IMPORTANCE  Cendakimab selectively targets interleukin (IL)-13, a type 2 cytokine implicated in atopic dermatitis (AD) pathogenesis, by inhibiting binding to its receptors (IL13R-α1 and IL13R-α2). Proof-of-concept work in AD supports using cendakimab for type 2 inflammatory diseases.

OBJECTIVE  To evaluate the efficacy and safety of cendakimab compared with placebo in patients with moderate to severe AD.

DESIGN, SETTING, AND PARTICIPANTS  This phase 2, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging clinical trial was conducted from May 2021 to November 2022. Adult patients with moderate to severe AD and inadequate response to topical medications were enrolled at 69 sites in 5 countries (US [n = 26], Japan [n = 17], Canada [n = 9], Poland [n = 9], and Czech Republic [n = 8]). Data were analyzed between April 25, 2023, and October 16, 2023.

INTERVENTIONS  Patients were randomized (1:1:1:1) to receive subcutaneous cendakimab, 360 mg, every 2 weeks; 720 mg, every 2 weeks; 720 mg, once weekly; or placebo.

MAIN OUTCOME AND MEASURE  Mean percentage change in Eczema Area and Severity Index scores from baseline to week 16. Hierarchical testing with multiplicity adjustment was performed for 720 mg, once weekly vs placebo, then 720 mg, every 2 weeks vs placebo, and then 360 mg, every 2 weeks vs placebo.

RESULTS  Overall, 221 patients were randomized, and 220 received study drug (95 women [43%]; mean [SD] age, 37.7 [13.9] years; 720 mg, once weekly [54 (24%)]; 720 mg, every 2 weeks [55 (25%)]; 360 mg, every 2 weeks [55 (25%)]; placebo [56 (26%)]). The primary efficacy end point was met for cendakimab, 720 mg, once weekly vs placebo (−84.4 vs −62.7; P = .003) but missed statistical significance for 720 mg, every 2 weeks (−76.0 vs −62.7; P = .06). The treatment effect for 360 mg, every 2 weeks (−16.3; nominal P = .03 vs placebo) was comparable with 720 mg, once weekly (−21.8); however, significance was not claimed because the hierarchical testing sequence was interrupted. Of patients with treatment-emergent adverse events leading to discontinuation, 4 (7.4%) received 720 mg, once weekly; 2 (3.6%) 720 mg, every 2 weeks; 1 (1.8%) 360 mg, every 2 weeks; and 2 (3.6%) placebo.

CONCLUSIONS AND RELEVANCE  The results of this randomized clinical trial indicated that cendakimab was effective, generally safe, and well-tolerated in patients with moderate to severe AD. The primary end point was met with a significant reduction in Eczema Area and Severity Index scores with 720 mg, once weekly at week 16. Cendakimab demonstrated progressive AD improvement at all doses during 16 weeks of treatment.

TRIAL REGISTRATION  ClinicalTrials.gov Identifier: NCT04800315

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A topic dermatitis (AD) is a common, chronic inflammatory skin disease with substantial patient burden. Severe pruritus associated with AD contributes to sleep impairments, anxiety, and depression, as well as reduced daily activities overall. People with AD are also at risk of developing other type 2 inflammatory disorders, including eosinophilic esophagitis, asthma, allergic rhinitis, and chronic sinusitis with nasal polyposis. Ultrasound phototherapy and systemic small molecule treatments are used in moderate to severe AD when a patient’s response to topical agents is inadequate. In particular, targeted biologic therapies are often required to treat moderate to severe AD. Biologics currently approved by the US Food and Drug Administration for first-line systemic therapy in moderate to severe AD include dupilumab and tralokinumab, which are anti–interleukin (IL)-4 receptor alpha (Rα) and anti–IL-13 monoclonal antibodies, respectively. Janus kinase inhibitors are an approved alternative for patients with moderate to severe AD who experienced an inadequate response to other biologic or systemic therapies, but these require laboratory monitoring and periodic safety monitoring.

The pathogenesis of AD is complex, but it is believed to result from various factors, including epidermal barrier defects, dysregulation of the innate immune system, and altered type 2 immunity. IL-13 is a primary cytokine involved in the type 2 inflammation that is associated with AD. IL-13, IL-13Rα1, and IL-13Rα2 are overexpressed in lesional AD keratinocytes that could promote lichenification. Cendakimab is a monoclonal, high-affinity, selective antibody that binds to IL-13, blocking the interaction of IL-13 with its receptors IL-13Rα1 and IL-13Rα2. We evaluated the efficacy and safety of treatment with cendakimab in patients with moderate to severe AD in a randomized, double-blind, phase 2 clinical trial.

Key Points

**Question** Is cendakimab efficacious and safe in patients with moderate to severe atopic dermatitis (AD)?

**Findings** In this randomized clinical trial of 221 patients with moderate to severe AD, treatment with cendakimab was efficacious after 16 weeks, demonstrating improvements in skin clearance, pruritus, and the extent and severity of AD compared with placebo. Cendakimab was generally safe and well-tolerated.

**Meaning** The results of this dose-ranging phase 2 randomized clinical trial established the efficacy and safety for cendakimab, an anti–interleukin-13 monoclonal antibody, in patients with moderate to severe AD.

### Methods

**Study Design**

This study was sponsored by Celgene (acquired by Bristol Myers Squibb in 2019) and was conducted according to the ethical principles defined in the Declaration of Helsinki and Good Clinical Practice guidelines as described by the International Council for Harmonisation (Supplement 1 and Supplement 2). The study received approval from the institutional review boards/ethics committees at each site, and all aspects of the study were performed according to applicable national, state, and local laws. Patients provided written informed consent.

This study was a phase 2, global, multicenter, randomized, double-blind, placebo-controlled, parallel-group, and dose-ranging study in adults with moderate to severe AD. After a 4-week screening period, eligible patients were randomized (1:1:1:1) to receive subcutaneous cendakimab 360 mg, every 2 weeks; 720 mg, every 2 weeks; 720 mg, once weekly; or placebo for 16 weeks (eFigure 1 in Supplement 3). Treatment was stratified by geographic region (Japan vs the rest of the world); outside of Japan, randomization was stratified by disease severity using a Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score of 3 (moderate) or 4 (severe). Randomization occurred on day 1 (baseline) through an interactive response technology system. Eligible patients included adults with moderate to severe AD and inadequate response to topical medications. Patients were required to apply a stable dose of topical emollient twice a day for 7 days or longer before the baseline visit and continue application throughout the study. Concomitant use of medications known to affect AD, including topical corticosteroids (except as a rescue therapy), systemic corticosteroids, mycophenolate mofetil, interferon gamma, Janus kinase inhibitors, biologic agents, topical calcineurin inhibitors, cyclosporine, azathioprine, methotrexate, and phototherapy, were prohibited during the study. Further details of the eligibility criteria and concomitant use of medications are provided in eMethods 1 in Supplement 3.

### End Points

The primary end point was the mean percentage change in Eczema Area and Severity Index (EASI) scores from baseline to week 16. Key secondary end points included the proportion of patients with a vIGA-AD score of clear (0) or almost clear (1) with a 2-point or greater reduction (vIGA-AD 0 or 1) at week 16 and the proportion of patients with a 75% or greater improvement in EASI scores (EASI-75) at week 16. Other secondary end points included the proportion of patients with a 4-point or greater reduction in Pruritus Numeric Rating Scale (P-NRS-4) scores at week 16.

Safety was assessed by evaluating adverse events (AEs), treatment-emergent AEs (TEAEs), serious AEs, discontinuations because of AEs, conjunctivitis cluster AEs (conjunctivitis, conjunctivitis bacterial, conjunctivitis allergic, keratitis, and ulcerative keratitis), herpes AEs (oral herpes, herpes simplex, herpes dermatitis, herpes ophthalmic, genital herpes simplex, and herpes virus infection), and AEs of special interest (AESI). Although not a specific concern with cendakimab, conjunctivitis cluster and herpes AEs have been observed in clinical trials of other agents that inhibit IL-13 and AESIs included anaphylactic reactions; severe or systemic hypersensitivity reactions; severe injection site reactions (lasting >24 hours); cancers; helminthic or parasitic infections;
Figure. Patient Disposition

Results

Patient Population
This randomized, double-blind, phase 2 study was conducted from May 17, 2021, to November 9, 2022, at 69 sites in 5 countries (9 sites in Canada, 26 sites in the US, 8 sites in the Czech Republic, 9 sites in Poland, and 17 sites in Japan). Overall, 221 patients were randomized, and 220 received the study drug (720 mg, once weekly [54 (24%)]; 720 mg, every 2 weeks [55 (25%)]; 360 mg, every 2 weeks [55 (25%)]; placebo [56 (26%)]) (Figure). More patients completed treatment in the cendakimab treatment groups (49 [89.1%] with 720 mg, once weekly; 50 [90.9%] with 720 mg, every 2 weeks; and 52 [94.5%] with 360 mg, every 2 weeks) than placebo (44 [78.6%]) (Figure). The primary reason for treatment discontinuation across all groups was AEs (4.1%). Other common reasons for discontinuation were loss to follow-up (2.3%), lack of efficacy (1.8%), and withdrawal by the patient (1.8%).

There were no clinically meaningful differences in baseline characteristics among the treatment arms; the mean (SD) age was 37.7 (13.9) years; 95 (43.2%) were women; 1 (0.5%) was American Indian/Alaska Native, 60 (27.3%) were Asian, 23 (10.5%) were Black, and 136 (61.8%) were White; the mean (SD) EASI score was 28.4 (10.8); and the mean (SD) number of years since AD onset was 26.3 (15.5) (Table 1). Approximately one-third of patients across treatment groups had a vIGA score for severe disease (Table 1).

Efficacy
The primary end point was met for cendakimab, 720 mg, once weekly vs placebo (EASI-adjusted mean difference from placebo, −21.8%; P = .003) but missed statistical significance for 720 mg, every 2 weeks vs placebo (−13.4%; P = .06) (Table 2; eTable 3 and eFigure 2 in Supplement 3). The treatment effect for 360 mg, every 2 weeks vs placebo was nominally significant (−16.3%; nominal P = .03); however, significance could not be claimed because the hierarchical testing sequence was interrupted. Sensitivity analyses confirmed the robustness of the effect of cendakimab on the primary end point, with adjusted mean differences in all doses tested vs the placebo dose ranging from −17.7% to −28.5% for 720 mg, once weekly; −13.3% to −29.5% for 720 mg, every 2 weeks; and −18.4% to −25.9% for 360 mg, every 2 weeks (eTable 3 in Supplement 3).

Compared with the placebo group (9.4%), more patients achieved a vIGA-AD score of 0 or 1 in the cendakimab groups

opportunistic infections; any severe infection, or those that required parenteral treatment; or oral treatment for more than 2 weeks).

Blood samples were obtained predose at study visits (baseline and weeks 1, 2, 4, 6, 8, 10, 12, 14, and 16). Biomarkers in serum, including lactate dehydrogenase (LDH), immunoglobulin E (IgE), eotaxin-3, periostin, and matrix metalloproteinase-12 (MMP12) levels, were measured. Biomarker data were calculated as the adjusted percentage change from baseline.

For the primary end point, the hypothesis testing was 2-sided and conducted at the .05 level of significance, applying hierarchical testing in the order of 720 mg, once weekly vs placebo; 720 mg, every 2 weeks vs placebo; and 360 mg, every 2 weeks vs placebo. Details on the methods used for the statistical analysis, as well as a description of the sensitivity analysis, are provided in eTables 1 and 2 and eMethods 2 in Supplement 3.
Table 1. Baseline and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n = 56)</th>
<th>Cendakimab 360 mg, every 2 weeks (n = 55)</th>
<th>Cendakimab 720 mg, every 2 weeks (n = 55)</th>
<th>Cendakimab 720 mg, once weekly (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>39.5 (14.2)</td>
<td>40.3 (14.2)</td>
<td>34.5 (13.8)</td>
<td>36.3 (13.0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>21 (37.5)</td>
<td>29 (52.7)</td>
<td>26 (47.3)</td>
<td>19 (35.2)</td>
</tr>
<tr>
<td>Male</td>
<td>35 (62.5)</td>
<td>26 (47.3)</td>
<td>29 (52.7)</td>
<td>35 (64.8)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>80.7 (21.3)</td>
<td>79.2 (20.5)</td>
<td>75.7 (16.5)</td>
<td>76.3 (14.9)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>27.6 (6.9)</td>
<td>27.8 (5.8)</td>
<td>26.7 (5.4)</td>
<td>26.5 (4.4)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaska Native</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Asian</td>
<td>13 (23.2)</td>
<td>14 (25.5)</td>
<td>14 (25.5)</td>
<td>19 (35.2)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (10.7)</td>
<td>5 (9.1)</td>
<td>8 (14.5)</td>
<td>4 (7.4)</td>
</tr>
<tr>
<td>White</td>
<td>37 (66.1)</td>
<td>36 (65.5)</td>
<td>33 (60.0)</td>
<td>30 (55.6)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Region/country</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>7 (12.5)</td>
<td>8 (14.5)</td>
<td>7 (12.7)</td>
<td>11 (20.4)</td>
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<tr>
<td>US</td>
<td>16 (28.6)</td>
<td>18 (32.7)</td>
<td>15 (27.3)</td>
<td>15 (27.8)</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>13 (23.2)</td>
<td>9 (16.4)</td>
<td>14 (25.5)</td>
<td>8 (14.8)</td>
</tr>
<tr>
<td>Poland</td>
<td>11 (19.6)</td>
<td>11 (20.0)</td>
<td>10 (18.2)</td>
<td>11 (20.4)</td>
</tr>
<tr>
<td>Japan</td>
<td>9 (16.1)</td>
<td>9 (16.4)</td>
<td>9 (16.4)</td>
<td>9 (16.7)</td>
</tr>
<tr>
<td>Years since AD onset, mean (SD)</td>
<td>26.3 (16.4)</td>
<td>30.4 (17.4)</td>
<td>27.2 (12.6)</td>
<td>21.1 (14.0)</td>
</tr>
<tr>
<td>Personal or family history of atopy</td>
<td>45 (80.4)</td>
<td>48 (87.3)</td>
<td>46 (83.6)</td>
<td>44 (81.5)</td>
</tr>
<tr>
<td>EASI score, mean (SD)b</td>
<td>30.0 (11.7)</td>
<td>27.1 (10.8)</td>
<td>30.7 (10.2)</td>
<td>25.9 (9.9)</td>
</tr>
<tr>
<td>vIGA scorec</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (3)</td>
<td>35 (62.5)</td>
<td>37 (67.3)</td>
<td>38 (69.1)</td>
<td>36 (66.7)</td>
</tr>
<tr>
<td>Severe (4)</td>
<td>21 (37.5)</td>
<td>18 (32.7)</td>
<td>17 (30.9)</td>
<td>18 (33.3)</td>
</tr>
<tr>
<td>BSA, mean (SD)</td>
<td>49.5 (23.5)</td>
<td>40.7 (19.7)</td>
<td>48.5 (23.6)</td>
<td>37.8 (17.9)</td>
</tr>
<tr>
<td>P-NRS score, mean (SD)d</td>
<td>7.8 (1.33)</td>
<td>7.8 (1.55)</td>
<td>7.9 (1.64)</td>
<td>7.8 (1.62)</td>
</tr>
<tr>
<td>SCORAD score, mean (SD)d</td>
<td>64.0 (13.5)</td>
<td>62.3 (11.6)</td>
<td>67.9 (12.0)</td>
<td>62.6 (11.3)</td>
</tr>
<tr>
<td>Prior systemic immunosuppressive usef</td>
<td>29 (51.8)</td>
<td>24 (43.6)</td>
<td>28 (50.9)</td>
<td>28 (51.9)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, atopic dermatitis; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSA, body surface area affected; EASI, Eczema Area and Severity Index; IFN-γ, interferon gamma; P-NRS, Pruritus-Numeric Rating Scale; SCORAD, Scoring Atopic Dermatitis Index; vIGA-AD, Validated Investigator Global Assessment for Atopic Dermatitis.

a Sex was investigator classified.
b EASI scores ranged from 0 to 72; higher scores indicate more severe disease.
c vIGA-AD score is (0) clear, (1) almost clear, (2) mild, (3) moderate, (4) severe.
d Worst pruritus in the past 24 hours Numeric Rating Scale (NRS) ranges from 0 (no itch) to 10 (worst imaginable itch).
e SCORAD scores range from 0 to 103; higher scores indicate more severe disease.
f Systemic immunosuppressive or immunomodulating drugs included azathioprine, cyclosporine, systemic corticosteroids, IFN-γ, Janus kinase inhibitors, methotrexate, and mycophenolate mofetil.

(720 mg, once weekly: 33.3%; nominal P = .004; 720 mg, every 2 weeks: 24.4%; nominal P = .06; 360 mg, every 2 weeks: 38.2%; nominal P < .001) (Table 2; eFigure 2 in Supplement 3). In addition, more patients achieved EASI-75 with cendakimab than placebo (720 mg, once weekly: 50.0%; nominal P = .02; 720 mg, every 2 weeks: 48.2%; nominal P = .03; 360 mg, every 2 weeks: 52.7%; nominal P = .01; placebo, 26.3%) (Table 2; eFigure 2 in Supplement 3). For vIGA-AD score of 0 or 1 and EASI-75, response rates of the 720 mg, once weekly and 360 mg, every 2 weeks groups were higher than the cendakimab 720 mg, every 2 weeks group. P-NRS-4 response rates were similar across cendakimab treatment groups (720 mg, once weekly: 33.3%; 720 mg, every 2 weeks: 34.5%; 360 mg, every 2 weeks: 32.7%) and greater than the placebo group (14.8%); these effects were observed as early as week 4 of treatment (Table 2; eFigure 2 in Supplement 3). The proportion of patients with 90% or greater improvement in EASI scores (EASI-90) were numerically higher across the cendakimab groups than the placebo group (31.5% with 720 mg, once weekly; 24.0% with 720 mg, every 2 weeks; 29.1% with 360 mg, every 2 weeks; and 13.4% with placebo). More patients with a baseline vIGA-AD score of 3 (moderate) had EASI-75 responses than patients with a baseline vIGA-AD score of 4 (severe) for the cendakimab, 720 mg, once weekly (36 [75.0%] vs 18 [61.1%]); cendakimab, 360 mg, every 2 weeks (37 [70.3%] vs 18 [61.1%]); and placebo groups (35 [42.9%] vs 21 [38.1%]), but not for the cendakimab, 720 mg, every 2 weeks group (38 [47.4%] vs 17 [58.8%]).

The inflammatory biomarkers, LDH and IgE, decreased with treatment (as anticipated) in patients with AD who experienced improvement. Decreases in LDL levels from baseline to week 16 were observed in all cendakimab treatment groups (mean [SD] U/L: 720 mg, once weekly, −45.8 [50.92]; 720 mg, every 2 weeks, −0.6 [83.03]; 360 mg, every 2 weeks, −0.9 [63.32]; to convert to μkat/L, multiply by 0.0167) and were numerically higher than the placebo group (−38.5 [108.88]). Mean (SD) IgE levels progressively decreased from baseline to week 16 in the cendakimab treatment groups (720 mg, once weekly: −128.53 [296.512] mg/dL; 720 mg, every 2 weeks: −190.07 [543.560] mg/dL; to convert to μkat/L, multiply by 0.0167) and were numerically higher than the placebo group (−190.07 [543.560] mg/dL; 360 mg, every 2 weeks: −0.9 [63.32]; to convert to μkat/L, multiply by 0.0167).
kimab administration in all 3 treatment groups, and these decreases in levels augmented over time through week 16 in cendakimab treatment groups than the levels observed with the placebo group.

**Rescue and Prohibited Medications**

Treatment with rescue and prohibited medications was initiated during the study by 24 patients (44.4%) receiving 720 mg, once weekly; 13 patients (23.6%) receiving 720 mg, every 2 weeks; 19 patients (34.5%) receiving 360 mg, every 2 weeks; and 28 patients (50.0%) receiving placebo. The proportion of patients who initiated use of rescue and prohibited medications by study day are provided in Table 4 in Supplement 3.

Sensitivity analyses with alternative approaches to the missing values and postrescue/prohibited medications did not change the overall conclusions of the primary analysis (eTable 3 in Supplement 3).

**Safety**

TEAEs were reported for 40 patients (74.1%) treated with cendakimab, 720 mg, once weekly; 41 (74.5%) treated with 720 mg, every 2 weeks; 38 (69.1%) treated with 360 mg, every 2 weeks; and 41 (73.2%) treated with placebo; most TEAEs were mild to moderate (Table 3). Overall, severe TEAEs were reported for 9 patients (4.1%) compared with 105 patients (47.7%) with moderate TEAEs and 46 (20.9%) with mild TEAEs. Rates of serious TEAEs and discontinuations because TEAEs were low and generally comparable among treatment groups (Table 3); the largest proportion of TEAEs leading to discontinuations was dermatitis atopic (5 [2.3%]).

Frequently reported TEAEs (≥2% of patients in any treatment groups) included dermatitis atopic, COVID-19, upper respiratory tract infection, and conjunctivitis allergic (eTable 5 in Supplement 3). For patients treated with cendakimab, serious TEAEs were reported for 3.7% of those treated with 720 mg, once weekly; 2 (1.8%) treated with 720 mg, every 2 weeks; and 1 (3.6%) treated with 360 mg, every 2 weeks, whereas 2 patients (7.1%) treated with placebo reported serious TEAEs (eTable 6 in Supplement 3).

AESIs were reported for 37 patients (16.8%) across groups; the most frequent AESIs were opportunistic infections (35 [15.9%]). These AESIs were reported with similar frequency across treatment groups, with herpes and COVID-19 being the most common opportunistic infection types (Table 4).

Nonserious mild or moderate herpes events were reported for 2 patients (3.7%) treated with 720 mg, once weekly; 3 patients (5.5%) treated with 720 mg, every 2 weeks or 360 mg, every 2 weeks; and 1 patient (1.8%) treated with placebo. Herpes simplex was the most frequently reported herpes event, with no cases of herpes zoster or eczema herpeticum observed. None of the herpes events resulted in treatment discontinuation.

The effect of the COVID-19 pandemic on safety appeared to be minimal, with COVID-19 events reported for 24 patients (10.9%), with a numerically higher proportion in the placebo group (9 patients [16.1%]) than the cendakimab groups (5 patients [9.3%] with 720 mg, once weekly; 6 [10.9%] with 720 mg, every 2 weeks; 4 [7.3%] with 360 mg, every 2 weeks) (Table 3); only 1 patient discontinued treatment because of a COVID-19 event. Rates of conjunctivitis AEs were greater in the cendakimab administration in all 3 treatment groups, and these decreases in levels augmented over time through week 16 in cendakimab treatment groups than the levels observed with the placebo group.

**Table 2. Efficacy End Points for Cendakimab at Week 16**

<table>
<thead>
<tr>
<th>Efficacy end point</th>
<th>Placebo (n = 56), %</th>
<th>Cendakimab 360 mg, every 2 weeks (n = 55)</th>
<th>Cendakimab 720 mg, every 2 weeks (n = 55)</th>
<th>Cendakimab 720 mg, once weekly (n = 54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in EASI, mean (SE) % change</td>
<td>−62.7 (5.5)</td>
<td>−78.9 (4.5)</td>
<td>−76.0 (4.2)</td>
<td>−84.4 (5.1)</td>
</tr>
<tr>
<td>Key secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with VIGA-AD 0 or 1, numerical proportion of responders, %</td>
<td>9.4</td>
<td>38.2</td>
<td>&lt;.001</td>
<td>24.4</td>
</tr>
<tr>
<td>Patients with EASI-75, numerical proportion of responders, %</td>
<td>26.3</td>
<td>52.7</td>
<td>.01</td>
<td>48.2</td>
</tr>
<tr>
<td>Other secondary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with P-NRS-4, numerical proportion of responders, %</td>
<td>14.8</td>
<td>32.7</td>
<td>0.05</td>
<td>34.5</td>
</tr>
<tr>
<td>Change in pruritus, mean (SE) % change</td>
<td>−33.0 (7.5)</td>
<td>−49.3 (5.9)</td>
<td>NA</td>
<td>−46.2 (5.3)</td>
</tr>
<tr>
<td>Time to pruritus response, median (95% CI), d</td>
<td>123 (119 to NE)</td>
<td>50 (27-111)</td>
<td>&lt;.001</td>
<td>76 (42-105)</td>
</tr>
<tr>
<td>Patients with EASI-90, numerical proportion of responders, %</td>
<td>13.4</td>
<td>29.1</td>
<td>NA</td>
<td>24.0</td>
</tr>
<tr>
<td>Change in SCORAD score, mean (SE) % change</td>
<td>−41.1 (5.6)</td>
<td>−60.2 (4.4)</td>
<td>NA</td>
<td>−55.5 (4.1)</td>
</tr>
<tr>
<td>Change in BSA affected, mean (SE) % change</td>
<td>−55.7 (6.9)</td>
<td>−66.6 (6.0)</td>
<td>NA</td>
<td>−64.0 (5.3)</td>
</tr>
</tbody>
</table>

Abbreviations: BSA, body surface area; EASI, Eczema Area and Severity Index; EASI-75, ≥75% improvement in EASI; EASI-90, ≥90% improvement in EASI; NA, not applicable; NE, not estimable; P-NRS-4, ≥4-point reduction in Pruritus-Numeric Rating Scale; SCORAD, Scoring Atopic Dermatitis; vIGA-AD 0 or 1, Validated Investigator Global Assessment for Atopic Dermatitis score of clear (0) or almost clear (1) with a 2-point or greater reduction.

* Nominal P value.
groups than the placebo group (Table 4). Conjunctivitis cluster events, including conjunctivitis, bacterial and allergic conjunctivitis, keratitis, and ulcerative keratitis, were reported across all groups; events were reported for 6 patients (11.1%) treated with cendakimab, 720 mg, once weekly; 5 (9.1%) treated with cendakimab, 360 mg, every 2 weeks; and 3 (5.4%) with placebo. The most common AE of the conjunctivitis cluster was allergic conjunctivitis (4 patients [7.4%] treated with 720 mg, once weekly; 7 [12.7%] with 720 mg, every 2 weeks; 5 [9.1%] with 360 mg, every 2 weeks; and 2 [3.6%] with placebo).

Overall, there were no clinically relevant trends or imbalances in serum chemistry, hematology, or urinalysis parameters across treatment groups. Abnormal laboratory parameters among patients who were treated with cendakimab were infrequent, transient, and did not result in treatment discontinuation.

### Discussion

In this phase 2 randomized clinical trial, the efficacy and safety of cendakimab, an anti-IL-13 monoclonal antibody, was established in patients with moderate to severe AD. The primary end point of change in EASI scores from baseline at week 16 was met for cendakimab, 720 mg, once weekly compared with placebo. Numerically greater reductions were observed with 720 mg, every 2 weeks and 360 mg, every 2 weeks doses than with the placebo dose, but significance could not be claimed because the hierarchical testing sequence was interrupted. The proportion of patients achieving the secondary end points of EASI-75, vIGA 0 or 1, and P-NRS-4 were numerically greater for those treated with cendakimab compared with placebo. Improvements in multiple efficacy end points were already observed with the lowest dose of cendakimab, 360 mg,
every 2 weeks. The use of rescue therapy and required/ permitted concomitant medications (eg, emollients) may have partially attenuated the treatment difference vs placebo.23 AD is a chronic and intermittent disease that is characterized by flares; thus, while consistent with other AD studies, a 16-week period may not be sufficient to assess the full efficacy and safety profile of cendakimab.21,26,27 Despite differences in dosing regimens and treatment duration, the proportion of patients achieving EASI-75, vIGA 0 or 1, and P-NRS-4 were overall similar to proportions from previous studies with biologics that block IL-13 function.9,10,22

Treatment with cendakimab, an anti-IL-13 monoclonal antibody that blocks the interaction of IL-13 with IL-13Rα1 and IL-13Rα2, also decreased inflammatory biomarkers in this study. Specifically, cendakimab decreased levels of key inflammatory and remodeling biomarkers (eotaxin-3, periostin, and MMP-12) during 16 weeks of treatment. These data suggest that cendakimab modulates pathways of inflammation, fibrosis, and tissue remodeling in AD. These findings also support the known mechanisms of IL-13 as the primary cytokine involved in type 2 inflammation that is associated with AD28 and potentially adds to the existing clinical evidence of cendakimab modulation in other type 2 inflammatory diseases, such as eosinophilic esophagitis. In addition, these data were consistent with observations for patients receiving other IL-13 inhibitors. Safety findings from this study were similar to findings in other phase 2 studies of biologic agents targeting IL-4 and IL-13 for treating moderate to severe AD.9,10,22,23,26,29 TEAEs were similar across treatment groups, with most events reported as mild or moderate. Rates of serious AEs were similar across groups.

Although rates of conjunctivitis were higher in the cendakimab groups compared with placebo, they were generally in the range of rates reported for other IL-13 inhibitors.23,26 This elevation could also be partially related to increased awareness and detection of conjunctivitis in AD clinical trials since the initial studies with dupilumab were conducted. Increased rates of conjunctivitis AEs are associated with IL-13 inhibitor treatments in AD in general23-25 and are hypothesized to have a mechanistic relationship.32-34 Ocular disease, such as conjunctivitis and keratitis, is commonly observed in patients with AD,35,36 and results with IL-13 inhibitors in other indications suggest that these adverse effects are mainly observed in patients with AD and not in other type 2 inflammatory disorders, such as eosinophilic esophagitis.36-38

Limitations

There were limitations associated with this study. Relatively high placebo response rates were observed across the primary and secondary end points. The required use of a non-medicated topical emollient and the use of rescue medications may have contributed to the high placebo response. Meta-analyses have shown that consistent use of topical treatments is associated with reduced disease severity and contributes to increased placebo responses.39,40 High placebo response rates were also observed in other clinical trials in AD.21,25-27 While AD is highly prevalent among pediatric patients, this study only examined treatment of adults with AD, thereby limiting the generalizability of the findings.1,41,42 In addition, the study was limited to a small number of countries (ie, Canada, the Czech Republic, Japan, Poland, and the US), which may limit the relevance of the results to the global population.

Conclusions

In this randomized clinical trial, treatment with cendakimab was well-tolerated and efficacious in patients with moderate to severe AD, demonstrating improvements in skin clearance (ie, body surface area affected), pruritus, and the extent and severity of AD (ie, EASI, vIGA-AD) after 16 weeks compared with treatment with placebo. The primary end point was reached for the highest dose. Cendakimab demonstrated progressive AD improvement at all doses during 16 weeks of treatment.

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