Dupilumab Efficacy and Safety in Adolescents with Moderate-to-Severe Atopic Dermatitis: Results from a Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel-Group, Phase 3 Study

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Disclosures
AbbVie, Anacor Pharmaceuticals, Celgene, Dermira, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, Leo Pharma, MedImmune, Menlo Therapeutics, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, Valeant Pharmaceuticals International, Inc. – consultant; Amgen, Anacor Pharmaceuticals, Celgene, Chugai Pharma USA, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, MedImmune, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Roivant Sciences, Sanofi, Tioga Pharmaceuticals, Inc., Vanda Pharmaceuticals, Inc. – grants/research funding.

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Background

- Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with atopic comorbidities\(^1\)
- Among adolescents, the estimated prevalence of AD is 8.6% in the USA,\(^2\) 10–15% in the UK,\(^3\) and ≤ 5–10% in most European countries\(^3\)
- AD profoundly affects quality of life of adolescents and family members\(^4\)
  - Itching affects mood and sleep quality
  - Patients commonly have behavioral problems (anxiety, depression)
  - Chronic and relapsing nature of the disease negatively affects family quality of life
- Limited treatment options are available for adolescents\(^5\)–\(^7\)
  - No systemic agent currently provides a favorable long-term benefit–risk profile for pediatric patients with AD inadequately controlled by topical therapies

Dupilumab: mechanism of action

- **Dupilumab** is a fully human *VelocImmune*-derived® monoclonal antibody directed against the IL-4Ra subunit of the IL-4 and IL-13 receptors\(^1\)

- **IL-4** and **IL-13** are type 2 cytokines that mediate many features of AD\(^1\)

- **Dupilumab** is approved in the EU for treatment of moderate-to-severe AD in adults who are candidates for systemic therapy and can be used with or without topical corticosteroids

\(\gamma_c\), common gamma chain; IL, interleukin; R, receptor; JAK, Janus kinase; STAT, signal transducer and activator of transcription; TYK2, tyrosine kinase type 2.

Objectives and study endpoints

Objectives

- To evaluate the efficacy and safety of dupilumab monotherapy versus placebo in adolescents with moderate-to-severe AD inadequately controlled by topical therapies

Study endpoints

- Co-primary
  - Proportion of patients with IGA score 0 or 1 at Week 16
  - Proportion of patients with EASI-75 at Week 16 (key secondary endpoint in USA)
- Key secondary
  - Percent change in EASI and peak pruritus NRS scores at Week 16
  - Proportion of patients with ≥ 3- or ≥ 4-point reduction in peak pruritus NRS score at Week 16
- Other secondary
  - EASI-50, EASI-90, percent change in SCORAD score, and changes in CDLQI, POEM, and HADS scores at Week 16

CDLQI, Children’s Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI-50/(-75)/(-90), ≥ 50%(75%)(90%) improvement from baseline in EASI score; HADS, Hospital Anxiety and Depression Scale; IGA, Investigator’s Global Assessment; POEM, Patient-Oriented Eczema Measure; NRS, Numerical Rating Scale; SCORAD, SCOring Atopic Dermatitis.
AD-1526: randomized, double-blind, placebo-controlled, parallel-group phase 3 trial of dupilumab in adolescents with moderate-to-severe AD

<table>
<thead>
<tr>
<th>Day –35 to Day –1</th>
<th>Baseline</th>
<th>Week 16</th>
<th>Week 28</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Age 12–17 years</td>
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<td></td>
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</tr>
<tr>
<td>• Moderate-to-severe AD</td>
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<td></td>
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<tr>
<td>• AD inadequately controlled by topical therapies</td>
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<tr>
<td>• Scores on IGA ≥ 3, EASI ≥ 16, pruritus NRS ≥ 4; BSA involvement ≥ 10%</td>
<td></td>
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<tr>
<td><strong>Washout</strong></td>
<td></td>
<td></td>
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<tr>
<td>• Prior medication</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Stratification</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• Body weight (&lt; 60 kg vs ≥ 60 kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• IGA score (3 vs 4)</td>
<td></td>
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</tr>
</tbody>
</table>

Loading dose on Day 1

- Placebo (n = 85)
- Dupilumab q4w 300 mg SC (n = 84)
- Dupilumab q2w 200 or 300 mg SC (n = 82)

Treatment period (16 weeks)

- Post-treatment options
  - Open-label extension
  - Safety follow-up through Week 28

Follow-up period (12 weeks)

- Baseline
- Week 16
- Week 28

Topical therapy and other systemic AD therapies were prohibited but allowed as rescue treatment for intolerable symptoms

Day 1

- 600 mg on Day 1.
- Patients with body weight < 60 kg at baseline received 200 mg after a loading dose of 400 mg on Day 1.

BSA, body surface area; q2w, every 2 weeks; q4w, every 4 weeks; R, randomization; SC, subcutaneous.
## Baseline demographics and characteristics

<table>
<thead>
<tr>
<th>Score range</th>
<th>Placebo (n = 85)</th>
<th>Dupilumab 300 mg q4w (n = 84)</th>
<th>Dupilumab 200 or 300 mg q2w (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>–</td>
<td>14.5 (1.8)</td>
<td>14.4 (1.6)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>–</td>
<td>53 (62.4)</td>
<td>52 (61.9)</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>–</td>
<td>12.3 (3.4)</td>
<td>11.9 (3.2)</td>
</tr>
<tr>
<td>Patients with IGA score 4, n (%)</td>
<td>0–4</td>
<td>46 (54.1)</td>
<td>46 (54.8)</td>
</tr>
<tr>
<td>EASI score</td>
<td>0–72</td>
<td>35.5 (14.0)</td>
<td>35.8 (14.8)</td>
</tr>
<tr>
<td>Peak pruritus NRS score</td>
<td>0–10</td>
<td>7.7 (1.6)</td>
<td>7.5 (1.8)</td>
</tr>
<tr>
<td>SCORAD score</td>
<td>0–103</td>
<td>70.4 (13.3)</td>
<td>69.8 (14.1)</td>
</tr>
<tr>
<td>CDLQI score</td>
<td>0–30</td>
<td>13.1 (6.7)</td>
<td>14.8 (7.4)</td>
</tr>
<tr>
<td>POEM score</td>
<td>0–28</td>
<td>21.1 (5.4)</td>
<td>21.1 (5.5)</td>
</tr>
<tr>
<td>HADS score</td>
<td>0–42</td>
<td>11.6 (7.8)</td>
<td>13.3 (8.2)</td>
</tr>
<tr>
<td>BSA affected by AD, %</td>
<td>0–100</td>
<td>56.4 (24.1)</td>
<td>56.9 (23.5)</td>
</tr>
</tbody>
</table>

Data are shown as mean (standard deviation) unless otherwise specified.
History of comorbid type 2 immune conditions

<table>
<thead>
<tr>
<th>Patients with at least 1 allergic condition, n (%)</th>
<th>Placebo (n = 85)</th>
<th>Dupilumab 300 mg q4w (n = 84)</th>
<th>Dupilumab 200 or 300 mg q2w (n = 82)</th>
<th>All patients (n = 251)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td>78 (91.8)</td>
<td>73 (88.0)</td>
<td>79 (96.3)</td>
<td>230 (92.0)</td>
</tr>
<tr>
<td><strong>Dupilumab 300 mg q4w</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>57 (67.1)</td>
<td>48 (57.8)</td>
<td>59 (72.0)</td>
<td>164 (65.6)</td>
</tr>
<tr>
<td>Asthma</td>
<td>46 (54.1)</td>
<td>42 (50.6)</td>
<td>46 (56.1)</td>
<td>134 (53.6)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>48 (56.5)</td>
<td>52 (62.7)</td>
<td>52 (63.4)</td>
<td>152 (60.8)</td>
</tr>
<tr>
<td>Allergic conjunctivitis</td>
<td>16 (18.8)</td>
<td>21 (25.3)</td>
<td>20 (24.4)</td>
<td>57 (22.8)</td>
</tr>
<tr>
<td>Hives</td>
<td>22 (25.9)</td>
<td>28 (33.7)</td>
<td>22 (26.8)</td>
<td>72 (28.8)</td>
</tr>
<tr>
<td>Chronic rhinosinusitis</td>
<td>7 (8.2)</td>
<td>6 (7.2)</td>
<td>6 (7.3)</td>
<td>19 (7.6)</td>
</tr>
<tr>
<td>Nasal polyps</td>
<td>2 (2.4)</td>
<td>1 (1.2)</td>
<td>2 (2.4)</td>
<td>5 (2.0)</td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>0</td>
<td>0</td>
<td>1 (1.2)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Other allergies*</td>
<td>62 (72.9)</td>
<td>53 (63.9)</td>
<td>58 (70.7)</td>
<td>173 (69.2)</td>
</tr>
</tbody>
</table>

*Including allergies to medications, animals, plants, mold, dust mites, etc.
## Prior use of systemic AD therapies

<table>
<thead>
<tr>
<th>Patients with prior systemic medication, n (%)</th>
<th>Placebo (n = 85)</th>
<th>Dupilumab 300 mg q4w (n = 84)</th>
<th>Dupilumab 200 or 300 mg q2w (n = 82)</th>
<th>All patients (n = 251)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td>21 (24.7)</td>
<td>27 (32.5)</td>
<td>21 (25.6)</td>
<td>69 (27.6)</td>
</tr>
<tr>
<td>Nonsteroidal immunosuppressants</td>
<td>17 (20.0)</td>
<td>15 (18.1)</td>
<td>20 (24.4)</td>
<td>52 (20.8)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1 (1.2)</td>
<td>1 (1.2)</td>
<td>0</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>12 (14.1)</td>
<td>6 (7.2)</td>
<td>14 (17.1)</td>
<td>32 (12.8)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>6 (7.1)</td>
<td>10 (12.0)</td>
<td>10 (12.2)</td>
<td>26 (10.4)</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>0</td>
<td>1 (1.2)</td>
<td>2 (2.4)</td>
<td>3 (1.2)</td>
</tr>
</tbody>
</table>
Co-primary endpoints: Patients with IGA 0 or 1 or EASI-75 at Week 16

IGA 0 or 1

- Placebo (n = 85) 2.4%
- Dupilumab 300 mg q4w (n = 84) 17.9%
- Dupilumab 200/300 mg q2w (n = 82) 24.4%

*P < 0.05, **P < 0.001 vs placebo. aPatient considered nonresponder after rescue treatment use.
Co-primary endpoints: Patients with IGA 0 or 1 or EASI-75 at Week 16

IGA 0 or 1

EASI-75

Placebo (n = 85)

Dupilumab 300 mg q4w (n = 84)

Dupilumab 200/300 mg q2w (n = 82)

** 24.4

0 10 20 30 40 50 60 70 80 90 100

Patients (%)

Placebo (n = 85)

Dupilumab 300 mg q4w (n = 84)

Dupilumab 200/300 mg q2w (n = 82)

2.4

17.9

8.2

100

** 38.1

** 41.5

Patients (%)

Censored data

Censored data

*P < 0.05, **P < 0.001 vs placebo. aPatient considered nonresponder after rescue treatment use.
Co-primary endpoints: Patients with IGA 0 or 1 or EASI-75 at Week 16

IGA 0 or 1

- Placebo (n = 85)
- Dupilumab 300 mg q4w (n = 84)
- Dupilumab 200/300 mg q2w (n = 82)

EASI-75

- Placebo (n = 85)
- Dupilumab 300 mg q4w (n = 84)
- Dupilumab 200/300 mg q2w (n = 82)

*P < 0.05, **P < 0.001 vs placebo. aPatient considered nonresponder after rescue treatment use. bAll observed values regardless of rescue treatment use.
Peak pruritus NRS score from baseline to Week 16

LS mean % change from baseline in peak pruritus NRS (± SE)\textsuperscript{a}

*P < 0.001 vs placebo. \textsuperscript{a}Weekly average of daily peak pruritus NRS score. LS, least squares; SE, standard error.
Percentage change in EASI score and patients with EASI-50 at Week 16

**LS mean % change from baseline in EASI score (± SE)**

- Placebo (n = 85)
- Dupilumab 300 mg q4w (n = 84)
- Dupilumab 200/300 mg q2w (n = 82)

**Patients with EASI-50 at Week 16 (%)**

- Placebo (n = 85)
- Dupilumab 300 mg q4w (n = 84)
- Dupilumab 200/300 mg q2w (n = 82)

-75 -70 -65 -60 -55 -50 -45 -40 -35 -30 -25 -20 -15 -10 -5 0 5 10 15 20 25 30 35 40 45 50 55 60 65 70 75

Week

-23.6

-64.8*

-65.9*

* P < 0.001 vs placebo.
Changes in CDLQI and POEM scores to Week 16

LS mean change in CDLQI score (± SE)

Week

-5.1
-8.5*
-8.8*
-10.1*

Placebo (n = 85)
Dupilumab 300 mg q4w (n = 84)
Dupilumab 200/300 mg q2w (n = 82)

LS mean change in POEM score (± SE)

Week

-3.8
9.5*
10.1*

Placebo (n = 85)
Dupilumab 300 mg q4w (n = 84)
Dupilumab 200/300 mg q2w (n = 82)

*P < 0.001 vs placebo.
### Adverse events during the 16-week treatment period

<table>
<thead>
<tr>
<th>Patients with event, n (%)</th>
<th>Placebo (n = 85)</th>
<th>Dupilumab 300 mg q4w (n = 84)</th>
<th>Dupilumab 200 or 300 mg q2w (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TEAE</strong></td>
<td>59 (69.4)</td>
<td>53 (63.9)</td>
<td>59 (72.0)</td>
</tr>
<tr>
<td>TEAE leading to discontinuation of study drug</td>
<td>1 (1.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious TEAE</td>
<td>1 (1.2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>The most common TEAEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis atopic (PT)</td>
<td>21 (24.7)</td>
<td>15 (18.1)</td>
<td>15 (18.3)</td>
</tr>
<tr>
<td>Skin infection (adjudicated)</td>
<td>17 (20.0)</td>
<td>11 (13.3)</td>
<td>9 (11.0)</td>
</tr>
<tr>
<td>Upper respiratory tract infection (PT)</td>
<td>15 (17.6)</td>
<td>6 (7.2)</td>
<td>10 (12.2)</td>
</tr>
<tr>
<td>Headache (PT)</td>
<td>9 (10.6)</td>
<td>4 (4.8)</td>
<td>9 (11.0)</td>
</tr>
<tr>
<td>Conjunctivitis(^b)</td>
<td>4 (4.7)</td>
<td>9 (10.8)</td>
<td>8 (9.8)</td>
</tr>
<tr>
<td>Nasopharyngitis (PT)</td>
<td>4 (4.7)</td>
<td>9 (10.8)</td>
<td>3 (3.7)</td>
</tr>
<tr>
<td>Infections and infestations (SOC)</td>
<td>37 (43.5)</td>
<td>38 (45.8)</td>
<td>34 (41.5)</td>
</tr>
<tr>
<td>Injection site reactions (HLT)</td>
<td>3 (3.5)</td>
<td>5 (6.0)</td>
<td>7 (8.5)</td>
</tr>
<tr>
<td>Herpes viral infections (HLT)</td>
<td>3 (3.5)</td>
<td>4 (4.8)</td>
<td>1 (1.2)</td>
</tr>
</tbody>
</table>

\(^a\)By PT, in ≥ 5% of patients in any treatment group. \(^b\)Includes the PTs atopic keratoconjunctivitis, conjunctivitis, conjunctivitis allergic, conjunctivitis bacterial, conjunctivitis viral.

HLT, MedDRA high-level term; MedDRA, Medical Dictionary for Regulatory Activities; PT, MedDRA preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.
Mean serum concentration of functional dupilumab

Dupilumab concentration over time

Nominal time (weeks)

Dupilumab (mg/L)

Nominal time (weeks)

- Dupilumab 200 mg q2w (n = 43)
- Dupilumab 200 or 300 mg q2w (n = 82)
- Dupilumab 300 mg q2w (n = 39)
- Dupilumab 300 mg q4w (n = 82)
Conclusions

- In adolescents with moderate-to-severe AD, dupilumab treatment resulted in clinically meaningful and statistically significant improvements in AD signs and symptoms (including pruritus) and quality of life.
- For most categorical endpoints, the q2w regimen was numerically superior to the q4w regimen.
- The safety profile of dupilumab was acceptable; rates of conjunctivitis and injection-site reactions were higher with dupilumab, whereas rates of AD exacerbation and non-herpetic skin infections were higher with placebo.
- Both placebo-corrected efficacy and safety of dupilumab in adolescents were similar to those observed in adults.