Dupilumab treatment results in early and sustained improvements in itch in adolescents and adults with moderate to severe atopic dermatitis: Analysis of the randomized phase 3 studies SOLO 1 and SOLO 2, AD ADOL, and CHRONOS

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Dupilumab treatment results in early and sustained improvements in itch in adolescents and adults with moderate to severe atopic dermatitis: Analysis of the randomized phase 3 studies SOLO 1 and SOLO 2, AD ADOL, and CHRONOS

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Disclosure: Dr Silverberg has been an investigator for AbbVie, AnaptysBio, Arena, Asana, Boehringer Ingelheim, Dermira, Dermavant, DS Biopharma, Eli Lilly, Galderma, GlaxoSmithKline, Glenmark, Kiniksa, LEO Pharma, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc, and Sanofi; a consultant for AbbVie, Eli Lilly, Galderma, Incyte, Kiniksa, LEO Pharma, Menlo Therapeutics, Pfizer, Realm, Regeneron Pharmaceuticals, Inc, and Sanofi; and a speaker for Regeneron Pharmaceuticals, Inc, and Sanofi. Dr Yosipovitch has been an advisory board member for AbbVie, Bayer, CeraVe, Eli Lilly, Galderma, Kiniksa, Menlo Therapeutics, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc, Sanofi, Sienna, and Trevi; and has received grants/research funding from Kiniksa, LEO Pharma, Pfizer, and Sun. Dr Simpson has been a consultant for AbbVie, Anacor, Celgene, Dermira, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, LEO Pharma, Medimmune, Menlo Therapeutics, Pfizer, Regeneron Pharmaceuticals, Inc, Sanofi, and Valeant Pharmaceuticals North America; and has received grants/research funding from Amgen, Anacor, Celgene, Chugai, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, Medimmune, Novartis, Pfizer, Regeneron Pharmaceuticals, Roivant, Sanofi, Tioga, and Vanda. Dr Kim has been a consultant for AbbVie, Concert, Incyte, Menlo Therapeutics, and Pfizer; served on the advisory board for Celgene, Kiniksa, Menlo Therapeutics, Regeneron Pharmaceuticals, Inc, Sanofi, and TheraVance Biopharma; holds stock in Gilead Sciences and Mallinckrodt; is the founder and chief scientific officer of Nuogen; and has received funding for research in the Kim laboratory from Celgene and LEO Pharma. Dr Wu has been an investigator for AbbVie, Amgen, Eli Lilly, Janssen, and Novartis; a consultant for AbbVie, Almirall, Amgen, Bristol-Myers Squibb, Celgene, Dermira, Dr Reddy’s Laboratories, Eli Lilly, Janssen, LEO Pharma, Novartis, Promius Pharma, Regeneron Pharmaceuticals, Inc, Sun Pharmaceutical, UCB, and Valeant Pharmaceuticals North America; and a speaker for AbbVie, Celgene, Novartis, Regeneron Pharmaceuticals, Inc, Sanofi Genzyme, Sun Pharmaceutical, UCB, and Valeant Pharmaceuticals North America. Drs Eckert, Guillemin, and Patel are employees of Sanofi and may hold stock and/or stock options in the company. Drs Chen, Ardeleanu, Bansal, Graham, and Gadkari are employees and shareholders of Regeneron Pharmaceuticals, Inc. Drs Kaur and Rossi are employees of Sanofi Genzyme and may hold stock and/or stock options in the company.

IRB approval status: Details of all 4 studies (SOLO 1 and 2: NCT02277743 and NCT02277769; CHRONOS: NCT02260986; AD ADOL: NCT03054428), along with primary efficacy and safety results, have been previously reported. All study documents and procedures were approved by the appropriate institutional review boards/ethics committees at each study site.

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Background: Pruritus (itch) is a cardinal symptom in atopic dermatitis (AD).

Objective: To evaluate the timing and effect of dupilumab on itch.

Methods: Analysis of data from 1505 patients with moderate to severe AD included in 4 randomized controlled studies, treated for up to 52 weeks. Adults received dupilumab 300 mg every 2 weeks or placebo monotherapy (SOLO 1: NCT02277743; SOLO 2: NCT02277769), with concomitant topical corticosteroids (CHRONOS: NCT02260986); adolescents (≥12 to <18 y) were treated with dupilumab monotherapy every 2 weeks (200 mg for baseline weight of <60 kg; 300 mg for baseline weight of ≥60 kg) or placebo (AD ADOL: NCT03054428).

Results: Dupilumab showed significant rapid improvements from baseline in daily Peak Pruritus Numerical Rating Scale scores versus placebo, by day 2 in adults and day 5 in adolescents. At treatment end, dupilumab vs placebo/control had greater least-squares mean percent change from baseline in the weekly average of Peak Pruritus Numerical Rating Scale scores: SOLO −47.5% vs −20.5%; AD-ADOL −47.9% vs −19.0%; CHRONOS −57.3% vs −30.9% (P < .0001 for all).

Limitations: Short duration of monotherapy trials (16 weeks).

Conclusion: Across 4 randomized trials, dupilumab treatment showed rapid and sustained improvements in the magnitude of itch, starting with first dose; responses progressively increased and were sustained through to the end of treatment, up to 1 year. (J Am Acad Dermatol 2020;82:1328-36.)

Key words: adolescents; adults; atopic dermatitis; CHRONOS; dupilumab; itch; LIBERTY; SOLO.

Atopic dermatitis (AD) is a chronic skin disease that affects 5% to 10% of adults and 0.2% to 24.6% of adolescents (13-17 years of age). AD is characterized by disruption of the skin barrier and up-regulation of type 2 immune responses. Pruritus (itch) is the hallmark and most burdensome symptom of AD. Itch profoundly affects patients’ daily lives and causes sleep disruption; these negative outcomes are worse with more severe itch.

Dupilumab, the first targeted systemic therapy for AD, is a fully human, VelocImmune-derived (Regeneron, Tarrytown, NY) monoclonal antibody that inhibits signaling of both interleukin (IL)-4 and IL-13, key inflammatory type 2 cytokines that drive type 2 inflammatory diseases such as AD and related asthma, allergic rhinitis, and food allergies. Dupilumab is approved in the United States for subcutaneous administration every 2 weeks for the treatment of patients aged 12 years and older with moderate to severe AD inadequately controlled with topical prescription therapies or for whom those therapies are not advisable, in Japan for the treatment of adult patients with AD not adequately controlled with existing therapies, and in the European Union for use in adults with moderate to severe AD who are candidates for systemic therapy. Dupilumab is also approved by the US Food and Drug Administration as an add-on maintenance treatment in patients aged 12 years or older with moderate to severe asthma with an eosinophilic phenotype or oral corticosteroid-dependent asthma regardless of eosinophilic phenotype. Finally, dupilumab is approved by the US Food and Drug Administration as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps.

In phase 3 trials in adults and adolescents (NCT02277743, NCT02277769, NCT02260986, and NCT03054428) with moderate to severe AD, dupilumab improved AD signs and symptoms, including skin lesions, patient quality of life, and psychological health. Safety data for the LIBERTY AD SOLO 1 and SOLO 2, LIBERTY AD ADOL, and LIBERTY AD...
CHRONOS studies showed dupilumab to be generally well tolerated, with an acceptable safety profile.17,18,20

The objective of this article is to report the timing, magnitude, and sustainability of the effect of dupilumab on different measures of itch, using data from 3 phase 3 trials of dupilumab in adults with moderate to severe AD and 1 phase 3 trial in adolescents with moderate to severe AD.

METHODS

Detailed descriptions of the study populations and methodology were previously published and are briefly summarized.17,18,20

Study design

LIBERTY AD SOLO 1 (NCT02277743) and SOLO 2 (NCT02277769) were 2 identically designed phase 3 randomized, multicenter, double-blind, placebo-controlled trials in adults with moderate to severe AD. LIBERTY AD ADOL (NCT03054428) was a phase 3 randomized, multicenter, double-blind, parallel-group, placebo-controlled trial in adolescents (aged ≥12 to <18 years) with moderate to severe AD. In these 3 trials, patients received dupilumab or placebo monotherapy for 16 weeks. LIBERTY AD CHRONOS (NCT02260986) was a phase 3 randomized, multicenter, double-blind, placebo-controlled trial in adults with moderate to severe AD in which patients were randomly assigned to receive dupilumab with topical corticosteroids (TCSs) or placebo with TCSs (control) for 52 weeks.

Ethics

All studies were conducted following the ethical principles of the Declaration of Helsinki, consistent with those of the International Council on Harmonisation Guidelines for Good Clinical Practice and local applicable regulatory requirements. All patients or their legal guardians provided written informed consent before undertaking any study procedures.

Patients

Detailed inclusion and exclusion criteria for all 4 studies were described previously.17,18,20 Patients enrolled in all 4 studies were adults (aged ≥18 years) or adolescents (aged ≥12 to <18 years) with moderate to severe AD, with chronic AD present for 3 or more years before screening in adults and at least 1 year in adolescents.

Outcomes assessed in this analysis

The Peak Pruritus Numerical Rating Scale (PP-NRS) is a well-defined, valid, and reliable, single-item measure to evaluate patient-reported intensity of the worst itch in the previous 24 hours on a scale of 0 to 10 (with 0 being no itch and 10 being worst itch imaginable) in adults with moderate to severe AD.21 The measure was completed daily from baseline through to week 16 in SOLO 1 and 2, AD ADOL, and CHRONOS, and weekly from week 17 to week 52 in CHRONOS, by using the ClinPhone (Parexel, Waltham, MA) interactive voice response system for SOLO 1 and 2 and CHRONOS, and an eDiary for AD ADOL. Patients were instructed to call in at about the same time on each scheduled data entry day between the hours of 5 AM and 11 PM. Clinically relevant within-person meaningful response was defined as a change from baseline of at least 2 to 4 points in the PP-NRS score.21 PP-NRS endpoints assessed in this analysis included the change in the daily PP-NRS score from baseline to week 2 (SOLO and AD ADOL only); proportions of patients with at least a 3- or 4-point improvement in the daily PP-NRS score from baseline to week 2 (SOLO and AD ADOL only); least-squares (LS) mean/percent change from baseline in the weekly average of the PP-NRS score at week 2, week 4, week 16 (all 4 studies), or week 52 (CHRONOS only); and the proportion of patients with at least a 3- or 4-point improvement from baseline in the weekly average of the PP-NRS score at week 2, week 4, week 16 (all 4 studies), and week 52 (CHRONOS only).

The Patient-Oriented Eczema Measure (POEM) is a 7-item, validated, patient-derived questionnaire used to assess the frequency of disease symptoms in children and adults with AD, and it includes an assessment of itch (item 1).22,23 The POEM endpoint presented in this article is the proportion of patients within each response category for the itch-related question Over the last week, on how many days has your skin been itchy because of your eczema? at week 16.

Both the PP-NRS and the POEM instruments are recommended for use in clinical trials by the Harmonising Outcome Measures for Eczema group.24

Statistical analysis

For the SOLO studies, efficacy data through week 16 were pooled for the dupilumab 300 mg every 2 weeks and placebo groups through week 16; for the AD ADOL and CHRONOS studies, data were collected through week 16 and week 52, respectively. Analyses were carried out with the full analysis set, which included all randomized patients.

Detailed descriptions of the statistical analyses for the primary and secondary endpoints of all 4 individual studies have been published.
Previously, Continuous endpoints were analyzed with an analysis of covariance model, with baseline measurement as the covariate and treatment, region (SOLO and CHRONOS only), baseline weight (AD ADOL only), and baseline Investigator’s Global Assessment strata as fixed factors. Categorical endpoints were analyzed with the Cochran-Mantel-Haenszel test adjusted by randomization strata (Investigator’s Global Assessment of 3/4 and region).

All analyses were performed with SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Patients

A total of 1379 adults were enrolled in SOLO 1 and 2 and received monotherapy, 251 adolescents were randomized in AD ADOL, and 740 adults received concomitant TCSs in CHRONOS. This article presents data for the control arm and the approved dupilumab every 2 weeks treatment groups. A total of 1505 patients were included in the analysis, and 645 of these received treatment with dupilumab every 2 weeks. Baseline demographics and disease characteristics for patients enrolled in SOLO 1, SOLO 2, AD ADOL, and CHRONOS were generally balanced among treatment groups.\(^{17,18,20}\)

Onset of action of dupilumab on itch

The dupilumab 300 mg every 2 weeks regimen showed a statistically significantly greater LS mean percent change improvement from baseline in daily itch versus placebo as early as day 2 in adults in SOLO pooled \((P < .01)\) and at day 5 in adolescents in AD ADOL \((P < .05)\) (Fig 1). The proportion of patients treated with dupilumab with at least a 3-point improvement from baseline in daily PP-NRS scores was significantly higher versus placebo as early as day 4 in SOLO pooled \((P < .01)\) and day 13 in AD ADOL \((P < .05)\) (Fig 2). Similarly, the proportion of patients treated with dupilumab with at least a 4-point improvement from baseline in daily PP-NRS scores was significantly higher versus placebo as early as day 4 \((P < .01)\) in SOLO pooled and day 7 \((P < .05)\) in AD ADOL (data not shown).

The efficacy of dupilumab on itch intensity

LS mean change and percent change from baseline in the weekly average of PP-NRS scores was significantly greater \((P < .05)\) in the dupilumab treatment groups versus placebo across all mono-therapy studies (SOLO pooled and AD ADOL) or versus control (CHRONOS) (Table 1). Significant improvements were observed versus placebo (SOLO pooled, AD ADOL) or control (CHRONOS) at all timepoints assessed \((P < .05)\) and were mostly progressively improving or maintained through week 16 (all studies, \(P < .0001\)) and week 52 (CHRONOS, \(P < .0001\)).

Similarly, the proportions of patients treated with dupilumab with at least a 3- or 4-point improvement from baseline in the weekly average of PP-NRS
scores were significantly greater versus placebo or control at all presented timepoints in SOLO pooled, AD ADOL, and CHRONOS ($P < .01$), except week 2 in AD ADOL (Table 1).

**Analysis of responses on the POEM itch question**

At baseline in all trials and across all treatment groups, most patients reported having itch every day of the past week (Fig 3). At week 16 in all trials, patients treated with dupilumab showed more pronounced improvements in responses given on the POEM itch question than those treated with placebo (SOLO pooled, AD ADOL) or control (CHRONOS), with more patients reporting 0 or 1 to 2 days with itch compared with baseline. These results were sustained through week 52 of CHRONOS, when a slight increase in patients reporting 0 or 1 to 2 days with itch was seen with dupilumab plus TCSs, and a small decrease was seen with control, compared with week 16 results.

**DISCUSSION**

Dupilumab with or without TCSs significantly improved itch in adult and adolescent patients with moderate to severe AD, consistent with previous phase 2 studies. Dupilumab showed a clinically meaningful improvement in itch versus placebo after the first dose in adults and adolescents across all trials. Furthermore, significant improvements were seen in the dupilumab versus placebo or dupilumab versus control groups in both the PP-NRS and the POEM Itch components, showing a consistent effect on itch with the first dose of dupilumab treatment. Although a high initial response was seen with control in the CHRONOS trial, the difference in response versus the dupilumab plus TCS group increased at later timepoints of the trial, when the benefit of dupilumab plus TCS treatment became more evident.

The key type 2 cytokines IL-4 and IL-13 are involved in atopic itch indirectly by activating IL-4 receptor $\alpha$ (IL-4R$\alpha$) and promoting thymic stromal lymphopoietin expression, which leads to activation of pruritoceptive receptors. IL-4 can also act as a sensitizer to other pruritogens, such as IL-31, by interaction with itch-sensory neurons; recent findings suggest that IL-4 mediates up-regulation of IL-31 receptor $\alpha$. By interacting with IL-4R$\alpha$ and blocking the effects of IL-4 and IL-13, dupilumab can serve to reduce atopic itch in addition to its effect on type 2 inflammation. Finally, the presence of IL-4R$\alpha$ on neurons from the dorsal root ganglia in mice (implicated in chronic itch) could explain the rapid onset of dupilumab on itch through inhibition of the receptor.

Itch is the most burdensome symptom of AD, with a direct impact on daily activities. Atopic itch has been associated with a decrease in quality of life, both directly and through sleep disturbance. In multiple studies in patients with moderate to severe AD, dupilumab treatment was shown to improve
Table I. PP-NRS scores in moderate to severe atopic dermatitis: weekly averaged endpoints

<table>
<thead>
<tr>
<th></th>
<th>SOLO pooled</th>
<th>AD ADOL</th>
<th>CHRONOS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Dupilumab</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>(n = 460)</td>
<td>300 mg q2w (n = 457)</td>
<td>(n = 85)</td>
</tr>
<tr>
<td>LS mean change from baseline in PP-NRS (SE), P value vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>-0.39 (0.078)</td>
<td>-1.57 (0.077), &lt;.0001</td>
<td>-0.65 (0.172)</td>
</tr>
<tr>
<td>Week 4</td>
<td>-0.85 (0.097)</td>
<td>-2.39 (0.093), &lt;.0001</td>
<td>-1.05 (0.217)</td>
</tr>
<tr>
<td>Week 16</td>
<td>-1.61 (0.132)</td>
<td>-3.52 (0.117), &lt;.0001</td>
<td>-1.54 (0.303)</td>
</tr>
<tr>
<td>Week 52</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LS mean percent change from baseline in PP-NRS (SE), P value vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>-4.4 (1.18)</td>
<td>-21.5 (1.17), &lt;.0001</td>
<td>-7.5 (2.48)</td>
</tr>
<tr>
<td>Week 4</td>
<td>-10.3 (1.49)</td>
<td>-32.9 (1.43), &lt;.0001</td>
<td>-12.5 (3.06)</td>
</tr>
<tr>
<td>Week 16</td>
<td>-20.5 (1.92)</td>
<td>-47.4 (1.71), &lt;.0001</td>
<td>-19.0 (4.09)</td>
</tr>
<tr>
<td>Week 52</td>
<td>NA</td>
<td>NA</td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Proportion of patients with an improvement of ≥3 points from baseline in PP-NRS, n/N1 (%), P value vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>23/447 (5.1)</td>
<td>77/451 (17.1), &lt;.0001</td>
<td>7/85 (8.2)</td>
</tr>
<tr>
<td>Week 4</td>
<td>53/447 (11.9)</td>
<td>161/451 (35.7), &lt;.0001</td>
<td>9/85 (10.6)</td>
</tr>
<tr>
<td>Week 16</td>
<td>67/447 (15.0)</td>
<td>220/451 (48.8), &lt;.0001</td>
<td>8/85 (9.4)</td>
</tr>
<tr>
<td>Week 52</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportion of patients with an improvement of ≥4 points from baseline in PP-NRS, n/N2 (%), P value vs placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 2</td>
<td>9/433 (2.1)</td>
<td>44/438 (10.0), &lt;.0001</td>
<td>4/84 (4.8)</td>
</tr>
<tr>
<td>Week 4</td>
<td>27/433 (6.2)</td>
<td>85/438 (19.4), &lt;.0001</td>
<td>4/84 (4.8)</td>
</tr>
<tr>
<td>Week 16</td>
<td>47/433 (10.9)</td>
<td>168/438 (38.4), &lt;.0001</td>
<td>4/84 (4.8)</td>
</tr>
<tr>
<td>Week 52</td>
<td>NA</td>
<td>NA</td>
<td></td>
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</table>

LS, Least squares; N1, number of patients with a PP-NRS score of at least 3 at baseline; N2, number of patients with a PP-NRS score of at least 4 at baseline; NA, not assessed; PP-NRS, Peak Pruritus Numerical Rating Scale; q2w, every 2 weeks; SE, standard error; TCS, topical corticosteroid.
quality of life and patient sleep, as well as symptoms of anxiety and depression. Although a correlation analysis between itch reduction and quality of life or sleep disturbance was not among the objectives of this article, part of the improvement seen with dupilumab in these measures of AD burden is likely attributable to improvement in itch. This is supported by an analysis of data from a smaller trial of dupilumab in adults with moderate to severe AD, which showed significant correlation between itch reduction and improvement in health-related quality of life.

The PP-NRS instrument measures itch intensity in the previous 24 hours, whereas POEM measures itch frequency in the previous week. In this analysis, patients treated with dupilumab reported improvements in itch with both instruments, showing a comprehensive effect on both the intensity of the worst itch and the frequency of itching episodes. Previously, significant improvements in itch were also reported for dupilumab by using the Scoring Atopic Dermatitis (SCORAD) Itch Visual Analog Scale score versus placebo, which has a recall period of 3 days. Assessment of the SCORAD Visual Analog Scale itch data from 4 dupilumab trials showed that a majority of patients treated with dupilumab achieved no or mild pruritus by the end of treatment.

Coupled with the long-term favorable safety of dupilumab treatment, these results support the notion that treatment with dupilumab provides rapid improvements and sustained itch control for long periods of time.

Most adults enrolled in these trials had AD for more than 20 years, whereas adolescents had a mean disease duration of more than 14 years. Although the rapid onset of effect on itch is highly beneficial in those patients who had AD for large parts of their life, this beneficial effect was also comprehensive (including clinically meaningful responses, assessed by at least a 3- or 4-point improvement in PP-NRS score) and sustained through the end of treatment, coupled with a favorable safety profile. Although not as detailed as the analyses presented here, comprehensive dupilumab effects on pruritus were also shown in adults among different racial subgroups (white, Asian, and black/African American) and among Japanese patients.

The very rapid effect on itch in these trials might be explained by the administration of a dupilumab loading dose on day 1 of the trials, because the loading dose allows systemic concentrations to reach a steady state more quickly.

The strength of this analysis lies in the fact that data were analyzed from prospective, randomized, placebo-controlled studies and that a large number of patients were evaluated in these analyses, totaling 1505 patients across all treatment groups and studies, including 645 patients treated with dupilumab every 2 weeks. To date, to our knowledge, this is the largest analysis of itch associated with AD.
The analysis is limited by the short duration of treatment in the SOLO and AD ADOL trials, in which treatment was administered for only 16 weeks; however, itch outcomes were sustained long-term in the 52-week CHRONOS trial. Another limitation is the fact that daily PP-NRS analyses (compared with weekly averaged analyses) were post hoc and were not statistically powered in any of these trials. Moreover, the number of patients studied in the adolescent trial was relatively small compared with the number of adults, and this could have led to the delayed achievement of statistically significant improvements in this population compared with adults.

CONCLUSIONS

Dupilumab versus placebo showed significant improvements in itch as early as day 2 in adult patients with AD and day 5 in adolescent patients with AD, and responses were sustained through the end of treatment. These results support the role of dupilumab in improving itch outcomes associated with moderate to severe AD, starting with the first dose of treatment and providing long-term sustained control.

REFERENCES


