface area of AD involvement of 10% or greater; an Eczema Area and Severity Index (EASI) score of 16 or higher (phase 2b, SOLO 1&2, and CHRONOS) or 20 or higher (CAFÉ); and a Pruritus Numerical Rating Scale (NRS) average score for maximum itch intensity of 3 or more (SOLO 1&2,

CHRONOS). In the phase 2b study, patients with AD not adequately controlled by topical treatments, or for whom topical treatment was inadvisable, were randomized to 16 weeks of treatment<sup>18</sup>; SOLO 1 and SOLO 2 were identically designed 16-week monotherapy trials that consisted of populations similar to the phase 2b study.<sup>19</sup> CHRONOS was conducted to evaluate the long-term (52 weeks) efficacy and safety of dupilumab when used with concomitant topical corticosteroids (TCSs) with or without topical calcineurin inhibitors, as well as a documented recent history of inadequate response to medium- to high-potency TCS ( $\pm$  topical calcineurin inhibitor as appropriate).<sup>24</sup> These patients were randomized to 52 weeks of treatment with dupilumab + TCS, or placebo + TCS. The CAFÉ trial evaluated the efficacy and safety of dupilumab with concomitant TCS in adult patients whose disease was not adequately controlled with, or who were intolerant to, oral cyclosporine A, or for whom cyclosporine A was not medically advisable.<sup>22</sup> Patients were randomized to 16 weeks of treatment with dupilumab + TCS or placebo + TCS.

## Outcomes

The EQ-5D is the most commonly used standardized instrument for assessing generic HRQoL across a wide range of chronic conditions.<sup>25,26</sup> The EQ-5D-3L, which was included in all the dupilumab trials, consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), of which the pain/discomfort dimension is the focus of the current analysis. The 3 levels of response for this dimension are “no pain or discomfort,” “moderate pain or discomfort,” and “extreme pain or discomfort.” The evaluated outcome was percentage of patients who reported “no pain or discomfort” at the evaluated time points. The relationship between pain/discomfort and outcomes was also investigated using data that were pooled from the SOLO 1&2 + CHRONOS trials. This included AD signs (EASI, Scoring Atopic Dermatitis [SCORAD] total score, and individual signs), AD symptoms (peak pruritus NRS, Patient-Oriented Eczema Measure [POEM]),<sup>27</sup> HRQoL (Dermatology Life Quality Index [DLQI]),<sup>28</sup> and symptoms of anxiety and depression assessed using the Hospital Anxiety and Depression Scale (HADS),<sup>29</sup> which includes subscales for anxiety and depression.

## Statistical Analyses

Analyses were conducted using the full analysis set. Risk differences for proportions of patients who reported “no pain or discomfort” reflect dupilumab minus placebo, with 95% confidence interval (95% CI) calculated using normal approximation. Comparisons between the dupilumab and placebo groups were conducted using the Cochran–Mantel–Haenszel test; values after first rescue treatment used were set to missing (censoring), and patients with missing assessment were considered nonresponders.

The relationships between pain/discomfort and other outcomes were evaluated using Spearman rank correlation coefficients, which were estimated post hoc. These correlation analyses were conducted on baseline scores. In addition, for those patients who reported at least “moderate pain/discomfort” on the EQ-5D-3L at baseline,

correlations were assessed for changes from baseline in outcomes at week 16 for the combined patient population from SOLO 1&2 + CHRONOS trials. Spearman coefficients ( $r$ ) 0.10 to 0.29, 0.3 to 0.49, and greater than 0.50 indicate low, moderate, and strong associations, respectively.<sup>30</sup> Data were pooled across treatment arms and trials for the correlation analyses because the hypotheses being tested revolved around the relationship between improvements in pain and other outcomes regardless of why the improvement occurred (drug or placebo with or without TCS).

To further explore the relationship between pain/discomfort and scratching, that is, if scratching was a potential source of patient-reported pain/discomfort, baseline treatment groups were pooled in each study and evaluated for the proportions of patients who had each level of reported response for EQ-5D-3L pain/discomfort (no, moderate, and extreme) stratified by the level of severity on the SCORAD excoriation item. Similarly, the association of peak itch severity with pain/discomfort was evaluated at baseline from the data pooled from SOLO 1&2 + CHRONOS trials; itch severity was measured using a numerical rating scale with severity strata of 0 to 3 for no/mild, 4 to 6 for moderate, and 7 to 10 for severe itch.<sup>31</sup>

All analyses were conducted using SAS, version 9.2 or above (SAS Institute, Cary, NC).

## RESULTS

### Population Characteristics

In each of the trials, baseline demographic and disease characteristics were balanced across treatment groups (Table 1). The proportions of patients who reported moderate-to-extreme pain/discomfort at baseline on the EQ-5D-3L were generally similar across treatment groups and across the trials (Fig. 1) and ranged from 72.9% to 83.1%; “no pain/discomfort” was reported at baseline by less than a quarter of the patients, regardless of the trial or treatment arm (17.0%–24.1%).

### Impact of Dupilumab on Pain/Discomfort

The proportions of patients treated with dupilumab, with or without TCS, who reported “no pain/discomfort” on EQ-5D-3L after 16 weeks of treatment ranged from 51.4% to 70.1% for the 300 mg q2w dose, from 48.3% to 62.7% for the 300 mg qw dose, and from 19.7% to 37.0% for placebo with or without TCS (Fig. 2); risk differences ranged from 22.3% (95% CI = 11.5%–33.1%) to 42.2% (95% CI = 26.6%–57.8%, all  $P \leq 0.0001$ ). Both dupilumab treatment groups showed significant difference from placebo at week 1 in SOLO 1&2 and CAFÉ (Figs. 2B, C) that was sustained through the end of the study period. In CHRONOS, significant difference from placebo + TCS was observed at week 2 for dupilumab 300 mg qw + TCS and at week 4 for dupilumab 300 mg q2w + TCS (Fig. 2D), with these effects maintained over the 52 weeks; risk differences at week 52 were 33.5% (95% CI = 17.7%–49.2%) and 42.2% (95% CI = 26.6%–57.8%) for the dupilumab q2w and qw treatment groups, respectively (both  $P \leq 0.0001$ ).

**TABLE 1. Baseline Characteristics Among the Treatment Groups in the Phase 2b Dose Ranging, SOLO 1&2 (Pooled), CHRONOS, and CAFÉ Studies**

| Variable                                       | Phase 2b Dose Ranging  |                                     |                                    | SOLO 1&2 Pooled         |                                      |                                     | CHRONOS                          |   |  | CAFÉ                             |   |  |
|--|------------------------|-------------------------------------|------------------------------------|-------------------------|--------------------------------------|-------------------------------------|----------------------------------|---|--|----------------------------------|---|--|
|  | Placebo qw<br>(n = 61) | Dupilumab<br>300 mg q2w<br>(n = 64) | Dupilumab<br>300 mg qw<br>(n = 63) | Placebo qw<br>(n = 460) | Dupilumab<br>300 mg q2w<br>(n = 457) | Dupilumab<br>300 mg qw<br>(n = 462) | Placebo<br>qw + TCS<br>(n = 315) | Dupilumab<br>300 mg<br>q2w + TCS<br>(n = 106) | Dupilumab<br>300 mg<br>qw + TCS<br>(n = 319) | Placebo<br>qw + TCS<br>(n = 108) | Dupilumab<br>300 mg<br>q2w + TCS<br>(n = 107) | Dupilumab<br>300 mg<br>qw + TCS<br>(n = 110) |
| Age,<br>median<br>(IQR), y                     | 36<br>(27.0–46.0)      | 40<br>(30.0–48.0)                   | 34<br>(29.0–43.0)                  | 37.0<br>(26.0–49.0)     | 36.0<br>(27.0–47.0)                  | 36.0<br>(26.0–49.0)                 | 34.0<br>(25.0–45.0)              | 40.5<br>(28.0–49.0)                           | 34.0<br>(26.0–45.0)                          | 37.5<br>(29.0–49.0)              | 38.0<br>(25.0–47.0)                           | 38.0<br>(29.0–48.0)                          |
| Male sex, n<br>(%)                             | 40<br>(65.6)           | 41<br>(64.1)                        | 43<br>(68.3)                       | 250<br>(54.3)           | 267<br>(58.4)                        | 281<br>(60.8)                       | 193<br>(61.3)                    | 62<br>(58.5)                                  | 191<br>(59.9)                                | 68<br>(63.0)                     | 65<br>(60.7)                                  | 66<br>(60.0)                                 |
| Race, n (%)                                    |                        |                                     |                                    |                         |                                      |                                     |                                  |   |  |                                  |   |  |
| Asian  | 15<br>(24.6)           | 15<br>(23.4)                        | 13<br>(20.6)                       | 106<br>(23.0)           | 98<br>(21.4)                         | 96<br>(20.8)                        | 83<br>(26.3)                     | 29<br>(27.4)                                  | 89<br>(27.9)                                 | 2<br>(1.9)                       | 2<br>(1.9)                                    | 2<br>(1.8)                                   |
| Black/<br>African<br>American                  | 6<br>(9.8)             | 7<br>(10.9)                         | 5<br>(7.9)                         | 36<br>(7.8)             | 23<br>(5.0)                          | 35<br>(7.6)                         | 19<br>(6.0)                      | 2<br>(1.9)                                    | 13<br>(4.1)                                  | 0                                | 0   | 2<br>(1.8)                                   |
| White  | 40<br>(65.6)           | 40<br>(62.5)                        | 44<br>(69.8)                       | 302<br>(65.7)           | 320<br>(70.0)                        | 317<br>(68.6)                       | 208<br>(66.0)                    | 74<br>(69.8)                                  | 208<br>(65.2)                                | 104<br>(96.3)                    | 104<br>(97.2)                                 | 105<br>(95.5)                                |
| Other/not<br>reported/<br>missing              | 0                      | 2<br>(3.1)                          | 1<br>(1.6)                         | 16<br>(3.5)             | 16<br>(3.5)                          | 14<br>(3.0)                         | 5<br>(1.6)                       | 1<br>(0.9)                                    | 9<br>(2.8)                                   | 2<br>(1.9)                       | 1<br>(0.9)                                    | 1<br>(0.9)                                   |
| IGA score =<br>4, n (%)                        | 29<br>(47.5)           | 30<br>(46.9)                        | 31<br>(49.2)                       | 225<br>(48.9)           | 223<br>(48.8)                        | 218<br>(47.2)                       | 147<br>(46.7)                    | 53<br>(50.0)                                  | 147<br>(46.1)                                | 52<br>(48.1)                     | 50<br>(46.7)                                  | 52<br>(47.3)                                 |
| Body<br>surface<br>area,<br>median<br>(IQR), % | 44<br>(32.0–71.0)      | 57<br>(32.5–74.5)                   | 46<br>(30.0–66.0)                  | 54.5<br>(36.0–75.0)     | 51.0<br>(36.5–71.0)                  | 52.8<br>(37.0–70.8)                 | 55.5<br>(40.0–75.0)              | 58.8<br>(43.5–78.5)                           | 52.0<br>(36.0–71.5)                          | 53.0<br>(38.3–69.3)              | 55.0<br>(44.0–66.0)                           | 55.8<br>(41.5–68.0)                          |
| SCORAD<br>total<br>score,<br>median<br>(IQR)   | 65.3<br>(58.4–75.5)    | 69.0<br>(58.5–78.7)                 | 64.8<br>(54.4–75.5)                | 68.5<br>(58.3–78.1)     | 66.6<br>(56.5–76.7)                  | 66.8<br>(58.1–77.0)                 | 64.1<br>(55.9–76.1)*             | 69.7<br>(60.4–79.8) <sup>†</sup>              | 65.3<br>(55.2–76.3) <sup>‡</sup>             | 67.5<br>(58.5–76.6)              | 66.7<br>(61.1–76.2)                           | 66.1<br>(55.4–75.4)                          |
| EASI,<br>median<br>(IQR)                       | 30.5<br>(20.8–40.0)    | 33.5<br>(19.8–46.0)                 | 27.6<br>(21.6–36.9)                | 31.1<br>(22.2–42.6)     | 29.7<br>(21.1–40.5)                  | 29.4<br>(21.7–41.7)                 | 29.6<br>(22.2–40.8)              | 30.9<br>(22.3–41.6)                           | 29.0<br>(21.6–40.7)                          | 31.7<br>(24.2–40.7)              | 31.6<br>(25.2–39.2)                           | 31.1<br>(24.5–39.0)                          |

|   |                     |                     |                     |                     |                     |                     |                     |                     |                     |                                  |                     |                     |
|---|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|----------------------------------|---------------------|---------------------|
| Weekly average of peak daily pruritus NRS, median (IQR) | 6.3<br>(5.0–8.0)    | 7.1<br>(5.3–8.3)    | 6.6<br>(5.7–7.7)    | 7.7<br>(6.4–8.7)    | 7.7<br>(6.3–8.8)    | 7.7<br>(6.3–8.7)    | 7.6<br>(6.3–8.6)    | 7.7<br>(6.6–8.5)    | 7.4<br>(6.0–8.6)    | 6.9<br>(4.9–8.1)                 | 7.0<br>(5.4–8.0)    | 6.4<br>(5.2–7.7)    |
| DLQI, median (IQR)                                      | 12.0<br>(9.0–16.0)  | 13.0<br>(10.0–20.5) | 14.0<br>(9.0–22.0)  | 15.0<br>(9.0–21.0)  | 14.0<br>(9.0–20.0)  | 15.0<br>(9.0–21.0)  | 14.0<br>(9.0–20.0)  | 13.5<br>(8.0–20.0)  | 14.0<br>(8.0–20.0)  | 13.0<br>(7.0–19.5)               | 14.0<br>(8.0–22.0)  | 13.0<br>(7.0–21.0)  |
| POEM, median (IQR)                                      | 20.0<br>(17.0–25.0) | 22.5<br>(17.0–25.5) | 21.0<br>(17.0–26.0) | 22.0<br>(16.0–26.0) | 21.0<br>(17.0–25.0) | 21.0<br>(17.0–26.0) | 20.0<br>(16.0–25.0) | 21.0<br>(16.0–25.0) | 20.0<br>(16.0–25.0) | 19.0<br>(14.0–24.0) <sup>§</sup> | 20.0<br>(15.0–24.0) | 19.0<br>(14.0–24.0) |
| HADS-A score, median (IQR)                              | 6.0<br>(4.0–8.0)    | 8<br>(4.0–11.0)     | 7<br>(4.0–9.0)      | 7.0<br>(4.0–10.0)   | 7.0<br>(4.0–10.0)   | 7.0<br>(4.0–10.0)   | 6.0<br>(4.0–10.0)   | 7.5<br>(4.0–10.0)   | 7.0<br>(4.0–9.0)    | 7.0<br>(4.0–11.0)                | 6.0<br>(4.0–10.0)   | 6.0<br>(4.0–10.0)   |
| HADS-D score, median (IQR)                              | 4<br>(2.0–8.0)      | 6.5<br>(2.0–10.0)   | 5.5<br>(2.5–9.0)    | 5.0<br>(2.0–9.0)    | 5.0<br>(2.0–9.0)    | 6.0<br>(2.0–9.0)    | 5.0<br>(2.0–8.0)    | 5.0<br>(2.0–8.0)    | 5.0<br>(2.0–8.0)    | 5.0<br>(2.0–8.0)                 | 5.0<br>(2.0–9.0)    | 6.0<br>(2.0–9.0)    |

\**n* = 313.

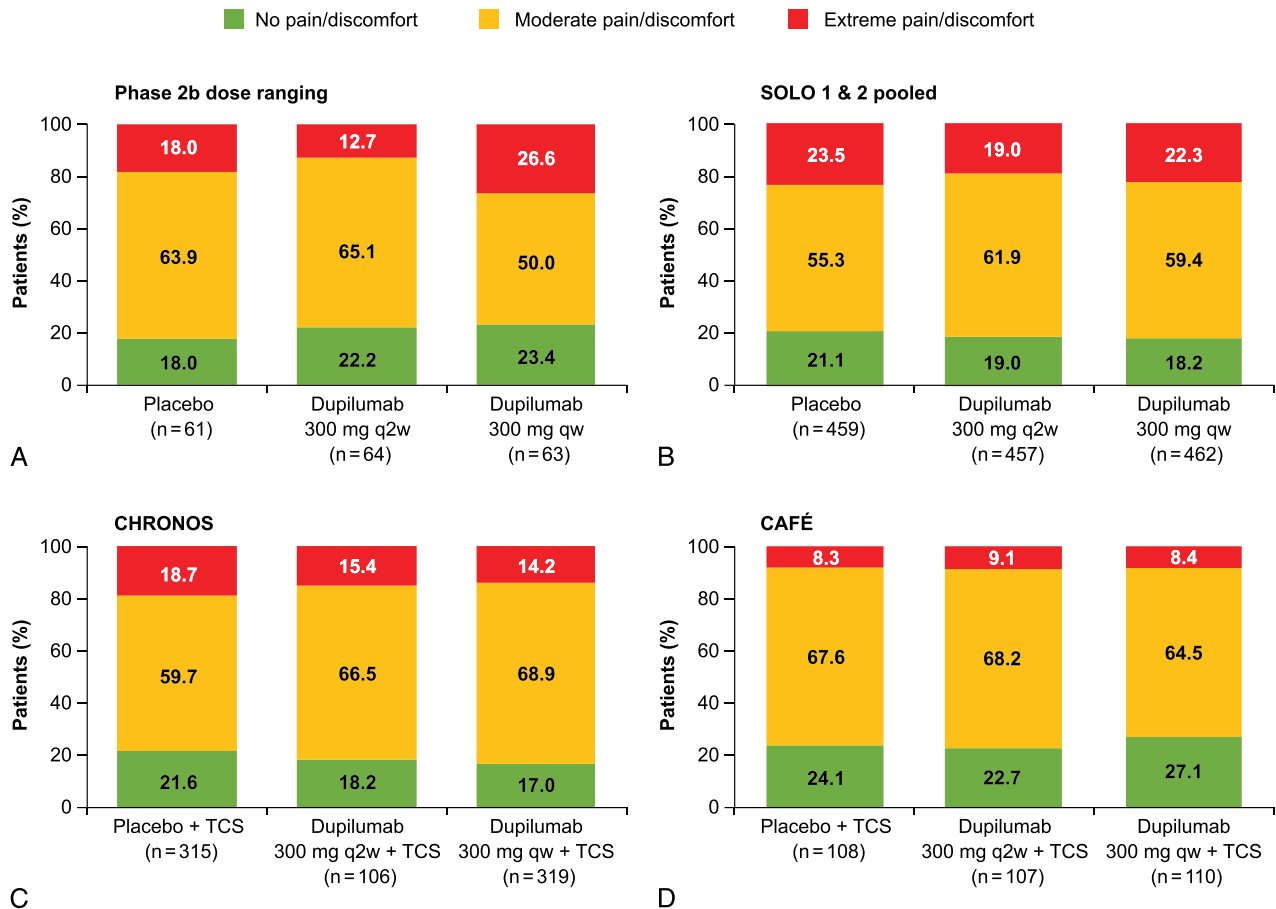
*†n* = 105.

*‡n* = 316.

*§n* = 107.

DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS-A, Hospital Anxiety and Depression Scale–Anxiety Subscale; HADS-D, Hospital Anxiety and Depression Scale–Depression Subscale; IGA, Investigator’s Global Assessment; IQR, interquartile range; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; qw, once weekly; q2w, every 2 weeks; SCORAD, Scoring Atopic Dermatitis; TCS, topical corticosteroid.





**Figure 1.** Pain/discomfort at baseline as reported by the patients on the EQ-5D pain/discomfort dimension.

### Correlation of Pain/Discomfort With Other AD Assessments

Correlations at baseline were weak between pain/discomfort and AD signs (EASI and SCORAD individual signs) and were of moderate strength for the total SCORAD score and other AD symptoms, including peak pruritus NRS and POEM (Table 2, Fig. 3). Baseline correlations were also moderate between pain/discomfort and HRQoL, as well as symptoms of anxiety and depression (Table 2). By contrast, among patients who had moderate-to-severe pain/discomfort at baseline, correlations of change in pain/discomfort at week 16 with changes in the total SCORAD score and the individual SCORAD signs were strong (Table 2). However, for other outcomes at week 16, the correlations between change in pain/discomfort ranged from weak (EASI, HADS-A) to moderate (POEM, DLQI, and HADS-D) strength (Table 2).

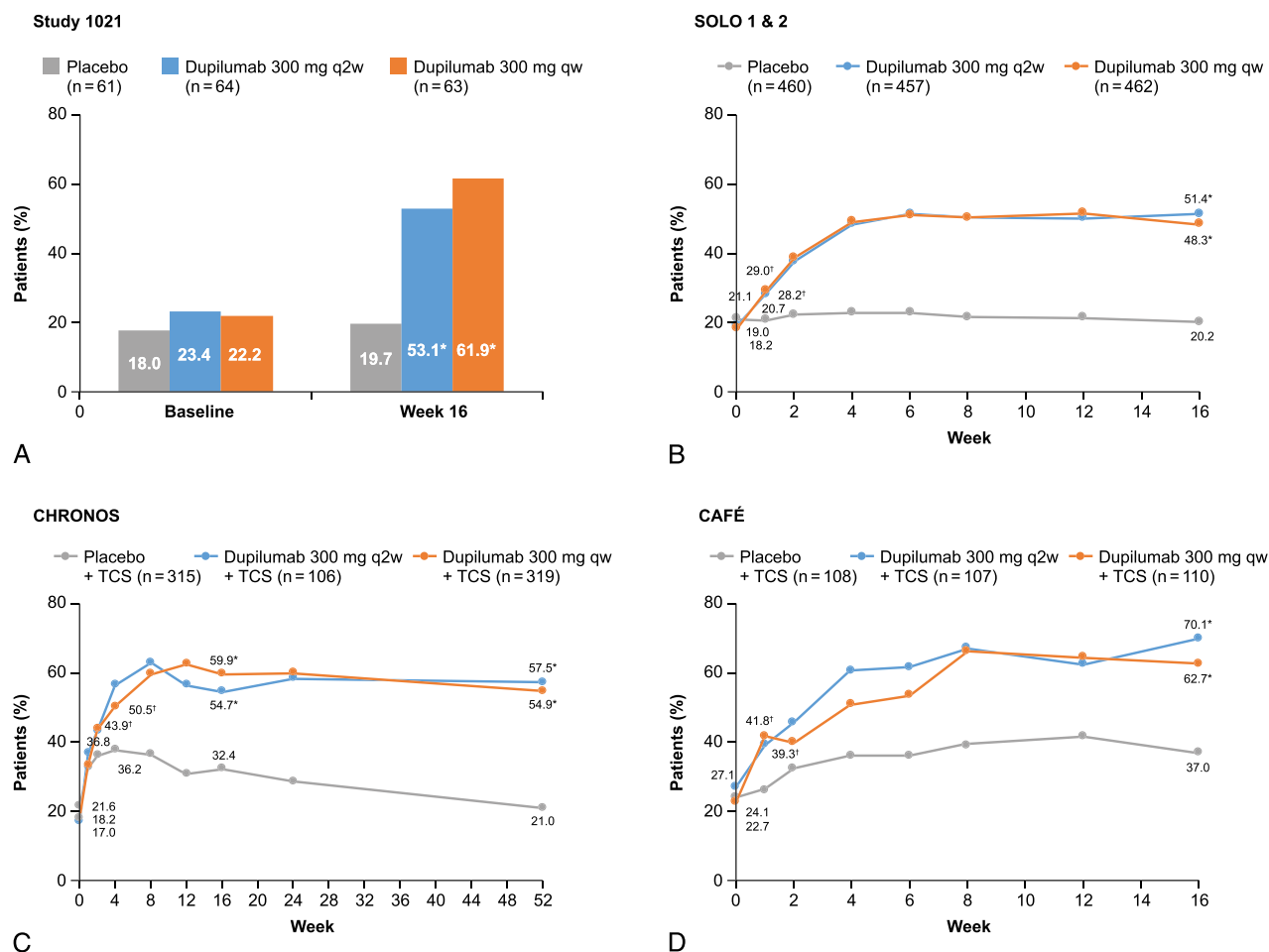
Pain/discomfort was reported by at least half of the patients, regardless of SCORAD excoriation severity, including 50.0% to 83.4% of the few patients who had no excoriations (Fig. 4). Except for a slightly higher proportion of patients with severe pain among the patients with severe SCORAD excoriations, the pattern of pain/discomfort in all 4 studies was generally similar across the excoriation

severity categories, with moderate pain/discomfort reported by 50.0% to 74.5% of the patients (Fig. 4).

### DISCUSSION

This study provides support for the presence of pain/discomfort in a substantial proportion of patients with AD. The lack of strong baseline correlations between pain/discomfort and other measures of AD signs and symptoms suggests that pain may be a distinct symptom in patients with AD and should be assessed independently, both as a measure of disease burden and as an outcome of treatment benefit. Such assessment is consistent with the recommendation of the Harmonizing Outcome Measures for Eczema group to explore the importance of pain in the treatment of AD.<sup>32</sup> The results of this study further suggest that treatment with dupilumab, with or without topical steroids, alleviates pain/discomfort in a significantly higher proportion of patients relative to placebo or TCS. Effects of dupilumab on pain/discomfort were consistently observed early after treatment initiation and were maintained throughout treatment duration, with most patients achieving no pain/discomfort at week 16.

In 2 recent cross-sectional studies of patients with AD from clinical practice settings in North America and Europe, higher pain severity



**Figure 2.** Proportions of patients who reported “no pain/discomfort” on the EQ-5D pain/discomfort dimension over the duration of the studies. Numbers are shown only for baseline, first significant time point versus placebo, week 16, and week 52 (CHRONOS). Values after first rescue treatment were set to missing (censored), and patients with missing responses at week 16 were considered nonresponders. \* $P \leq 0.0001$  and † $P < 0.05$  versus placebo.

was reported by the patients with more severe AD.<sup>33,34</sup> However, large SDs in pain scores in these studies suggest wide variability in presence and perceptions of pain across patients. The patient-reported burden of skin symptoms, HRQoL, sleep, and mental health increases with greater pain severity, with itch and pain showing additive effects.<sup>10</sup>

Pain/discomfort in AD is likely multifactorial, resulting from a variety of sources. These sources may include disease pathology, causing pain that is secondary to intense cutaneous inflammation or as an effect of broken (cracked, fissured, excoriated) skin, infections, and scratching in response to itch. However, it should be noted that a substantial proportion of patients reported pain/discomfort regardless of the presence and severity of excoriations indicative of scratching. Although a previous study found that patients commonly reported pain that originated from scratching,<sup>15</sup> the presence of moderate pain/discomfort in similar proportions of patients across excoriation severity categories in all studies suggests that such pain/discomfort is, at least in part, independent of scratching. Pain/discomfort may also potentially result from the stinging/burning after application of topical products, although

poor tolerability of topicals has been reported as a cause of pain in only a few (10%) of the patients with AD pain.<sup>15</sup>

Across the dupilumab phase 3 studies, correlations of pain/discomfort with AD individual signs and symptoms were weak at baseline, including for excoriations. These weak correlations support the hypothesis that pain/discomfort in patients with AD is not necessarily a secondary manifestation of scratching, lesions, or otherwise damaged skin. Correlations with DLQI and HADS were moderate at baseline.

At the end of treatment, improvement in pain/discomfort was strongly correlated with the total SCORAD and each of the SCORAD individual signs. Although the effects of pain on HRQoL are well recognized,<sup>35</sup> the stronger correlations at end of treatment relative to baseline between pain/discomfort and the total SCORAD and SCORAD individual signs may be suggestive of the overall effect of dupilumab treatment on the underlying disease rather than a direct relationship between these outcomes. Thus, evidence from this study and others suggests that treatment efficacy related to pain should be assessed independent of skin-related signs and symptoms,



**TABLE 2. Correlation Between EQ-5D-3L Pain/Discomfort Dimension With AD Outcomes Using Pooled Data From the SOLO 1&2 + CHRONOS Studies**

| Correlation                      | n    | Spearman <i>r</i> (95% CI) | <i>P</i> |
|----------------------------------|------|----------------------------|----------|
| Baseline scores                  |      |                            |          |
| SCORAD*                          |      |                            |          |
| Total score                      | 2119 | 0.317 (0.278–0.354)        | <0.0001  |
| Erythema                         | 2119 | 0.167 (0.125–0.208)        | <0.0001  |
| Edema/papulation                 | 2119 | 0.160 (0.118–0.201)        | <0.0001  |
| Oozing/crusting                  | 2119 | 0.125 (0.083–0.166)        | <0.0001  |
| Excoriation                      | 2119 | 0.150 (0.108–0.191)        | <0.0001  |
| Lichenification                  | 2119 | 0.068 (0.025–0.110)        | 0.0018   |
| Dryness                          | 2119 | 0.052 (0.009–0.094)        | 0.0176   |
| EASI                             | 2117 | 0.215 (0.174–0.256)        | <0.0001  |
| Peak pruritus NRS                | 2112 | 0.391 (0.354–0.426)        | <0.0001  |
| POEM                             | 2116 | 0.436 (0.401–0.470)        | <0.0001  |
| DLQI                             | 2117 | 0.477 (0.443–0.509)        | <0.0001  |
| HADS-A                           | 2045 | 0.328 (0.288–0.366)        | <0.0001  |
| HADS-D                           | 2045 | 0.370 (0.332–0.407)        | <0.0001  |
| Change from baseline at week 16† |      |                            |          |
| SCORAD*                          |      |                            |          |
| Total score                      | 1707 | 0.748 (0.726–0.768)        | <0.0001  |
| Erythema                         | 1707 | 0.628 (0.598–0.655)        | <0.0001  |
| Edema/papulation                 | 1707 | 0.644 (0.615–0.671)        | <0.0001  |
| Oozing/crusting                  | 1707 | 0.652 (0.624–0.678)        | <0.0001  |
| Excoriation                      | 1707 | 0.668 (0.641–0.693)        | <0.0001  |
| Lichenification                  | 1707 | 0.628 (0.599, 0.656)       | <0.0001  |
| Dryness                          | 1707 | 0.582 (0.550–0.613)        | <0.0001  |
| EASI                             | 1601 | 0.296 (0.251–0.340)        | <0.0001  |
| Peak pruritus NRS                | 1582 | 0.422 (0.381–0.462)        | <0.0001  |
| POEM                             | 1598 | 0.465 (0.426–0.503)        | <0.0001  |
| DLQI                             | 1600 | 0.462 (0.423–0.500)        | <0.0001  |
| HADS-A                           | 1548 | 0.267 (0.220–0.312)        | <0.0001  |
| HADS-D                           | 1546 | 0.338 (0.293–0.382)        | <0.0001  |

\*Missing scores were set to worst case for both pain and SCORAD.

†Patients with moderate-to-severe EQ-5D-3L pain/discomfort at baseline.

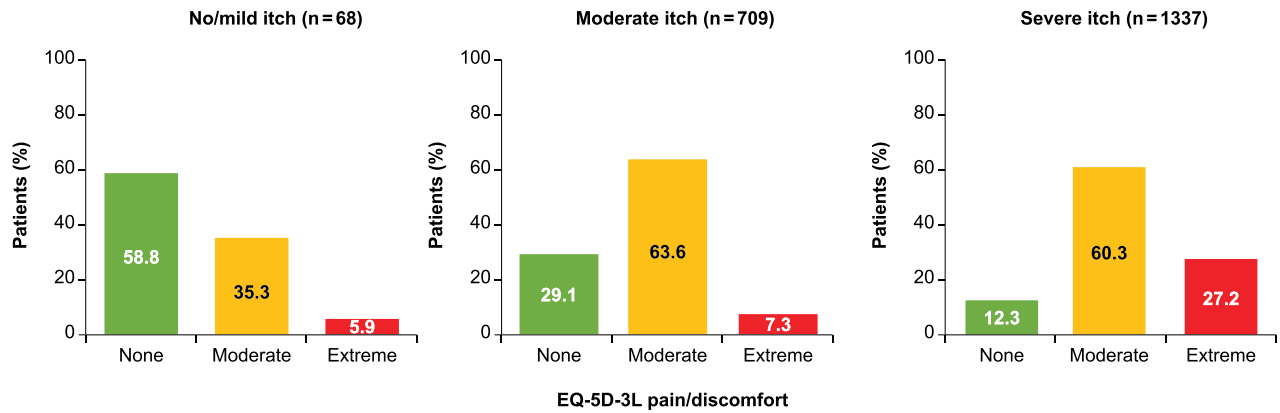
CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HADS-A, Hospital Anxiety and Depression Scale–Anxiety Subscale; HADS-D, Hospital Anxiety and Depression Scale–Depression Subscale; NRS, numerical rating scale; POEM, Patient-Oriented Eczema Measure; SCORAD, Scoring Atopic Dermatitis.

including itch; the nociceptive complaints in AD may be related to both peripheral and central neural sensitization that is common in inflammatory skin diseases.<sup>36,37</sup>

The mechanism by which dupilumab reduces pain in AD is not clear, but its demonstrated efficacy in AD stems from binding to IL-4Ra, thus inhibiting both IL-4 and IL-13 signaling pathways.<sup>38</sup> Dupilumab has been shown to significantly alleviate inflammatory skin lesions and help restore skin integrity<sup>39,40</sup>; reducing inflammation can be expected to result in lower levels of inflammatory mediators of pain, and skin integrity may protect sensory nerve endings against external nociceptive stimuli.

Mechanisms involved in the transduction and generation of itch and pain have been extensively reviewed,<sup>41–43</sup> and both IL-4 and IL-13 signaling pathways may be involved in nociceptive signal processing.<sup>44</sup> In addition, IL-4Ra seems to mediate chronic itch by sensitizing sensory neurons to pruritogens, with the type 2 inflammatory

cytokines IL-4 and IL-13 demonstrating an ability to activate itch-sensory pathways in human sensory neurons.<sup>45,46</sup> Because these neurons are nociceptors, the implication is that they can conduct both itch and pain signals. This overlap and crosstalk between itch and pain pathways may account for the observation that in patients with AD, stimuli that are normally painful have been reported to evoke itching.<sup>47,48</sup> This also suggests that by blocking IL-4 and IL-13 signaling in sensory neurons, dupilumab may potentially have a dual effect on itch and pain, which is supported by the recent report that molecular effects induced by dupilumab include downregulation of IL-31.<sup>40</sup> Interleukin-31 and its receptor have been shown to be associated with itch and pain signaling, with effects that suggest pain and itch pathways share nerve fibers.<sup>49,50</sup> Further analyses are warranted to explore the extent to which the effects of dupilumab on pain are direct or mediated through reduction of itch.

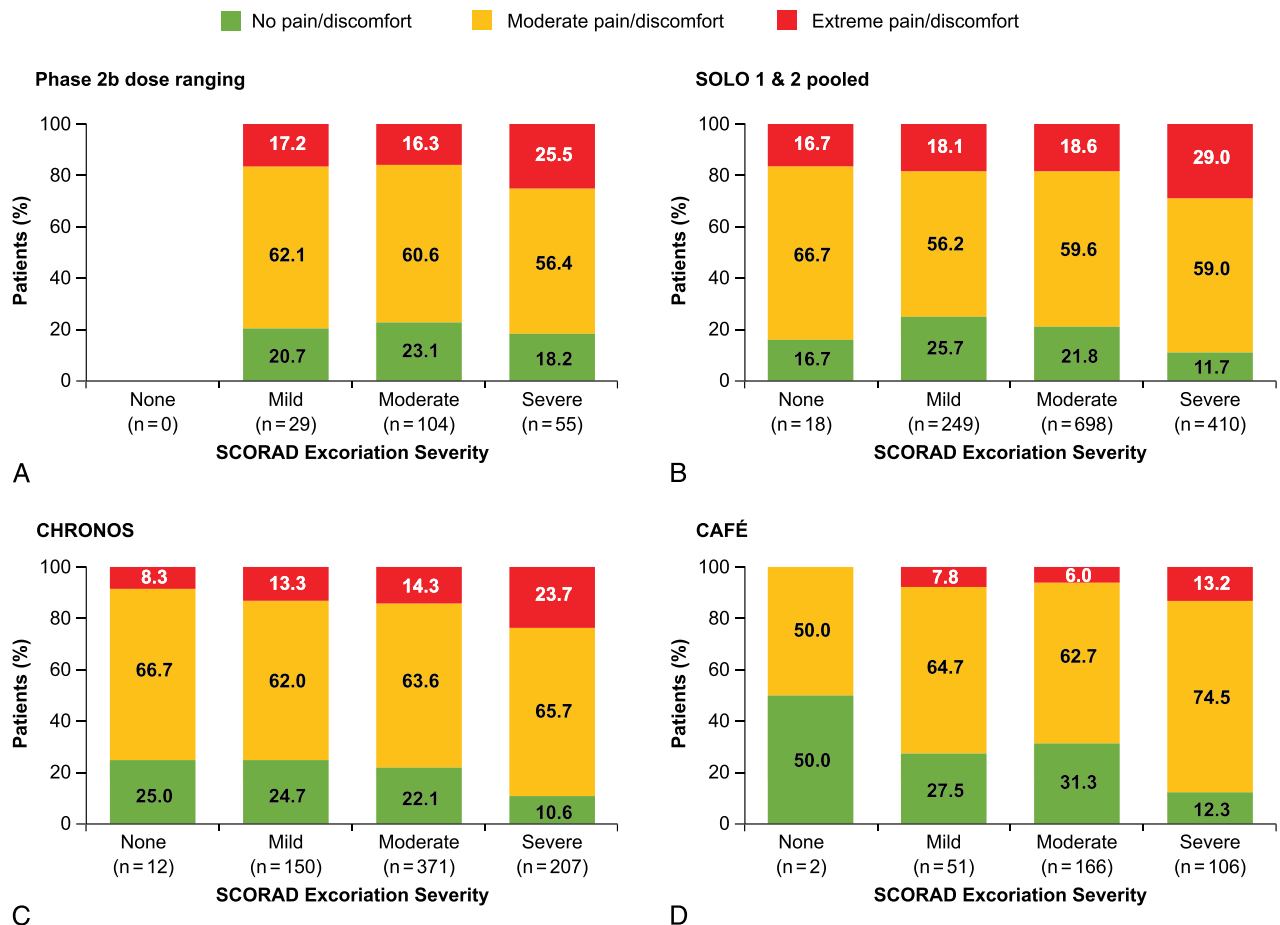


**Figure 3.** Association of peak itch severity with pain/discomfort using the baseline data pooled from the SOLO 1&2 + CHRONOS trials.

**Strengths and Limitations**

A key strength of this analysis is the ability to examine the prevalence and burden of pain and to evaluate the efficacy of dupilumab on pain, in a large international sample of 2632 patients with AD across multiple clinical trials conducted in 28 countries. In addition, concurrent assessment of several patient and clinician-reported

measures of AD signs, symptoms, and HRQoL allowed exploration of the relationship between pain and these other domains. A limitation of this study is the use of a broad assessment of pain/discomfort rather than a more specific assessment of skin pain. However, the results regarding the presence and impact of pain are consistent with recent studies that specifically assessed skin pain in patients with AD.<sup>10,11</sup>



**Figure 4.** Association of the SCORAD excoriation severity with pain/discomfort using the baseline data of pooled treatment groups.

## CONCLUSIONS

Observations across studies, including this report, suggest that pain is common in AD. Although pain may comprise part of a mechanistically overlapping spectrum of discomforting sensations that includes itch, it likely represents a distinct symptom of AD and is reported by a substantial proportion of patients with AD, regardless of the presence and severity of excoriations. Consistent results from multiple clinical trials demonstrated that dupilumab with and without TCS reduced pain/discomfort in adults with moderate-to-severe AD and that this reduction is likely to be, at least in part, independent of its effects on itch. Although further research is needed to enhance our understanding of pain in AD with regard to its prevalence and pathways of initiation and propagation, the overall implications of the accumulating data reflect the need for regular assessment of pain and its effects on AD, both in clinical trials and with regard to patient management strategies in clinical practice.

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