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ORIGINAL RESEARCH

Risankizumab in Patients with Moderate-to-Severe Atopic Dermatitis: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study

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ABSTRACT

Introduction: Atopic dermatitis (AD) is a heterogeneous disease, with involvement of the T-helper cell (Th) 2, Th22, and potentially Th17 pathways, supporting the use of interleukin (IL)-23 and IL-22 blockade in AD.

Methods: This phase 2, multicenter, randomized, double-blind, placebo-controlled trial (NCT03706040) evaluated the efficacy and safety of risankizumab, an IL-23 inhibitor, in patients (≥ 12 years old) with moderate-to-severe AD, defined by an Eczema Area and Severity Index (EASI) ≥ 16, affected body surface area ≥ 10%, and a Validated Investigator Global Assessment for AD (vIGA-AD) score ≥ 3. Patients were randomized 2:2:1 to 16-week treatment with risankizumab 150 mg, risankizumab 300 mg, or placebo in period A; patients receiving placebo were re-randomized 1:1 to risankizumab 150 mg or 300 mg and patients receiving risankizumab continued on their randomized dose in 36-week period B. Study drug was administered at baseline and weeks 4, 16, 28, and 40. The primary endpoint was the proportion of patients achieving a ≥ 75% reduction from baseline in EASI (EASI 75) at week 16. Safety was analyzed in all randomized patients who received study medication.

Results: Neither the risankizumab 150 mg (n = 69) nor the 300 mg dose group (n = 69) demonstrated a significantly higher proportion of patients achieving EASI 75 at week 16 compared with the placebo group (n = 34; treatment difference [95% CI] 13.0% [–1.7 to 27.7%; P = 0.084] and 10.0% [–4.6 to 24.6%; P = 0.179], respectively). Most adverse events were mild to moderate in severity; five patients receiving risankizumab reported serious adverse events, including two patients who reported cellulitis.

Conclusions: Risankizumab was generally well tolerated, with no new safety concerns identified. The study's primary endpoint was not met, with no significant difference in the proportion of patients achieving an EASI 75 response at

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week 16 with risankizumab 150 mg or 300 mg versus placebo.
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Keywords: Atopic dermatitis; Interleukin-23; Risankizumab

Key Summary Points

Why carry out this study?

Although the two predominant helper T-cell subsets, Th2 and Th22, are recognized across major atopic dermatitis (AD) subtypes, some research findings suggest that AD may be a multi-axis immune disease with involvement of the Th2, Th22, and potentially Th17 pathways, supporting the use of interleukin (IL)-23 and IL-22 blockade in AD.

This proof-of-concept study compared the efficacy and safety of risankizumab, an IL-23 inhibitor, versus placebo for the treatment of moderate-to-severe AD in adult and adolescent patients.

What was learned from the study?

Although risankizumab was generally well tolerated, the proportion of patients achieving the primary endpoint, a 75% reduction from baseline in EASI (EASI 75) at week 16 with risankizumab 150 mg or 300 mg was not significantly different from placebo.

Findings from this study as well as those from a previous secukinumab phase 2 AD trial suggest that IL-17/IL-23 blockade is not clinically effective in AD.

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin condition that affects an estimated 14% of children and 7% of adults in the United States [1] and 1–3% of adults worldwide [2], with large variations across countries and ethnicities [3, 4]. AD is characterized by recurrent patches of red, scaly, and oozing lesions accompanied by pruritus that may often be severe [5] and is associated with multiple comorbid conditions, such as rhinitis, food allergies, and asthma [6, 7]. The pathophysiology of AD comprises a complex interplay between inflammation, environmental factors, genetics, and skin barrier dysfunction. The goals of therapy are to reduce pruritus and establish persistent disease control [5]. Although certain systemic treatments (e.g., dupilumab, upadacitinib) address the needs of some patients with moderate-to-severe AD, a large unmet need for short- and long-term safe and efficacious treatments still exists in this population.

Atopic dermatitis phenotypically is a heterogeneous disease. The two predominant helper T cell subsets, Th2 and Th22, are recognized across major subtypes of AD; however, other specific subtypes of AD, including Asian-origin, pediatric, and intrinsic, have a pronounced interleukin (IL)–17 component as well as tissue patterning that corresponds with typical psoriasis histopathology [7, 8]. In addition, there is evidence that the Th17/IL-23 axis is upregulated in patients with AD [9, 10], and it has been shown that IL-23 is released after scratching, which polarizes dendritic cells to drive an IL-22 response of epidermal thickening [11]. Together, these findings suggest that AD may be a multi-axis immune disease with involvement of the Th2, Th22, and potentially Th17 pathways, supporting the use of IL-23 and IL-22 blockade in AD.

Risankizumab inhibits IL-23 by binding to its p19 subunit [12] and has been approved for the treatment of adult patients with moderate-to-severe psoriasis, active psoriatic arthritis, and moderately to severely active Crohn's disease [13]. This proof-of-concept study compared the safety and efficacy of risankizumab versus placebo for the treatment of moderate-to-severe AD in adult and adolescent patients.

METHODS

Eligible adult and adolescent (≥ 12 years old) patients with a physician-confirmed diagnosis of AD according to the Hanifin and Rajka criteria [14], were enrolled if onset of symptoms were at least 2 years before the baseline visit. Patients had moderate-to-severe AD as defined by an Eczema Area and Severity Index (EASI) score ≥ 16, affected body surface area ≥ 10%, and a Validated Investigator Global Assessment for AD (vIGA-AD) score ≥ 3. Patients were also required to have a weekly average daily Worst Pruritus Numeric Rating Scale (WP-NRS) value of ≥ 4 at baseline. Patients with a past inadequate response to topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) or for whom topical treatments were deemed medically inadvisable were also included after appropriate washout.

Patients were not eligible if they had an active systemic infection in the prior 2 weeks, were immunocompromised, were being concurrently treated with medications that would interfere with results, had other skin comorbidities, or were pregnant. Prior exposure to biologic immunomodulatory agents (e.g., omalizumab, dupilumab, rituximab) or systemic or topical Janus kinase (JAK) inhibitors was prohibited. Exposure to non-biologic systemic therapy, such as methotrexate, cyclosporine, azathioprine, phosphodiesterase 4 inhibitors, mycophenolate mofetil, and corticosteroids (except inhaled, topical ophthalmic, or intranasal corticosteroids), phototherapy, or traditional Chinese medicines were not permitted within 4 weeks of the baseline visit and during the study. Topical treatments, including TCS, TCI, prescription moisturizers, or moisturizers containing additives (e.g., ceramide, hyaluronic acid, urea, heparin, filaggrin) were not permitted within 10 days of the baseline visit.

Study Design

This study was a phase 2, multicenter, randomized, double-blind, placebo-controlled trial (ClinicalTrials.gov, NCT03706040). The study included a screening period of up to 35 days, a 16-week double-blind treatment period (period A), a 36-week double-blind treatment period (period B), and a follow-up period of 20 weeks after the last study drug administration. During period A, patients were randomized 2:2:1 to treatment with risankizumab 150 mg, risankizumab 300 mg, or placebo. Patients receiving placebo who completed period A and entered period B were re-randomized 1:1 to risankizumab 150 mg or 300 mg; patients receiving risankizumab continued on their randomized dose in period B.

Patients were randomized via an Interactive Response Technology system, which assigned a unique identification number that corresponded with a specific medication kit packaged with risankizumab or matching placebo to fulfill the study design and maintain blinding. Randomization was stratified by baseline disease severity (moderate [vIGA-AD 3] vs. severe [vIGA-AD 4]) and geographic region (Japan vs. rest of world). The investigators, study site personnel, and patients remained blinded for the duration of the study; the sponsor was blinded for period A but unblinded after the primary analysis at week 16.

Study medication was administered at baseline (study day 0) and weeks 4, 16, 28, and 40. Patients were administered four pre-filled syringes (PFS) for each dose by a healthcare professional at each study site. Patients in the placebo group received four placebo PFS (period A only), those in the risankizumab 150 mg group received two risankizumab 75-mg PFS and two placebo PFS, and those in the risankizumab 300 mg group received 4 risankizumab 75-mg PFS. All patients were required to use an additive-free bland emollient twice daily for ≥ 7 days before baseline and during the study.

Efficacy Assessments

The primary efficacy endpoint was the proportion of patients achieving at least a 75% reduction from baseline in EASI (EASI 75) at week 16. Ranked secondary endpoints were (1) the proportion of patients achieving a vIGA-AD response of 0 or 1 (on a five-point scale) with

a ≥ 2-point reduction from baseline at week 16 and (2) the proportion of patients achieving a ≥ 4 point-reduction in WP-NRS from baseline to week 16.

Safety Assessments

Safety was assessed by monitoring treatment emergent adverse events (TEAEs), serious adverse events, and adverse events (AEs) of safety interest. AEs were coded according to the Medical Dictionary for Regulatory Activities, version 23.0. Vital signs and clinical laboratory testing were performed throughout the study. Electrocardiograms and physical examinations were performed at screening, baseline (physical examination only), and at week 52 or premature discontinuation. TEAEs were defined as any event with onset or worsening on or after the first dose of study drug and no more than 140 days after the last dose of study drug. For patients who entered periods A and B, AEs with an onset or worsening date on or after the first dose of study drug in period A and before the first dose of study drug in period B were recorded as AEs in period A.

Anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were determined from blood collected by venipuncture at baseline and weeks 4, 16, and 52. The number and percentage of patients with ADA and NAb were calculated by dose group.

Statistical Analyses

All efficacy analyses were performed using the intent-to-treat population, which included all randomized patients. The primary analysis was performed after all ongoing patients completed week 16. Assuming an EASI 75 response rate of 15% in the placebo group, a sample size of 155 patients (62 patients each for the risankizumab 150 mg and 300 mg groups and 31 patients for the placebo group) was estimated to provide more than 90% power to detect a difference of at least 36% between each risankizumab group and the placebo group using a two-sided test at a 0.025 significance level.

Safety analyses were performed for all randomized patients who received ≥ 1 dose of the study drug and were grouped "as treated" by the first dose the patient received for periods A and B. Additionally, safety was assessed in an "all-risankizumab" population that included all patients who received ≥ 1 dose of risankizumab in the study.

Pairwise comparison of the primary endpoint and the ranked secondary endpoints was conducted, with each of the two risankizumab groups (risankizumab 150 and 300 mg) compared against the placebo group using the Cochran–Mantel–Haenszel test, stratified by baseline disease severity (moderate [vIGA-AD 3] vs. severe [vIGA-AD 4]). For the primary and secondary endpoints and other binary endpoints, missing data were handled using non-responder imputation with multiple imputation to handle missing data due to COVID-19. For continuous efficacy endpoints, treatment groups were compared using mixed-effect model repeated measurement, with categorical fixed effects of treatment, visit, and treatment-by-visit interaction, adjusting for the stratification factor of vIGA-AD categories (moderate vs. severe), and corresponding continuous baseline value. The least squares (LS) mean change from baseline estimates and 95% CIs of the LS mean changes between each risankizumab treatment group compared with placebo were reported. An observed case approach was used for analyses of long-term efficacy in period B.

Ethics

The study was conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. A local and/or central independent ethics committee or institutional review board approved the study protocol and related documents for each study site (Table S1). Patients provided written informed consent before initiation of any screening or

study-related procedures. For adolescents, authorization and/or consent was provided by a parent or legal guardian, where applicable.

RESULTS

This study was conducted from December 27, 2018, (first patient visit) to April 26, 2021, (last patient last visit). A total of 243 patients were screened in the study from the United States, Puerto Rico, Canada, Japan, and Australia; of these, 172 fulfilled patient selection criteria and were randomized 2:2:1 to risankizumab 150 mg (n = 69), risankizumab 300 mg (n = 69), or placebo (n = 34; Fig. 1). Of 172 patients, 144 (83.7%) completed period A and entered period B; 71 of 144 patients (49.3%) completed the study. The mean age of study participants was 43.3 years, ranging from 14 to 83 years. Patient demographics at baseline were similar across treatment groups. Baseline disease characteristics were also similar across treatment groups, with the overall population having a baseline mean EASI of 30, mean vIGA-AD of 3.4, and WP-NRS of 7.4. Each treatment arm had similar proportions of patients with vIGA-AD scores of 3 and 4 (Table 1).

The study was terminated after the primary analysis, thus, efficacy results reported herein focus on period A.

Efficacy

Neither the risankizumab 150 mg nor the 300 mg dose group demonstrated a statistically significantly higher proportion of patients achieving EASI 75 at week 16 compared with placebo (95% CI treatment difference: 13.0% [–1.7 to 27.7%; P = 0.084] and 10.0% [–4.6 to 24.6%; P = 0.179], respectively; Table 2 and Fig. 2). Because the testing hierarchy was broken after this step, no statistical significance can be claimed for other efficacy endpoints. The percentage (95% CI) of patients who achieved a vIGA-AD response of 0 or 1 with a ≥ 2-point reduction from baseline at week 16 was 5.9% (0.0–13.8%) for placebo, 14.5% (6.2–22.8%) for risankizumab 150 mg, and 5.8% (0.3–11.3%) for risankizumab 300 mg (Table 2 and Fig. 2). Numerically greater proportions of patients from both the risankizumab 150 mg (13.6%) and 300 mg (15.2%) groups achieved a WP-NRS reduction of ≥ 4 points from baseline at week 16 compared with the placebo group (0%; Table 2 and Fig. 2).

Safety Assessments

In both period A and period B of the study, risankizumab was generally well tolerated. Most AEs were mild to moderate in severity and did not lead to discontinuation of study drug. In period A, investigators reported AEs for 24 (70.6%), 38 (55.11%), and 39 (56.5%) patients in the placebo, risankizumab 150 mg, and risankizumab 300 mg groups, respectively (Table 3). The most common AEs reported with risankizumab were worsening of AD, nasopharyngitis, and pruritus. There were no serious AEs reported with risankizumab in period A. In period B, worsening of AD and nasopharyngitis were the most common AEs (Table 4). Five patients reported serious AEs, including two patients who reported cellulitis. No serious AEs led to discontinuation of risankizumab.

For the all-risankizumab population (Table 5), no adjudicated major adverse cardiovascular events (MACE), active tuberculosis infections, serious hypersensitivity, nor adjudicated anaphylactic reactions were reported among AEs of safety interest. Treatment-emergent serious infections and malignancies were observed for a small number of patients. One death attributed to COVID-19 was reported during the study in a patient receiving placebo during period A.

Effect of Immunogenicity on Risankizumab Serum Exposure

Pre-existing ADAs were detected in 1.9% (3/155) of patients who received at least one dose of risankizumab during the study duration. In evaluable patients who received risankizumab, the incidence of treatment-emergent ADAs to risankizumab was 10.9% (15/138) during weeks 0 to 52, with only 4 patients testing positive for

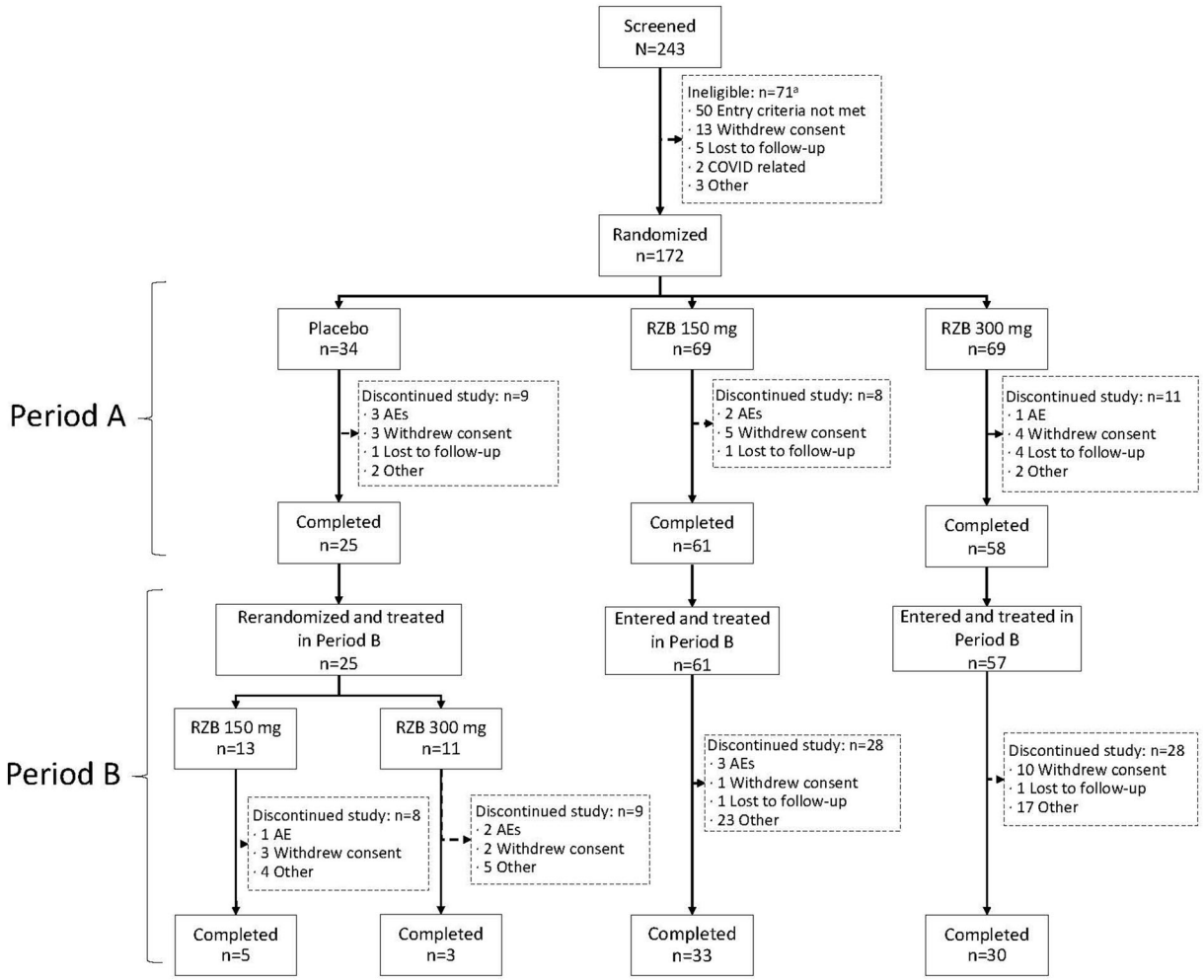

Fig. 1 Disposition flow chart of patient inclusion. *AEs* adverse events, *RZB* risankizumab. [a]The sum of the counts for reasons for ineligibility may be greater than the number of ineligible patients because patients were counted under each reason given

NAbs over the study duration. Due to the limited number of patients who developed ADA and/or NAb, the impact of immunogenicity on risankizumab exposure and efficacy cannot be interpreted.

DISCUSSION

This phase 2, multicenter, randomized, double-blind, placebo-controlled study is the first to investigate the efficacy and safety of the IL-23p19 inhibitor risankizumab as monotherapy in adult and adolescent patients for the treatment of moderate-to-severe AD inadequately controlled by topical medications. Enrolled patients had a longstanding diagnosis of AD, with a similar baseline disease profile as the patients in dupilumab, upadacitinib, and secukinumab phase 2 or 3 AD studies [15–18]. In the current study, a risankizumab 150-mg dose was selected based on findings that this dose provided maximum efficacy in risankizumab psoriasis trials [19], and a higher risankizumab 300-mg dose was included based on the reported higher inflammatory burden of AD versus psoriasis[7, 20]. The primary efficacy endpoint—the proportion of patients achieving an EASI 75 response at week 16—was not significantly different between either the

Table 1 Baseline patient demographics and disease characteristics

Characteristic	Placebo (n = 34)	Risankizumab 150 mg (n = 69)	Risankizumab 300 mg (n = 69)
Sex, n (%)			
Male	21 (61.8)	38 (55.1)	37 (53.6)
Female	13 (38.2)	31 (44.9)	32 (46.4)
Age, years, mean (SD)	45.5 (19.7)	41.7 (15.1)	43.8 (16.6)
Race, n (%)			
White	17 (50.0)	39 (56.5)	36 (52.2)
Black or African American	7 (20.6)	8 (11.6)	11 (15.9)
Asian	8 (23.5)	21 (30.4)	20 (29.0)
Other	2 (5.9)	1 (1.4)	2 (2.9)
Weight, kg, mean (SD)	82.9 (22.9)	79.7 (20.1)	78.3 (21.2)
BMI, kg/m^2, mean (SD)	28.3 (7.2)	27.3 (5.9)	27.2 (5.8)
< 25, n (%)	13 (38.2)	28 (40.6)	29 (42.0)
$25- < 30$, n (%)	9 (26.5)	22 (31.9)	17 (24.6)
≥ 30, n (%)	12 (35.3)	19 (27.5)	23 (33.3)
Disease duration, years, mean (SD)	14.2 (13.2)	21.4 (17.7)	19.3 (14.6)
EASI, mean (SD)[a]	30.9 (12.3)	31.1 (14.0)	28.7 (11.2)
vIGA-AD score, mean (SD)[b]	3.4 (0.5)	3.4 (0.5)	3.4 (0.5)
3 (moderate), n (%)	20 (58.8)	40 (58.0)	39 (56.5)
4 (severe), n (%)	14 (41.2)	29 (42.0)	30 (43.5)
WP-NRS, mean (SD)[c]	7.2 (1.5)	7.3 (1.8)	7.6 (1.9)
BSA affected, %, mean (SD)	44.8 (22.2)	46.3 (24.1)	42.9 (23.3)
SCORAD score, mean (SD)	65.2 (12.9)	68.6 (15.0)	64.9 (12.8)
DLQI, mean (SD)	13.1 (7.6)	15.6 (7.3)	16.2 (7.5)

BMI body mass index, *BSA* body surface area, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *SCORAD* scoring atopic dermatitis, *vIGA-AD* Validated Investigator Global Assessment for Atopic Dermatitis, *WP-NRS* Worst Pruritus Numeric Rating Scale

[a]Full scale range: 0 (none) to 72 (most severe)

[b]Full scale range: 0 (clear) to 4 (severe)

[c]Full scale range: 0 (no itch) to 10 (worst imaginable itch)

Table 2 Primary and key secondary outcomes ITT population

Endpoint	*n*	Responders, % (95% CI)	Adjusted % difference (95% CI)	Nominal *P* value
EASI 75 at week 16				
Placebo	34	11.8% (0.9–22.6%)		
Risankizumab 150 mg	69	24.6% (14.5–34.8%)	13.0% (−1.7 to 27.7%)	0.084
Risankizumab 300 mg	69	21.7% (12.0–31.5%)	10.0% (−4.6 to 24.6%)	0.179
vIGA-AD 0/1 with ≥ 2-point reduction from baseline at week 16				
Placebo	34	5.9% (0.0–13.8%)		
Risankizumab 150 mg	69	14.5% (6.2–22.8%)	8.7% (−2.5 to 20.0%)	0.129
Risankizumab 300 mg	69	5.8% (0.3–11.3%)	0.0% (−9.4 to 9.4%)	0.994
WP-NRS with ≥ 4-point reduction from baseline at week 16				
Placebo	33	0.0		
Risankizumab 150 mg	66	13.6% (5.4–21.9%)	13.7% (5.4–22.1%)	0.001
Risankizumab 300 mg	66	15.2% (6.5–23.8%)	15.3% (6.6–24.0%)	< 0.001

EASI 75 ≥ 75% reduction from baseline in Eczema Area and Severity Index, *ITT* intent to treat, *vIGA-AD* Validated Investigator Global Assessment for Atopic Dermatitis, *WP-NRS* Worst Pruritus Numeric Rating Scale

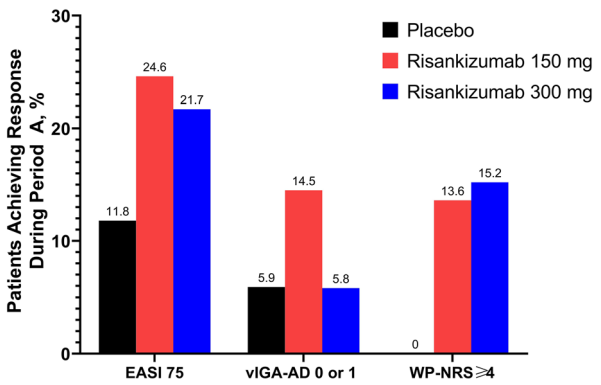

Fig. 2 Key efficacy outcomes at week 16[a]. *EASI 75* ≥ 75% improvement from baseline in Eczema Area and Severity Index, *vIGA 0 or 1* Validated Investigator Global Assessment of 0 or 1 with ≥ 2-point reduction from baseline, *WP-NRS* ≥ *4* Worst Pruritus Numeric Rating Scale ≥ 4-point reduction from baseline. [a]Results for categorical endpoints are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19

risankizumab 150 mg (24.6%) or 300 mg (21.7%) group and placebo (11.8%). The testing hierarchy was broken after this step, and no statistical significance can be claimed for other efficacy endpoints. Risankizumab did not provide a better response than placebo as measured by vIGA-AD. A numerically greater proportion of patients receiving risankizumab versus placebo showed improvement in itch at week 16 compared with placebo as assessed by WP-NRS. The response rates were lower than what has been observed in other clinical trials in AD [16, 18]. As a result of the minimal change in lesions and disease severity, the study was terminated after the primary analysis at week 16 (period A).

In the all-risankizumab population, most AEs were mild or moderate in severity and few led to discontinuation of risankizumab. The most frequently reported AEs were related to AD (i.e., worsening of AD and pruritus) and infections, such as nasopharyngitis and upper respiratory tract infections. Serious AEs were infrequent, with only cellulitis occurring in more than one patient ($n = 2$). Among areas of safety interest, there were no adjudicated MACE, active tuberculosis infections, hypersensitivity reactions, or adjudicated anaphylactic reactions in patients treated with risankizumab.

Table 3 Patients with treatment-emergent adverse events in period A

Adverse events, *n* (%)	Placebo (*n* = 34)	Risankizumab 150 mg (*n* = 69)	Risankizumab 300 mg (*n* = 69)
Any TEAE	24 (70.6)	38 (55.1)	39 (56.5)
Most common AEs[a]			
Worsening of AD	8 (23.5)	19 (27.5)	16 (23.2)
Pruritus	2 (5.9)	2 (2.9)	5 (7.2)
Nasopharyngitis	0	4 (5.8)	4 (5.8)
Serious AEs[b]	3 (8.8)	0	0
AEs leading to discontinuation	7 (20.6)	4 (5.8)	2 (2.9)
AEs leading to death	1 (2.9)	0	0
COVID-19–related deaths	1 (2.9)	0	0
AEs of safety interest			
Opportunistic infections excluding tuberculosis and herpes zoster[c]	1 (2.9)	1 (1.4)	0
Malignant tumors	1 (2.9)	0	0
Malignant tumors excluding NMSC	1 (2.9)	0	0
Serious hypersensitivity	1 (2.9)	0	0
Serious infections	1 (2.9)	0	0
Adjudicated anaphylactic reaction	0	0	0
MACE	0	0	0
Tuberculosis	0	0	0

AD atopic dermatitis, *AE* adverse event, *MACE* major adverse cardiovascular event, *NMSC* non-melanoma skin cancer, *TEAE* treatment-emergent adverse event

[a]AEs reported in ≥ 5% of patients in either risankizumab treatment group

[b]Serious AEs included COVID-19 leading to death, stage 1 cervical cancer leading to discontinuation, and worsening of AD leading to discontinuation; none of the serious AEs was considered to be treatment-related

[c]Includes human polyomavirus infection in 1 patient receiving placebo and Kaposi's varicelliform eruption in 1 patient receiving risankizumab 150 mg

Recently, dupilumab, upadacitinib, and secukinumab clinical trial data for the treatment of AD that measured EASI 75 response rates were published. Higher EASI 75 response rates were achieved at week 16 for the JAK inhibitor upadacitinib (60.1–79.7% vs. 13.3–16.3% for placebo) and the IL-4/IL-13 antagonist dupilumab (44.0–52.0% vs. 15% for placebo) [16, 18]. As with risankizumab, phase 2 study findings for the IL-17a antagonist secukinumab, paralleled findings in our study, showing lower response rates for the percentage improvement in EASI at week 16 [17]. Findings from our study as well as those from the secukinumab phase 2 AD trial [17] suggest that IL-17/IL-23 blockade is not clinically effective in AD.

Although this was a well-designed, fully powered, large phase 2 study, as with most randomized controlled clinical trials, the

Table 4 Patients with treatment-emergent adverse events in period B

Adverse events, *n* (%)	Placebo/ Risankizumab 150 mg (*n* = 13)	Placebo/ Risankizumab 300 mg (*n* = 11)	Risankizumab 150 mg (*n* = 61)	Risankizumab 300 mg (*n* = 57)
Any TEAE	6 (46.2)	5 (45.5)	29 (47.5)	29 (50.9)
Most common AEs[a]				
Worsening of AD	2 (15.4)	1 (9.1)	7 (11.5)	5 (8.8)
Nasopharyngitis	0	0	4 (6.6)	3 (5.3)
Cellulitis	0	0	1 (1.6)	2 (3.5)
Blood creatine phosphokinase increased	0	0	0	2 (3.5)
C-reactive protein increased	0	0	2 (3.3)	0
Pruritus	0	0	2 (3.3)	0
Toothache	0	2 (18.2)	0	0
COVID-19-related TEAE	0	0	0	1 (1.8)
Serious AEs[b]	0	0	2 (3.3)	3 (5.3)
AEs leading to discontinuation	2 (15.4)	0	2 (3.3)	0
AEs leading to death	0	0	0	0
AEs of safety interest				
Opportunistic infections excluding tuberculosis and herpes zoster[c]	0	0	1 (1.6)	1 (1.8)
Serious infections	0	0	1 (1.6)	1 (1.8)
Malignant tumors	0	0	1 (1.6)	0
Adjudicated anaphylactic reaction	0	0	0	0
Malignant tumors excluding NMSC	0	0	0	0
MACE	0	0	0	0
Serious hypersensitivity	0	0	0	0
Tuberculosis	0	0	0	0

AD atopic dermatitis, *AEs* adverse events, *MACE* major adverse cardiovascular event, *NMSC* non-melanoma skin cancer, *TEAE* treatment-emergent adverse event

[a]AEs reported in $\geq$ 2 patients in any treatment group

[b]In the risankizumab 150 mg group, serious AEs included cardiac arrhythmia and cellulitis; the investigator believed there was a reasonable possibility that the cellulitis was treatment-related. In the risankizumab 300 mg group, serious AEs included worsening of osteoarthritis (n = 1); amaurosis fugax (n = 1); and coccyx fracture, vertebral fracture, and cellulitis in 1 patient; none of the serious AEs was considered to be treatment-related

[c]Includes 1 patient each with cellulitis and 1 patient each with Kaposi's varicelliform eruption in the continuous risankizumab 150 mg and 300 mg groups

Table 5 Patients with treatment-emergent adverse events in the all-risankizumab population

Adverse events, *n* (%)	Risankizumab 150 mg *n* = 82	Risankizumab 300 mg *n* = 80	Overall *N* = 162
Any TEAE	57 (69.5)	55 (68.8)	112 (69.1)
Most common AEs[a]			
Worsening of AD	27 (32.9)	20 (25.0)	47 (29.0)
Nasopharyngitis	8 (9.8)	7 (8.8)	15 (9.3)
Pruritus	4 (4.9)	5 (6.3)	9 (5.6)
URTI	2 (2.4)	4 (5.0)	6 (3.7)
Impetigo	1 (1.2)	4 (5.0)	5 (3.1)
COVID-19–related TEAE	0	1 (1.3)	1 (0.6)
Serious AEs[b]	2 (2.4)	3 (3.8)	5 (3.1)
AEs leading to discontinuation	8 (9.8)	2 (2.5)	10 (6.2)
AEs leading to death	0	0	0
AEs of safety interest			
Serious infections	1 (1.2)	1 (1.3)	2 (1.2)
Opportunistic infections excluding tuberculosis and herpes zoster[c]	1 (1.2)	1 (1.3)	2 (1.2)
Malignant tumors	1 (1.2)	0	1 (0.6)
Adjudicated anaphylactic reaction	0	0	0
Malignant tumors excluding NMSC	0	0	0
MACE	0	0	0
Serious hypersensitivity	0	0	0
Tuberculosis	0	0	0

AD atopic dermatitis, *AEs* adverse events, *MACE* major adverse cardiovascular event, *NMSC* non-melanoma skin cancer, TEAE treatment-emergent adverse event, *URTI* upper respiratory tract infection

[a]AEs reported in > 3% of patients in the overall risankizumab population

[b]In the risankizumab 150-mg group, serious AEs included cardiac arrhythmia and cellulitis; the investigator believed there was a reasonable possibility that the cellulitis was treatment-related. In the risankizumab 300-mg group, serious AEs included worsening of osteoarthritis ($n = 1$); amaurosis fugax ($n = 1$); and coccyx fracture, vertebral fracture, and cellulitis in 1 patient; none of the serious AEs was considered to be treatment-related

[c]Includes 1 patient each with cellulitis and 1 patient each with Kaposi's varicelliform eruption in the continuous risankizumab 150 mg and 300 mg groups

constraints of the trial's entry criteria may have limited the study's patient population, excluding some patients with AD who would be treated in real clinical practice.

CONCLUSIONS

Although risankizumab was generally well tolerated, efficacy of risankizumab 150 mg or

300 mg was not demonstrated in patients with AD.

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Compliance with Ethics Guidelines. The study was conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. A local and/or central independent ethics committee or institutional review board approved the study protocol and related documents for each study site (Table S1). Patients provided written informed consent before initiation of any screening or study-related procedures. For adolescents, authorization and/or consent was provided by a parent or legal guardian, where applicable.

Data Availability. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the

following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html

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