JAMA Dermatology | Original Investigation

Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis
A Randomized Clinical Trial

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IMPORTANCE Atopic dermatitis (AD) is a chronic, recurrent, inflammatory skin disease with an unmet need for treatments that provide rapid and high levels of skin clearance and itch improvement.

OBJECTIVE To assess the safety and efficacy of upadacitinib vs dupilumab in adults with moderate-to-severe AD.

DESIGN, SETTING, AND PARTICIPANTS Heads Up was a 24-week, head-to-head, phase 3b, multicenter, randomized, double-blinded, double-dummy, active-controlled clinical trial comparing the safety and efficacy of upadacitinib with dupilumab among 692 adults with moderate-to-severe AD who were candidates for systemic therapy. The study was conducted from February 21, 2019, to December 9, 2020, at 129 centers located in 22 countries across Europe, North and South America, Oceania, and the Asia-Pacific region. Efficacy analyses were conducted in the intent-to-treat population.

INTERVENTIONS Patients were randomized 1:1 and treated with oral upadacitinib, 30 mg once daily, or subcutaneous dupilumab, 300 mg every other week.

MAIN OUTCOMES AND MEASURES The primary end point was achievement of 75% improvement in the Eczema Area and Severity Index (EASI75) at week 16. Secondary end points were percentage change from baseline in the Worst Pruritus Numerical Rating Scale (NRS) (weekly average), proportion of patients achieving EASI100 and EASI90 at week 16, percentage change from baseline in Worst Pruritus NRS at week 4, proportion of patients achieving EASI75 at week 2, percentage change from baseline in Worst Pruritus NRS (weekly average) at week 1, and Worst Pruritus NRS (weekly average) improvement of 4 points or more at week 16. End points at week 24 included EASI75, EASI90, EASI100, and improvement of 4 points or more in Worst Pruritus NRS from baseline (weekly average). Safety was assessed as treatment-emergent adverse events in all patients receiving 1 or more dose of either drug.

RESULTS Of 924 patients screened, 348 (183 men [52.6%]; mean [SD] age, 36.6 [14.6] years) were randomized to receive upadacitinib and 344 were randomized to receive dupilumab (194 men [56.4%]; mean [SD] age, 36.9 [14.1] years); demographic and disease characteristics were balanced among treatment groups. At week 16, 247 patients receiving upadacitinib (71.0%) and 210 patients receiving dupilumab (61.1%) achieved EASI75 (P = .006). All ranked secondary end points also demonstrated the superiority of upadacitinib vs dupilumab, including improvement in Worst Pruritus NRS as early as week 1 (mean [SE], 31.4% [1.7%] vs 8.8% [1.8%]; P < .001), achievement of EASI75 as early as week 2 (152 [43.7%] vs 60 [17.4%]; P < .001), and achievement of EASI100 at week 16 (97 [27.9%] vs 26 [7.6%]; P < .001). Rates of serious infection, eczema herpeticum, herpes zoster, and laboratory-related adverse events were higher for patients who received upadacitinib, whereas rates of conjunctivitis and injection-site reactions were higher for patients who received dupilumab.

CONCLUSIONS AND RELEVANCE During 16 weeks of treatment, upadacitinib demonstrated superior efficacy vs dupilumab in patients with moderate-to-severe AD, with no new safety signals.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03738397

JAMA Dermatol. 2021;157(9):1047-1055. doi:10.1001/jamadermatol.2021.3023
Published online August 4, 2021. Corrected on December 15, 2021.

Visual Abstract

Supplemental content

CME Quiz at jamacmelookup.com and CME Questions page 1135

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Atopic dermatitis (AD) is characterized by a chronic and relapsing nature, eczematous morphology, and intense pruritus.[1,2] It is driven by proinflammatory mediators, such as interleukin 4 (IL-4), IL-13, IL-22, IL-31, interferon gamma (IFN-γ), and thymic stromal lymphopoietin (TSLP), that transduce signals via the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway.[3,4] Dupilumab, a fully human monoclonal antibody directed against the shared IL-4 receptor subunit α of IL-4 and IL-13 receptors, is approved for the treatment of moderate-to-severe AD; however, fewer than half of patients achieve clear or almost clear skin after 16 weeks of dupilumab monotherapy, with maximal responses achieved after week 12.[5] Thus, there is a need for additional treatment options that provide improved clinical responses to a greater proportion of patients and in a more rapid manner.

Upadacitinib is an oral, reversible, small molecule JAK inhibitor engineered to have increased selectivity for JAK1 vs JAK2, JAK3, and tyrosine kinase 2, with the intention of improving efficacy and safety for an improved benefit-risk profile compared with other, less-selective JAK inhibitors.[6] Upadacitinib is approved in the United States, European Union, and other countries to treat moderately or severely active rheumatoid arthritis, and is being developed for the treatment of AD and other immune-mediated inflammatory diseases.[6] Results from 1 phase 2b[7] and 3 pivotal phase 3 clinical trials (Measure Up 1, Measure Up 2, and AD Up)[8,9] demonstrated that once-daily upadacitinib (15 or 30 mg) is a well-tolerated and effective treatment option for patients with moderate-to-severe AD. Here, we assess the safety and efficacy of upadacitinib vs dupilumab in adults with moderate-to-severe AD.

Key Points

Question Are the efficacy and safety of oral upadacitinib superior to subcutaneous dupilumab in adults with moderate-to-severe atopic dermatitis (AD)?

Findings This randomized, blinded, head-to-head comparator clinical trial of 692 patients with moderate-to-severe AD demonstrated clinically meaningful skin clearance and itch relief, with statistically significant superiority for upadacitinib compared with dupilumab. There were no new safety signals reported for either upadacitinib or dupilumab.

Meaning Upadacitinib provides superior and more rapid skin clearance and itch relief with tolerable safety compared with dupilumab in patients with moderate-to-severe AD.

Methods

Study Design

Heads Up (NCT03738397) was a 24-week, head-to-head, phase 3b, multicenter, randomized, double-blinded, double-dummy, active-controlled clinical trial comparing the safety and efficacy of upadacitinib with dupilumab in adults with moderate-to-severe AD. This clinical trial was conducted from February 21, 2019, to December 9, 2020, at 129 centers located in 22 countries across Europe, North and South America, Oceania, and the Asia-Pacific region. Heads Up had a 35-day screening period, a 24-week double-blinded treatment period, and a 12-week follow-up visit or the option to enter an open-label upadacitinib extension study. Independent ethics committees or institutional review boards approved the trial protocol, informed consent form(s), and recruitment materials before patient enrollment. This clinical trial was conducted in accord with the International Conference for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki.[10] Patients provided written informed consent before screening. This study followed the Consolidated Standards of Reporting Trials (CONSORT) guideline (trial protocol in Supplement 1).

Patients

Eligible patients were adults aged 18 to 75 years with diagnosed AD using the Hanifin and Rajka criteria[11] who were candidates for systemic therapy (inadequate response to topical treatments for AD, documented use of systemic treatment for AD, or topical treatments for AD otherwise medically inadvisable) and who had moderate-to-severe disease (defined as ≥10% of body surface area affected by AD, Eczema Area and Severity Index [EASI] ≥16, validated Investigator's Global Assessment for AD score ≥3 at screening and baseline visits, and weekly average Worst Pruritus Numerical Rating Scale [NRS] score ≥4 at baseline). Prior use of JAK inhibitors or dupilumab was prohibited. eTable 1 in Supplement 2 has complete patient eligibility criteria.

Clinical Trial Procedures

Patients were randomized 1:1 to receive 30 mg of upadacitinib via extended-release tablet administered orally once daily until week 24 or 300 mg of dupilumab administered as a subcutaneous injection every 2 weeks after a loading dose of 600 mg, starting at week 2 and until week 22 (eFigure 1 in Supplement 2). Rescue therapy, defined as any topical or systemic immunomodulatory treatment initiated for AD, could be given at any time per investigator discretion. Patients who received rescue therapy were considered nonresponders for binary end points after the initiation of rescue therapy.

Efficacy Parameters

Efficacy was assessed as upadacitinib superiority compared with dupilumab, with the primary end point being 75% improvement in EASI (EASI75) at week 16. Ranked secondary end points were: percentage change from baseline in Worst Pruritus NRS, achievement of EASI100 and EASI90 at week 16, percentage change from baseline in Worst Pruritus NRS at week 4, achievement of EASI75 at week 2, percentage change from baseline in Worst Pruritus NRS at week 1, and Worst Pruritus NRS improvement of 4 points or more at week 16. Additional unranked end points were assessed at week 24, including achievement of EASI75, EASI90, and EASI100, as well as improvement of 4 points or more in Worst Pruritus NRS. The Worst Pruritus NRS end points were based on weekly averages of daily pruritus scores. Dermatology Life Quality Index and Patient-Oriented Eczema Measure data were not collected after baseline in this study.

Safety Parameters

Safety was assessed as treatment-emergent adverse events (TEAEs) in all patients who received 1 or more dose of study drug through follow-up (30 days after the last dose of upadacitinib or 84 days after the last dose of dupilumab); a TEAE was defined as any adverse event (AE) that began or worsened in severity after initiation of upadacitinib or dupilumab. All AEs presented were treatment-emergent, unless otherwise noted.

Statistical Analysis

Statistical analysis was conducted on an intent-to-treat basis. The primary approach for evaluating categorical end points was NRI-C (Nonresponder Imputation incorporating Multiple Imputation [MI] to handle missing data due to COVID-19). The initial NRI approach was revised to NRI-C because of the COVID-19 pandemic, which may have prevented visits owing to logistical restrictions; additional details regarding the NRI-C approach are outlined in the eMethods in Supplement 2. Multiplicity-adjusted results were obtained via a hierarchical testing procedure, controlling the overall type I error rate of all primary and ranked secondary end points at the 2-sided 0.05 level (eFigure 2 in Supplement 2).

Results

Patient Disposition

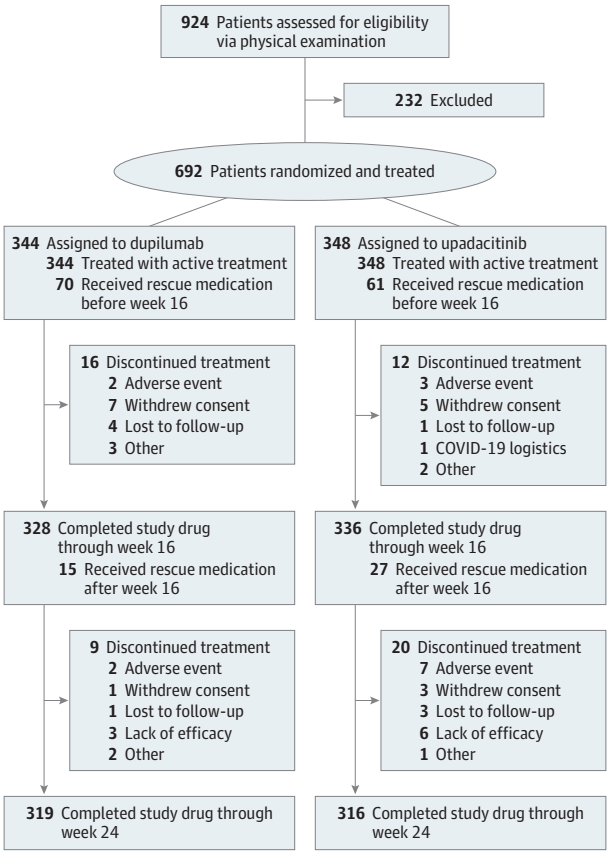
A total of 924 patients were screened, of whom 232 were excluded and 692 were enrolled and treated; 348 (183 men [52.6%]; mean [SD] age, 36.6 [14.6] years) received upadacitinib, and 344 (194 men [56.4%]; mean [SD] age, 36.9 [14.1] years) received dupilumab. The number of patients who discontinued treatment was low overall; 316 (90.8%) completed upadacitinib treatment, and 319 (92.7%) completed dupilumab treatment (**Figure 1**); 336 patients (96.6%) completed 16 weeks of upadacitinib treatment, and 328 patients (95.3%) completed 16 weeks of dupilumab treatment. Eighty-seven upadacitinib-treated patients (25.0%) and 85 dupilumab-treated patients (24.7%) received rescue therapy and were considered nonresponders for visits after receiving rescue therapy.

Demographic and baseline characteristics were balanced among the upadacitinib-treated and dupilumab-treated groups, including key measures of disease activity: mean (SD) EASI (30.8 [12.5] and 28.8 [11.5], respectively) and proportion of patients with severe validated Investigator's Global Assessment for AD (174 [50.0%] and 173 [50.3%], respectively) (**Table 1**).

Efficacy Outcomes

The proportion of patients who achieved EASI75 at week 16 was significantly greater for patients receiving upadacitinib than those receiving dupilumab (247 [71.0%] vs 210 [61.1%]; adjusted difference, 10.0% (95% CI, 2.9%-17.0%; $P = .006$) (**Table 2**), thereby meeting the primary end point of EASI75 at week 16 for superiority of upadacitinib compared with dupilumab. The response rate was calculated using the NRI-C approach. The results based on NRI-C were consistent with those based on NRI-NC (the traditional NRI approach), given that the number of patients with missing values owing to COVID-19 for the primary end point was low (1.6% [11 of 692]) (eTables 2 and 3 in Supplement 2). Most patients in both treatment groups did not receive rescue therapy (eTable 4 in Supplement 2).

Figure 1. Patient Disposition Through Week 24



CONSORT diagram for patient enrollment, randomization, and discontinuation. The primary reason for discontinuation is listed. EASI indicates Eczema Area and Severity Index.

Onset of action was more rapid for upadacitinib, with the proportion of patients achieving EASI75 at week 2 significantly greater for those receiving upadacitinib compared with those receiving dupilumab (152 of 348 [43.7%] vs 60 of 344 [17.4%]; $P < .001$) (Table 2). Significantly greater proportions of patients achieved high levels of efficacy (EASI90 and EASI100) at week 16 with upadacitinib compared with dupilumab (EASI90, 211 [60.6%] vs 133 [38.7%]; $P < .001$; EASI100, 97 [27.9%] vs 26 [7.6%]; $P < .001$). The mean (SD) percentage improvement from baseline Worst Pruritus NRS was significantly greater for upadacitinib-treated patients compared with dupilumab-treated patients as early as week 1 (31.4% [1.7%] vs 8.8% [1.8%]; $P < .001$) and week 4 (59.5% [2.2%] vs 31.7% [2.2%]; $P < .001$), and significant differences were maintained through week 16 (66.9% [1.9%] vs 49.0% [2.0%]; $P < .001$). Furthermore, the proportion of patients achieving a clinically meaningful improvement in itch (Worst Pruritus

Table 1. Baseline Demographic and Disease Characteristics of Patients[a]

Characteristic	Patients, No. (%)	
	Dupilumab, 300 mg (n = 344)	Upadacitinib, 30 mg (n = 348)
Sex		
Male	194 (56.4)	183 (52.6)
Female	150 (43.6)	165 (47.4)
Age, mean (SD) [range], y	36.9 (14.09) [18-76]	36.6 (14.61) [18-76]
Age group, y		
<40	226 (65.7)	228 (65.5)
≥40 to <65	101 (29.4)	102 (29.3)
≥65	17 (4.9)	18 (5.2)
Disease duration since diagnosis, mean (SD), y	25.0 (14.8)	23.5 (14.7)
Weight, mean (SD), kg	75.6 (18.4)	78.8 (22.3)
BMI, mean (SD)	25.99 (5.72)	26.99 (6.53)[b]
BSA, mean (SD), %	44.4 (22.8)	48.2 (24.0)
vIGA-AD score		
3 (Moderate)	171 (49.7)	174 (50.0)
4 (Severe)	173 (50.3)	174 (50.0)
EASI, mean (SD)	28.8 (11.5)	30.8 (12.5)
Worst Pruritus NRS [weekly average], mean (SD)	7.5 (1.7)	7.4 (1.6)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSA, body surface area; EASI, Eczema Area and Severity Index; NRS, Numerical Rating Scale; vIGA-AD, validated Investigator's Global Assessment.

[a] Baseline demographic and disease characteristics assessed upon entry to Heads Up (study M16-046).

[b] Data shown for 347 patients.

NRS improvement ≥4 points from baseline) at week 16 was higher for those who received upadacitinib compared with those who received dupilumab (188 of 340 [55.3%] vs 120 of 336 [35.7%]; $P < .001$). Thus, the study met all ranked secondary efficacy end points, demonstrating that upadacitinib achieved significantly greater improvements in both investigator- and patient-reported outcomes compared with dupilumab.

Numerically greater proportions of upadacitinib-treated vs dupilumab-treated patients achieved EASI75 as early as week 1 (55 of 348 [15.9%] vs 19 of 344 [5.5%]) and at week 4 (243 of 348 [69.9%] vs 123 of 344 [35.9%]) (**Figure 2**A). Similar differences were observed for achievement of EASI90 at week 2 (64 of 348 [18.5%] vs 20 of 344 [5.8%]) and week 8 (206 of 48 [59.2%] vs 86 of 344 [25.1%]) (Figure 2B). Positive differences between proportions of upadacitinib-treated vs dupilumab-treated patients for achievement of EASI100 were also observed at week 4 (29 of 348 [8.3%] vs 6 of 344 [1.7%]) and maintained through week 16 (97 of 348 [27.9%] vs 26 of 344 [7.6%]) (Figure 2C). In addition, upadacitinib-treated patients had significantly greater reductions than dupilumab-treated patients in mean (SE) Worst Pruritus NRS as early as week 1 (−31.4% [1.7%] vs −8.8% [1.8%]) and maintained through week 16 (−66.9% [1.9%] vs −49.0% [2.0%]) (Figure 2D).

A greater proportion of upadacitinib-treated than dupilumab-treated patients achieved EASI75 (223 of 348 [64.2%] vs 205 of 344 [59.5%]; $P = .21$ for upadacitinib vs dupilumab without adjustment for multiplicity) at week 24 (eTable 5 in Supplement 2). In addition, EASI90 was achieved at week 24 by 194 of 348 upadacitinib-treated patients (55.6%) and EASI100 was achieved at week 24 by 95 of 348 upadacitinib-treated patients (27.3%), while EASI90 was achieved at week 24 by 164 of 344 dupilumab-treated patients (47.6%; $P = .04$ for upadacitinib vs dupilumab without adjustment for multiplicity) and EASI100 was achieved at week 24 by 45 of 344 dupilumab-treated patients (13.1%; $P < .001$ for upadacitinib vs dupilumab without adjustment for multiplicity). Upadacitinib-treated patients also had greater improvement from baseline in mean (SD) Worst Pruritus NRS than dupilumab-treated patients at week 24 (63.1% [2.7%] vs 54.7% [2.8%]; $P = .03$ for upadacitinib vs dupilumab without adjustment for multiplicity).

Safety Outcomes

The safety profile of upadacitinib in this study was consistent with that observed in 1 phase 2b[7] and 3 pivotal phase 3 clinical trials (Measure Up 1, Measure Up 2, and AD Up)[8,9] (**Table 3**). No new safety risks of upadacitinib were observed in this AD study compared with other AD studies. The 16-week incidence rates of TEAEs were 71.6% in upadacitinib-treated patients (249 of 348) and 62.8% in dupilumab-treated patients (216 of 344). The rates of serious TEAEs and AEs leading to study drug discontinuation were 2.9% (10 of 348) and 2.0% (7 of 348) for upadacitinib and 1.2% (4 of 344) and 1.2% (4 of 344) for dupilumab, respectively. One death due to influenza-associated bronchopneumonia was reported in a 40-year-old upadacitinib-treated patient.

Through 16 weeks of treatment, the most frequently reported AE among patients treated with upadacitinib was acne (55 [15.8%]), whereas acne was reported by 9 patients treated with dupilumab (2.6%) (Table 3). All acne events were mild or moderate in severity, primarily involved the face and trunk, and did not result in scarring; none led to study drug discontinuation. The most frequently reported AE among patients treated with dupilumab was conjunctivitis (29 [8.4%]), whereas conjunctivitis was reported by 5 patients treated with upadacitinib (1.4%). All conjunctivitis cases were mild or moderate in severity, and none led to study drug discontinuation.

Among AEs of special interest, rates of serious infection (4 [1.1%] vs 2 [0.6%]), eczema herpeticum (1 [0.3%] vs 0%), and herpes zoster (7 [2.0%] vs 3 [0.9%]) were numerically higher for patients treated with upadacitinib than those treated with dupilumab, all at generally low levels (Table 3). Each of the serious infections was reported in a single patient. No eczema herpeticum or herpes zoster event was considered to be serious. All herpes zoster events were mild or moderate in severity, and none led to study drug discontinuation. Most herpes zoster events involved a single dermatome; 2 herpes zoster events involved 3 or more dermatomes, and 1 had ophthalmic involvement (periorbital skin) in the upadacitinib group.

The rate of hepatic disorders was higher among patients treated with upadacitinib than those treated with dupilumab (10 [2.9%] vs 4 [1.2%]) (Table 3). Most of the hepatic disorders were transaminase elevations that were mild or moderate in severity, transient, and reported as singular

Table 2. Primary and Ranked Secondary End Points

End point	Time point	Dupilumab, 300 mg (n = 344)	Upadacitinib, 30 mg (n = 348)	Difference	*P* value
Primary end point					
Achievement of EASI75[a]	Week 16	210 (61.1) [55.9 to 66.2]	247 (71.0) [66.2 to 75.8]	10	.006
Secondary end points in order of ranking					
% Change from baseline in worst pruritus NRS[b]	Week 16	−49.0 (2.0) [−52.9 to −45.2]	−66.9 (1.9) [−70.6 to −63.2]	−17.84	<.001
No.		251	258		
Achievement of EASI100[a]	Week 16	26 (7.6) [4.8 to10.4]	97 (27.9) [23.2 to 32.6]	20.3	<.001
Achievement of EASI90[a]	Week 16	133 (38.7) [33.6 to 43.9]	211 (60.6) [55.4 to 65.7]	21.8	<.001
% Change from baseline in Worst Pruritus NRS[b]	Week 4	−31.7 (2.2) [−36.1 to −27.3]	−59.5 (2.2) [−63.8 to −55.2]	−27.8	<.001
No.		310	333		
Achievement of EASI75[a]	Week 2	60 (17.5) [13.5 to 21.5]	152 (43.7) [38.4 to 48.8]	26.0	<.001
% Change from baseline in Worst Pruritus NRS[b]	Week 1	−8.8 (1.8) [−12.3 to −5.3]	−31.4 (1.7) [−34.9 to −28.0]	−22.7	<.001
No.		327	337		
Worst Pruritus NRS improvement ≥4 points[a,c]	Week 16	120 (35.7) [30.7 to 41.0]	188 (55.3) [49.9 to 60.5]	19.3	<.001
No.	NA	336	340	NA	NA

Abbreviations: EASI75, 75% improvement in the Eczema Area and Severity Index; NA, not applicable; NRS, Numerical Rating Scale.

[a] No. (%) [95% CI].

[b] Least-squares mean (SD) [95% CI].

[c] Analyzed for patients with Worst Pruritus NRS of 4 points or higher at baseline.

abnormalities without recurrence; none were serious, and 2 upadacitinib-treated patients discontinued study drug owing to transaminase elevation. Rates of anemia (7 [2.0%] vs 1 [0.3%]), neutropenia (6 [1.7%] vs 2 [0.6%]), and creatinine phosphokinase elevations (23 [6.6%] vs 10 [2.9%]) were higher for patients treated with upadacitinib than those treated with dupilumab, respectively. There was a single event of thrombocytopenia (grade 1 in severity) reported in a patient treated with upadacitinib. Most of these laboratory test-related AEs were mild or moderate in severity, transient, and reported as singular abnormalities without recurrence, with only 1 event deemed serious (decreased hemoglobin reported in the dupilumab-treated group); none of these events led to study drug discontinuation. No drug-induced liver injury or rhabdomyolysis events were reported.

One case of malignant neoplasm was reported in each treatment group: 1 breast carcinoma in a 68-year-old upadacitinib-treated patient (after week 16; eTable 6 in Supplement 2) and 1 keratoacanthoma in a 69-year-old dupilumab-treated patient. No cases of adjudicated venous thromboembolic events, major adverse cardiovascular events, active tuberculosis, or gastrointestinal perforation were reported in either treatment group. Safety data through the end of the monitoring period are summarized in eTable 6 in Supplement 2.

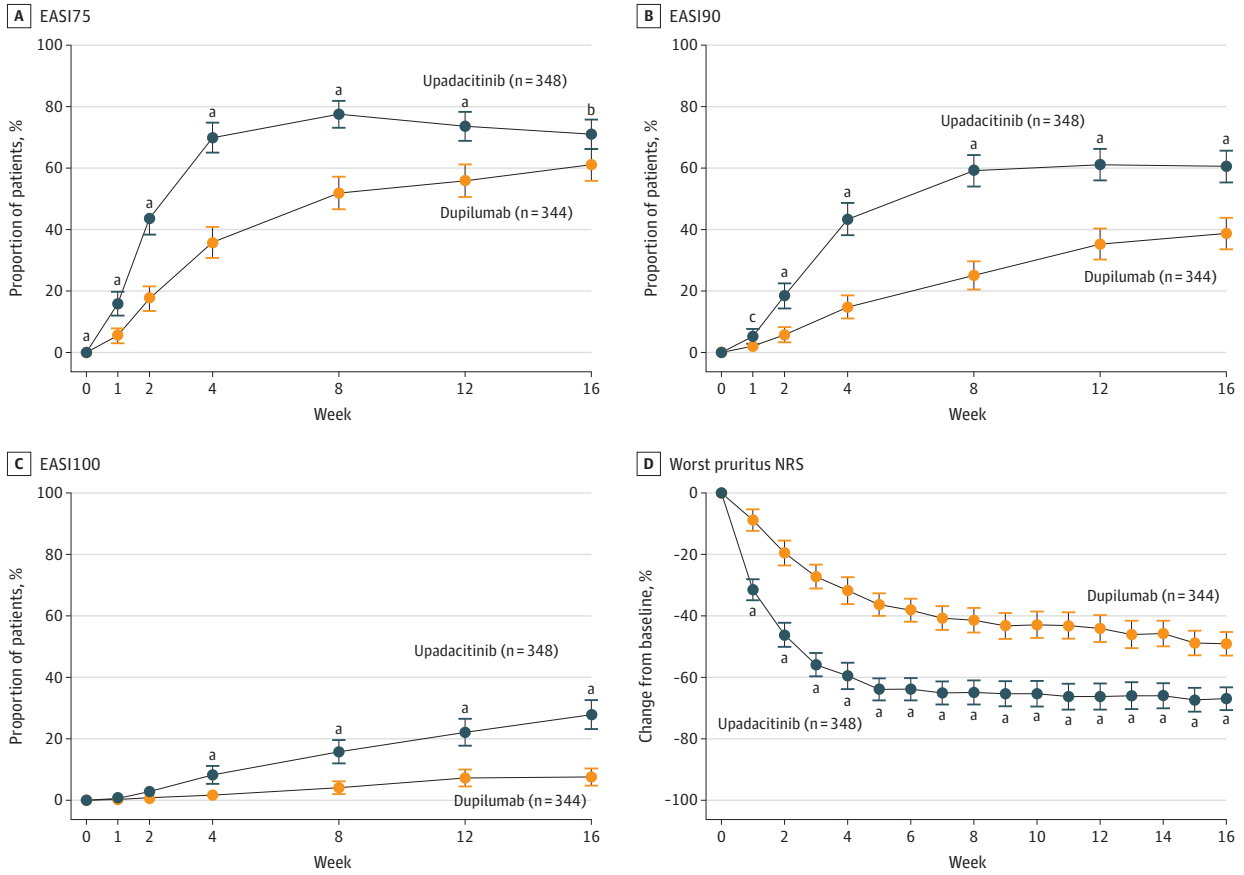
Five nonserious cases of COVID-19 were reported during the study—4 in the upadacitinib group and 1 in the dupilumab group. Treatment was temporarily interrupted for 3 upadacitinib patients and resumed after resolution of the infection. Treatment was not interrupted for the fourth upadacitinib patient or the dupilumab patient.

Discussion

To our knowledge, Heads Up is the first study directly comparing upadacitinib with dupilumab for AD and is now the sixth clinical trial examining upadacitinib for the indication. This study met the primary end point of EASI75 at week 16 and all ranked secondary end points, demonstrating superiority of upadacitinib vs dupilumab for the treatment of adults with moderate-to-severe AD. The most significant differences between upadacitinib and dupilumab were in the rapidity of onset and the ability to better achieve high levels of skin clearance (eg, EASI90 and EASI100). At week 24, upadacitinib-treated patients continued to show numerically better results compared with dupilumab-treated patients for measures of skin clearance and itch relief. Upadacitinib was generally safe and well tolerated with no new safety risks observed.

Despite the approval of dupilumab in recent years, there remains an unmet need for therapies that provide better efficacy outcomes, such as clear or almost clear skin, for patients with moderate-to-severe AD. Achievement of higher levels of efficacy in AD is associated with greater improvements in health-related quality of life.[12] The relatively high proportions of patients treated with upadacitinib

Figure 2. Efficacy Over Time



A, Proportion of patients achieving 75% improvement in Eczema Area and Severity Index (EASI75) B, Proportion of patients achieving 90% improvement in EASI (EASI90). C Proportion of patients achieving 100% improvement in EASI (EASI100). D, Mean percentage change in Worst Pruritus Numerical Rating Scale (NRS) for patients treated with upadacitinib or dupilumab by nonresponder imputation incorporating multiple imputation to handle missing data due to COVID-19. Error bars indicate 95% CIs (synthetic result based on *t* test distribution from the PROC MIANALYZE procedure in SAS if there were missing data due to COVID-19 or was based on the normal approximation to the binomial distribution if there were no missing data due to COVID-19).

[a] $P \leq .001$.

[b] $P \leq .01$.

[c] $P \leq .05$.

achieving EASI90 and EASI100 at week 16, reported here and elsewhere,[7-9] may become important regarding future AD treatment goals. A similar shift has occurred in recent years with the treatment of patients with another chronic inflammatory skin disease, psoriasis, where treatment success shifted from 75% improvement in the Psoriasis Area and Severity Index to 90% and 100% improvement (PASI90 and PASI100, respectively). As the effectiveness of new drugs for psoriasis have improved, the higher relative improvement scores PASI90 and PASI100 have become the benchmark for systemic therapies, and we expect to see a similar trend in AD treatment benchmarks.

Treatment effect (including skin and itch improvement) was also experienced more rapidly with upadacitinib compared with dupilumab. Statistically significant skin improvement as measured by EASI75 was attained as early as week 2 with upadacitinib, and significantly higher rates of clinically meaningful improvements in itch were reported as early as week 1. It is well established that patients prefer treatments with a rapid onset of action.[13-15] Upadacitinib-treated patients achieved significantly higher rates of the stringent skin improvement thresholds EASI90 and EASI100 compared with dupilumab.

Several key inflammatory cytokines are involved in the pathogenesis of AD signal via JAK1, including IL-4 and IL-13 (epidermal barrier dysfunction), IL-22 (epidermal hyperproliferation), IL-31 (itch neuron stimulation), IFN-γ (lesion chronicity), and TSLP (T_H2 cell differentiation).[3,4,16] Dupilumab targets the shared IL-4 and IL-13 receptor. By selectively inhibiting JAK1, upadacitinib abrogates the signaling of a wider range of proinflammatory mediators, including IL-4, IL-13, IL-22, IL-31, IFN-γ, and TSLP. The simultaneous inhibition of multiple pathways may contribute to the efficacy and rapidity effects of upadacitinib compared with dupilumab.

The safety profile of upadacitinib in this study was consistent with that noted in 1 phase 2b trial[7] and 3 pivotal phase 3 clinical trials (Measure Up 1, Measure Up 2, and AD Up),[8,9] with no new safety risks observed. In contrast to pre-

vious studies of JAK inhibitors in patients with rheumatoid arthritis, higher rates of acne were reported in studies of upadacitinib in patients with AD. Of note, acne has also been among the most frequently reported TEAEs for other JAK inhibitors in AD (abrocitinib and baricitinib); the mechanism underlying this AE is unclear.[17-19] The rate of study drug discontinuation secondary to AEs was numerically higher with upadacitinib. Rates of serious infection, eczema herpeticum, herpes zoster, and laboratory- test-related AEs were numerically higher with upadacitinib, while the rates of conjunctivitis and injection-site reactions were numerically higher with dupilumab. No venous thromboembolic events, major adverse cardiovascular events, or gastrointestinal perforations were reported with either treatment. Overall, these observations were consistent with the known safety profile of each drug.

Limitations

This study has some limitations. The data reported here are results through 24 weeks of treatment, with primary and ranked secondary end points at week 16. Longer-term data are being collected in a separate open-label extension study. Although not necessarily a limitation, this study evaluated both upadacitinib and dupilumab as monotherapy treatments, and patients who received any topical agent as rescue therapy were treated as nonresponders after receipt of rescue therapy. In real-world practice, many patients use systemic therapies in combination with topical therapies[20]; concomitant use of topical corticosteroids is addressed in a separate study of upadacitinib for AD.[9]

To maintain blinding, the monotherapy treatments of oral upadacitinib and subcutaneous dupilumab were each accompanied by a placebo for the opposite therapy, but there was no comparison against placebo as tested in the pivotal studies of these treatments. When dupilumab, 300 mg every 2 weeks, was given as monotherapy in SOLO1 and SOLO2, 51% and 44% of patients, respectively, achieved EASI75 at week 16 when compared with 15% and 12% for placebo, respectively.[5] Higher response rates for dupilumab may have been observed in the present study owing to the lack of a placebo comparator and subsequent responder or efficacy assessor bias. However, this potential bias did not seem to impact response rates in the upadacitinib group; in the upadacitinib placebo-controlled monotherapy studies, Measure Up 1 and Measure Up 2, 79.7% and 72.9% of patients treated with upadacitinib, 30 mg once daily, achieved EASI75 at week 16, respectively, compared with 16.3% and 13.3% for placebo, respectively.[8]

Conclusions

Overall, upadacitinib was well tolerated and provided superior efficacy compared with dupilumab after 16 weeks of treatment in adults with moderate-to-severe AD. Upadacitinib achieved higher levels of skin clearance and itch relief with a more rapid onset of action vs dupilumab. Upadacitinib is an effective treatment option for patients with moderate-to-severe AD and may help inform future treatment decisions.

Table 3. TEAEs Through Week 16 for All Patients Receiving 1 Dose or More of Study Drug

TEAE	Patients, No. (%)	
	Dupilumab, 300 mg (n = 344)	Upadacitinib, 30 mg (n = 348)
AE	216 (62.8)	249 (71.6)
AE with reasonable possibility of being drug-related[a]	122 (35.5)	153 (44.0)
Severe AE	14 (4.1)	25 (7.2)
SAE	4 (1.2)	10 (2.9)
SAE with reasonable possibility of being drug related[a]	2 (0.6)	4 (1.1)
AE leading to discontinuation of study drug	4 (1.2)	7 (2.0)
AE leading to death[b]	0	1 (0.3)
AEs of special interest		
Serious infections	2 (0.6)	4 (1.1)
Opportunistic infection, excluding tuberculosis and herpes zoster[c]	0	1 (0.3)
Herpes zoster	3 (0.9)	7 (2.0)
Active tuberculosis	0	0
Nonmelanoma skin cancer[d]	1 (0.3)	0
Malignant neoplasm, excluding NMSC	0	0
Lymphoma	0	0
Hepatic disorder[e]	4 (1.2)	10 (2.9)
Adjudicated gastrointestinal perforations	0	0
Anemia	1 (0.3)	7 (2.0)
Neutropenia	2 (0.6)	6 (1.7)
Lymphopenia	0	2 (0.6)
Creatine phosphokinase elevation	10 (2.9)	23 (6.6)
Renal dysfunction	1 (0.3)	1 (0.3)
Adjudicated major adverse cardiovascular events	0	0
Adjudicated venous thromboembolic events	0	0
TEAEs reported by ≥5% in either treatment group		
Acne[f]	9 (2.6)	55 (15.8)
Dermatitis atopic	29 (8.4)	24 (6.9)
Upper respiratory tract infection	13 (3.8)	22 (6.3)
Blood CPK level increased	10 (2.9)	23 (6.6)
Nasopharyngitis	22 (6.4)	20 (5.7)
Headache	21 (6.1)	14 (4.0)
Conjunctivitis	29 (8.4)	5 (1.4)

Abbreviations: AE, adverse event; CPK, creatine phosphokinase; NMSC, nonmelanoma skin cancer; SAE, serious AE; TB, tuberculosis; TEAE, treatment-emergent adverse event.

[a] As assessed by investigator.

[b] A 40-year-old woman who had bronchopneumonia associated with influenza A was found deceased at home on study day 70.

[c] All opportunistic infections were eczema herpeticum.

[d] Keratoacanthoma, no reasonable possibility of association with study drug according to the investigator.

[e] Hepatic disorders: most were elevated transaminase levels.

[f] Most acne events consisted primarily of inflammatory papules, pustules, and comedones, involving the face. All events were nonserious. None led to treatment discontinuation.

ARTICLE INFORMATION

Accepted for Publication: June 26, 2021.

Published Online: August 4, 2021. doi:10.1001/jamadermatol.2021.3023

Correction: This article was corrected on December 15, 2021, to fix a percentage and include *P* values at week 24 in the Results section and to add more data to eTable 5 in Supplement 2.

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Author Contributions: Drs Ladizinski and Chu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
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Statistical analysis: Teixeira, Hu, Wu.
Obtained funding: Teixeira, Chu.
Administrative, technical, or material support: Teixeira, Simpson, Liu, Eyerich.
Supervision: Blauvelt, Teixeira, de Bruin-Weller, Barbarot, Prajapati, Chu, Eyerich.

Conflict of Interest Disclosures: Dr Blauvelt reported receiving personal fees and reimbursement for performing clinical studies from AbbVie and Regeneron; and personal fees from Sanofi during the conduct of the study; and served as a scientific adviser and/or clinical study investigator for Abcentra, Aligos, Almirall, Amgen, Arcutis, Arena, ASLAN, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly and Company, Evommune, Forte, Galderma, Incyte, Janssen, Landos, Leo, Novartis, Pfizer, Rapt, Sun Pharma, and UCB Pharma. Drs Teixeira, Hu, Wu, Liu, Ladizinski, and Chu are full-time employees of AbbVie Inc, and may hold AbbVie stock and/or stock options. Dr Simpson reported receiving grants from AbbVie, Amgen, Eli Lilly, Incyte, Kyowa Hakko Kirin, Leo Pharmaceuticals, Merck, Novartis, Pfizer, Regeneron, Sanofi, Tioga, and Vanda; personal fees from AbbVie, Amgen, Arena, BenevolentAI Bio Limited, BiomX Ltd, Bluefin Biomedicine Inc, Boehringer Ingelheim, Boston Consulting Group, Collective Acumen LLC (CA), Coronado, Dermira, Eli Lilly, Evidera, ExcerptaMedica, Forte Bio RX, Incyte, Janssen, Kyowa Kirin Pharmaceutical Development, Leo Pharm, Medscape LLC, Novartis, Ortho Dermatologics, Pfizer, Pierre Fabre Dermo Cosmetique, Regeneron, Roivant, Sanofi Genzyme, SPARC India, and Valeant outside the submitted work. Dr Costanzo reported receiving grants from AbbVie during the conduct of the study; grants from Novartis and Galderma; and personal fees from Janssen, UCB, Lilly, and Sanofi outside the submitted work. Dr de Bruin-Weller reported receiving grants from and serving as a speaker, advisory board member, and consultant for AbbVie; serving as a speaker and consultant for Almirall; serving as an advisory board member for Arena; serving as an advisory board member for ASLAN; serving as a speaker and advisory board member for Galderma; serving as an advisory board member for Janssen; serving as a speaker, advisory board member, and consultant for Pfizer; grants from Eli Lilly, Leo Pharma, Regeneron, and Sanofi Genzyme outside the submitted work. Dr Barbarot reported receiving grants from Novartis; and personal fees from Sanofi, Leo Pharma, AbbVie, Janssen, Lilly, Pfizer, UCB, and Almirall during the conduct of the study. Dr Prajapati reported receiving personal fees from AbbVie, Actelion, Amgen, AnaptysBio, Aralez, Arcutis, Aspen, Bausch Health, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Cipher, Concert, Dermira, Eli Lilly, Galderma, GlaxoSmithKline, Homeocan, Incyte, Janssen, Leo Pharma, Medexus, Novartis, Pediapharm, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharma, Tribute, UCB, and Valeant outside the submitted work. Dr Lio reported receiving grants from AOBiome, Regeneron/Sanofi Genzyme, and AbbVie; personal fees from Regeneron/Sanofi Genzyme, Leo, Eli Lilly, Pfizer, Galderma, L'Oreal, Almirall, ASLAN Pharma Advisory board, Dermavant, Pierre Fabre, Menlo Therapeutics, IntraDerm, Exeltis, AOBiome, Arbonne, and Amyris; stock options from Micreos and; other royalties from patented product from Theraplex; in addition, Dr Lio had a patent for Theraplex AIM moisturizer pending Theraplex company. Dr Chu reported receiving personal fees from AbbVie during the conduct of the study; and personal fees from AbbVie outside the submitted work. Dr Eyerich reported receiving grants and personal fees from AbbVie during the conduct of the study; personal fees from Almirall, BMS, Lilly, Leo, Janssen, Novartis, UCB, and Sanofi; and grants from Lilly, Leo, Janssen, Novartis, and UCB outside the submitted work. No other disclosures were reported.

Funding/Support: AbbVie funded the research for these studies and provided writing support for this manuscript.

Role of the Funder/Sponsor: AbbVie Inc participated in the study design; study research; collection, analysis, and interpretation of data; and writing, reviewing, and approving this manuscript for submission.

Data Sharing Statement: See Supplement 3.

Additional Information: AbbVie and the authors thank all study investigators for their contributions and the patients who participated in this study. Priya S. Mathur, PhD, AbbVie, provided medical writing support in production of this publication; she was compensated as a full-time employee of AbbVie Inc.

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