JAMA Dermatology | Original Investigation

Efficacy and Safety of Continuous Risankizumab Therapy vs Treatment Withdrawal in Patients With Moderate to Severe Plaque Psoriasis
A Phase 3 Randomized Clinical Trial

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IMPORTANCE Risankizumab selectively inhibits interleukin 23, a cytokine that contributes to psoriatic inflammation.

OBJECTIVE To evaluate the efficacy and safety of risankizumab vs placebo and continuous treatment vs withdrawal in adults with moderate to severe plaque psoriasis.

DESIGN, SETTING, AND PARTICIPANTS Multinational, phase 3, randomized, double-blind, placebo-controlled trial conducted from March 6, 2016, to July 26, 2018. A total of 507 eligible patients had stable moderate to severe chronic plaque psoriasis for 6 months or longer, body surface area involvement greater than or equal to 10%, Psoriasis Area and Severity Index (PASI) greater than or equal to 12, and a static Physician's Global Assessment (sPGA) score greater than or equal to 3. Intention-to-treat analysis was conducted.

INTERVENTIONS Patients were randomized (4:1, interactive response technology) to risankizumab, 150 mg, subcutaneously, or placebo at weeks 0 and 4 (part A1). All patients received risankizumab at week 16. At week 28, patients randomized to risankizumab who achieved an sPGA score of 0/1 were rerandomized 1:2 to risankizumab or placebo every 12 weeks (part B).

MAIN OUTCOMES AND MEASURES Co-primary end points for the part A1 phase included proportions of patients achieving greater than or equal to 90% improvement in PASI (PASI 90) and sPGA score of 0/1 at week 16. The PASI measures severity of erythema, infiltration, and desquamation weighted by area of skin involvement over the head, trunk, upper extremities, and lower extremities; scores range from 0 (no disease) to 72 (maximal disease activity). The sPGA assesses average thickness, erythema, and scaling of all psoriatic lesions; scores range from 0 (clear) to 4 (severe), with 0/1 indicating clear or almost clear. Primary and secondary end points in part B included proportion of rerandomized patients achieving an sPGA score of 0/1 at week 52 (primary) and week 104 (secondary).

RESULTS Of 563 patients screened, 507 were randomized to risankizumab (n = 407) or placebo (n = 100). Most patients were men (356 [70.2%]); median age was 51 years (interquartile range, 38-60 years). At week 16, 298 patients (73.2%) in the treatment group vs 2 patients (2.0%) receiving placebo achieved a PASI 90 response, and 340 patients (83.5%) receiving risankizumab vs 7 patients (7.0%) receiving placebo achieved sPGA 0/1 scores (placebo-adjusted differences: PASI 90: 70.8%; 95% CI, 65.7%-76.0%; sPGA 0/1: 76.5%; 95% CI, 70.4%-82.5%; $P < .001$ for both). At week 28, 336 responders were rerandomized to risankizumab (n = 111) or treatment withdrawal (n = 225). At week 52, the sPGA 0/1 score was achieved by 97 patients (87.4%) receiving risankizumab vs 138 patients (61.3%) receiving placebo. At week 104, the sPGA 0/1 score was achieved by 90 patients (81.1%) receiving risankizumab vs 16 patients (7.1%) receiving placebo (placebo-adjusted differences: week 52: 25.9%; 95% CI, 17.3%-34.6%; week 104: 73.9%; 95% CI, 66.0%-81.9%; $P < .001$ for both). Rates of treatment-emergent adverse events were similar between risankizumab (186 [45.7%]) and placebo (49 [49.0%]) in part A1 and remained stable over time.

CONCLUSIONS AND RELEVANCE Risankizumab showed superior efficacy compared with placebo through 16 weeks and treatment withdrawal through 2 years. Risankizumab was well tolerated, with no unexpected safety findings during the 2-year trial.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02672852

JAMA Dermatol. doi:10.1001/jamadermatol.2020.0723
Published online April 8, 2020.

Supplemental content

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Psoriasis is a chronic, immune-mediated disease affecting approximately 100 million people worldwide.[1,2] Psoriasis has a negative influence on patients' quality of life and increases the risk for early mortality and prevalence of comorbidities, including cardiovascular disease, hypertension, hyperlipidemia, diabetes, and depression.[3-5] Complete or nearly complete clearance is now achievable with available biologic treatments targeting various cytokines involved in disease pathogenesis, namely interleukin 17 [IL-17], IL-23, and tumor necrosis factor α[6,7]; however, durability of response with many biologic agents is limited in clinical practice after 1 to 2 years due to loss of treatment effect over time.[8-10]

A key regulatory cytokine, IL-23 is essential for pathogenic T helper 17 cell differentiation, activation, and survival.[6] In psoriasis, the IL-23/T helper 17 cell pathway is activated, which influences cutaneous plaque formation and chronic inflammation.[6,11] Clinical trials demonstrated that selective inhibition of IL-23 through antibodies targeting the p19 subunit produced high and durable efficacy associated with reductions in inflammatory cytokine expression in skin.[12-16] Selective inhibition of IL-23 may offer additional safety benefits over biologic agents that target IL-17 by preserving function of IL-23–independent, IL-17–producing cells that are involved in mucocutaneous defense and barrier tissue integrity.[17]

Risankizumab is a humanized immunoglobulin G1 monoclonal antibody that binds with high affinity to the p19 subunit and selectively inhibits IL-23.[18] Throughout its clinical trial program, risankizumab administered every 12 weeks demonstrated consistently high and durable efficacy,[15,19,20] showing sustained efficacy in 88% of week 16 Psoriasis Area and Severity Index (PASI) 90 responders through 52 weeks of treatment in UltIMMa-1 and UltIMMa-2.[16] Previous phase 3 trials in patients with moderate to severe plaque psoriasis have also demonstrated superior efficacy for risankizumab vs placebo, adalimumab, and ustekinumab at week 16, which was sustained through weeks 44 vs adalimumab and 52 vs ustekinumab.[15,16]

Herein, we report the results of IMMhance (NCT02672852), which evaluated the efficacy and safety of risankizumab vs placebo through 16 weeks in patients with moderate to severe plaque psoriasis; maintenance of response following drug withdrawal and the response after retreatment in patients who experienced disease recurrence after drug withdrawal were also evaluated.

Key Points

Question Is continuous risankizumab treatment efficacious and safe in adults with moderate to severe plaque psoriasis?

Findings In this 2-part, phase 3 randomized clinical trial in 507 patients, a significantly greater proportion of patients treated with risankizumab vs placebo achieved a treatment response at week 16 and with long-term continuous risankizumab compared with withdrawal to placebo at 52 and 104 weeks. Rates of treatment-emergent adverse events were similar to those with placebo and remained stable over time.

Meaning These findings support the use of 12-week risankizumab dosing as an efficacious and well-tolerated regimen for maintenance of clinical efficacy in patients with moderate to severe plaque psoriasis.

Methods

Study Design and Patients

The IMMhance study was a 2-year, phase 3, multinational, double-blind placebo-controlled trial with randomized withdrawal and retreatment comparing risankizumab, 150 mg, with placebo. The trial was conducted at 60 sites in Australia, Belgium, Canada, Czech Republic, France, Germany, Japan, South Korea, and the US. The trial protocol is available in Supplement 1.

Eligible patients (≥18 years of age) had stable moderate to severe chronic plaque psoriasis for 6 months or longer, with or without psoriatic arthritis, with body surface area involvement greater than or equal to 10%, PASI greater than or equal to 12, and static Physician's Global Assessment (sPGA) score greater than or equal to 3. The PASI measures the severity of erythema, infiltration, and desquamation weighted by the area of skin involvement over the head, trunk, upper extremities, and lower extremities; the scores range from 0 (no disease) to 72 (maximal disease activity). In clinical trials, greater than or equal to 75% improvement is often considered clinically meaningful. The sPGA assesses average thickness, erythema, and scaling of all psoriatic lesions; scores range from 0 (clear) to 4 (severe), with 0/1 indicating clear or almost clear. Primary and secondary end points in part B included the proportion of rerandomized patients achieving an sPGA score of 0/1 at week 52 (primary) and week 104 (secondary). Further details are available in the eMethods in Supplement 2. Patients were required to be candidates for systemic therapy or phototherapy; complete inclusion and exclusion criteria are listed in eTable 1 in Supplement 2.

The trial was conducted in accord with Good Clinical Practice Guidelines as defined by the International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, the Declaration of Helsinki,[21] and applicable local regulations. All study-related documents were approved by an institutional review board or institutional ethics committee at each trial site, and all patients provided written informed consent before participation. Participants did not receive financial compensation.

In parts A and B, patients were randomly assigned via interactive response technology using block randomization. Randomizations were stratified by baseline weight (≤100 vs >100 kg) and prior exposure to a tumor necrosis factor α inhibitor (yes vs no). Patients, investigators, and study personnel involved in trial conduct or analysis remained blinded to randomized treatment assignments until study completion. To maintain blinding, risankizumab and its matching placebo were identical in appearance.

Following a screening period (1-6 weeks), patients entered a 16-week double-blind treatment period (part A1). All patients in part A1 were randomly assigned 4:1 to receive risankizumab, 150 mg, or placebo subcutaneously at weeks 0

and 4 (eFigure 1 in Supplement 2). At week 16, all patients received risankizumab, 150 mg (part A2). At week 28 (entry double-blind part B), patients initially randomized to risankizumab who achieved an sPGA score of 0 or 1 (0/1) at week 28 were randomly assigned 1:2 to continue risankizumab, 150 mg, or placebo (withdrawal of treatment) every 12 weeks (weeks 28-88). Patients with an inadequate response to initial therapy (sPGA ≥2 at week 28) received open-label risankizumab, 150 mg, every 12 weeks. Patients initially assigned to placebo who achieved sPGA 0/1 were crossed over to receive blinded administration of risankizumab, 150 mg, every 12 weeks (weeks 28-88). Starting from week 32, patients who had responded to treatment and then experienced relapse (sPGA score ≥3) in part B were retreated with open-label risankizumab, 150 mg. Final follow-up was at week 104.

Outcomes

In part A1, the coprimary end points were the achievement of PASI 90 and sPGA 0/1 at week 16. The ranked secondary end points were (in ranked order) achievement of PASI 75, PASI 100, sPGA 0, and Dermatology Life Quality Life Index (DLQI) 0/1 at week 16. In part B, the primary end point was achievement of sPGA 0/1 at week 52. The ranked secondary end point was achievement of sPGA 0/1 at week 104. Additional prespecified end points included achievement of PASI 75, PASI 90, PASI 100, sPGA 0/1, sPGA 0, and DLQI 0/1 at all visits. Additional prespecified end points among patients rerandomized at week 28 also included time to loss of PASI 90 and time to relapse (sPGA ≥3). A complete list of ranked secondary outcomes evaluated is included in eTable 2 in Supplement 2; efficacy outcomes assessments are detailed in the eMethods in Supplement 2.

Safety was evaluated by the number and percentage of patients with treatment-emergent adverse events (AEs) and laboratory abnormalities, and through characterization of reported AEs. Treatment-emergent AEs were defined as any AE occurring after the first dose of study drug and up to 105 days after the last dose of study drug. All AEs were coded using the Medical Dictionary for Regulatory Activities (https://www.meddra.org/), with their severity assessed using the Rheumatology Common Toxicity Criteria, version 2.0.[22] Severe AEs were defined as any with a grade greater than or equal to 3 according to Rheumatology Common Toxicity Criteria, version 2.0. All cardiovascular events—regardless of severity—were adjudicated by an independent major adverse cardiovascular events adjudication committee.

Statistical Analysis

Based on outcomes from phase 1 and phase 2 risankizumab trials,[19,20] the proportion of patients achieving PASI 90 and sPGA 0/1 at week 16 was expected to be at least 65% and 80%, respectively, for risankizumab and 5% for placebo. Based on an interim analysis from a phase 2 risankizumab trial,[20] the proportion of risankizumab responders who will lose their sPGA 0/1 response was expected to be, at most, 10% of patients rerandomized to continue risankizumab treatment and approximately 25% of patients rerandomized to treatment withdrawal at week 52. Assuming that 80% of the patients receiving risankizumab will achieve sPGA 0/1 vs 5% receiving placebo at week 28, rerandomization of risankizumab responders to either continue risankizumab or withdrawal of treatment in a 1:2 scheme would require at least 102 patients to be rerandomized to risankizumab and 204 rerandomized to withdrawal to have at least 90% power to detect a difference in sPGA 0/1 at week 52. This sample size would require 400 patients to be assigned to risankizumab (100 for placebo using a 4:1 randomization) at the initial randomization. The power for comparing the proportion of patients achieving PASI 90 and sPGA 0/1 at week 16 was expected to be greater than 99%.

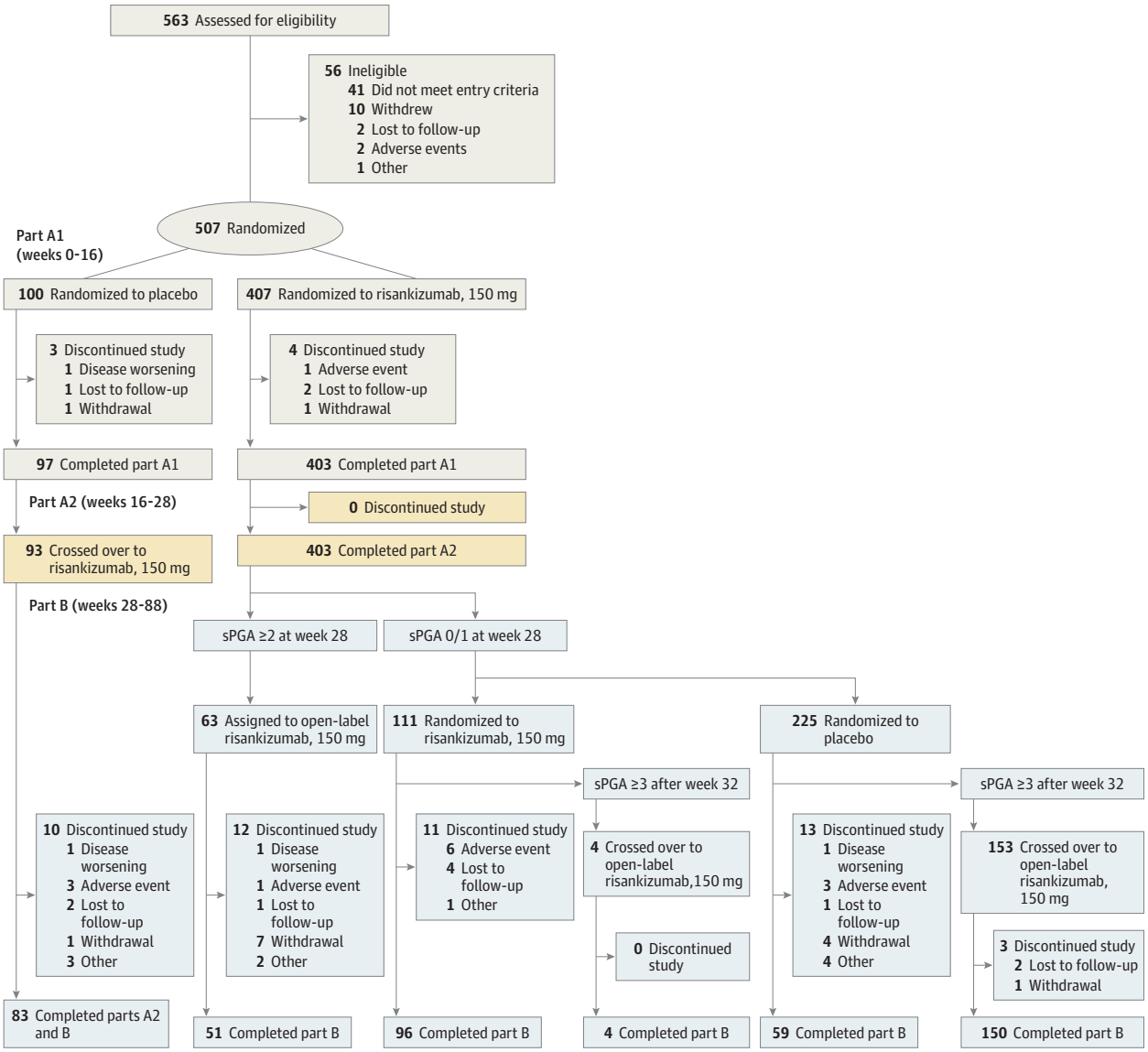
Efficacy was analyzed in the intention-to-treat population, namely, all randomized patients in part A1 and those rerandomized at week 28 in part B. Sensitivity analyses were prespecified and conducted using the per-protocol population (eTable 3 in Supplement 2) for the primary end points in parts A1 and B to ensure consistency of efficacy findings when patients with a protocol deviation were excluded. Safety was assessed in all patients who received at least 1 dose of study drug. Additional details of the statistical methods are described in eMethods in Supplement 2. In both parts of the study, a step-down procedure was used to test each comparison at a significance level of .05 with the overall α level preserved at .05. All primary and ranked secondary end points were categorical and, as such, were tested using the Cochran-Mantel-Haenszel risk difference estimate stratified by baseline weight (≤100 kg vs >100 kg) and prior exposure to a tumor necrosis factor α inhibitor (0 vs ≥1). Analyses were conducted using SAS, version 9.4 (SAS Institute Inc) or higher using the UNIX operating system.

Results

The trial was conducted from March 6, 2016, to July 26, 2018. Of 563 patients assessed for eligibility, 507 were randomly assigned to risankizumab (n = 407) or placebo (n = 100) (**Figure 1**); 500 of 507 patients (98.6%) completed part A1, and 496 of 507 patients (97.8%) entered part A2, of which 443 patients (87.4%) completed part B. Protocol deviations were reported in 49 of 507 patients (9.7%) (eTable 4 in Supplement 2). In part A, 407 patients receiving risankizumab and 100 patients receiving placebo were included in the analysis of coprimary end points. In part B, 111 patients rerandomized to risankizumab and 225 patients rerandomized to treatment withdrawal were included in the analysis of the primary end point.

Demographics and disease characteristics were similar at baseline (**Table 1**). Most patients were men (356 [70.2%]), median age was 51 years (interquartile range [IQR], 38-60 years), and median weight was 89.7 kg (IQR, 76.5-103.6 kg). The majority of patients were white (402 [79.3%]) followed by Asian (79 [15.6%]) race; 281 patients (55.4%) had previous exposure to biologic agent therapy. Demographics and baseline disease characteristics were also similar between patients rerandomized to risankizumab vs placebo in part B (Table 1) (n = 336), and overall were similar to patients initially randomized to risankizumab (eTable 5 in Supplement 2). Fifty-five patients without active tuberculosis who had positive interferon-

Figure 1. Trial Profile



Number of patients represents those in intention-to-treat analysis. sPGA indicates static Physician's Global Assessment.

gamma release assay (QuantiFERON; Qiagen) test results (24 with and 31 without tuberculosis prophylaxis treatment) were included in this study.

In part A, 298 patients (73.2%) receiving risankizumab vs 2 patients (2.0%) receiving placebo achieved a PASI 90 response ($P < .001$), and 340 patients (83.5%) receiving risankizumab vs 7 patients (7.0%) receiving placebo achieved sPGA 0/1 scores (placebo-adjusted differences: PASI 90: 70.8%; 95% CI, 65.7%-76.0%; sPGA 0/1: 76.5%; 95% CI, 70.4%-82.5%; $P < .001$ for both) (**Table 2**; eFigure 2 in Supplement 2). A significantly greater proportion of patients receiving risankizumab also achieved secondary end points of PASI 75 (361 [88.7%]), sPGA 0 (189 [46.4%]), PASI 100 (192 [47.2%]), and DLQI 0/1 (266 [65.4%]) vs placebo (8 [8.0%], 1 [1.0%], 1 [1.0%], and 3 [3.0%], respectively (Table 2; eFigure 2 and eFigure 3 in Supplement 2). In part B, a significantly greater proportion of patients rerandomized to continuous risankizumab (97 [87.4%]) achieved the primary end point of sPGA 0/1 at week 52 and ranked secondary end point of sPGA 0/1 (90 [81.1%]) at week 104 compared with those rerandomized to withdrawal of treatment to placebo (138 [61.3%] and 16 [7.1%]), respectively (placebo-adjusted differences: week 52: 25.9%; 95% CI, 17.3%-34.6%; week 104: 73.9%; 95% CI, 66.0%-81.9%; $P < .001$ for both) (Table 2, **Figure 2**). Results for the primary end points from sensitivity analyses in the per-protocol population were consistent with results in the intention-to-treat population: 296 (74.0%) and 335 (83.8%) patients receiving risankizumab achieved PASI 90 and sPGA 0/1 at week 16 vs 2 (2.0%) and 6 (6.1%) patients receiving placebo, respectively (eTable 6 in Supplement 2) and 96 (88.1%) patients receiving

Table 1. Baseline Demographics and Disease Characteristics of the Intention-to-Treat Population

Characteristic	No. (%) of Patients			
	Part A1 (4:1)		Part B (Rerandomization 1:2)	
	Risankizumab (n = 407)	Placebo (n = 100)	Risankizumab/ risankizumab (n = 111)	Risankizumab/ placebo (n = 225)
Age, median (IQR), y	51 (40-60)	48 (37-57)	49 (37-60)	51 (40-58)
Sex				
Male	283 (69.5)	73 (73.0)	83 (74.8)	156 (69.3)
Female	124 (30.5)	27 (27.0)	28 (25.2)	69 (30.7)
Race				
White	320 (78.6)	82 (82.0)	82 (73.9)	177 (78.7)
Black or African American	18 (4.4)	2 (2.0)	6 (5.4)	10 (4.4)
Asian	64 (15.7)	15 (15.0)	23 (20.7)	34 (15.1)
Other	5 (1.2)	1 (1.0)	0	4 (1.8)
Weight, kg				
Median (IQR)[a]	88.6 (75.9-103.8)	92.4 (77.5-103.2)	87.1 (73.8-103.6)	88.0 (76.7-101.9)
≤100	283 (69.5)	68 (68.0)	79 (71.2)	159 (70.7)
>100	124 (30.5)	32 (32.0)	32 (28.8)	66 (29.3)
BMI, median (IQR)	30.0 (26.1-35.3)	30.9 (25.5-35.2)	29.6 (25.8-33.4)	30.0 (26.1-34.9)
PASI, median (IQR)	17.2 (14.3-22.1)	18.9 (15.8-22.5)	17.0 (14.4-22.2)	17.4 (14.4-21.8)
sPGA				
Moderate	323 (79.4)	77 (77.0)	86 (77.5)	185 (82.2)
Severe	84 (20.6)	23 (23.0)	25 (22.5)	40 (17.8)
BSA involvement, median (IQR), %	19 (14-32)	23 (14-37)	19 (14-30)	20 (14-32)
Prior nonbiologic systemic therapy	191 (46.9)	42 (42.0)	54 (48.6)	106 (47.1)
Any prior biologic therapy	230 (56.5)	51 (51.0)	57 (51.4)	125 (55.6)
Prior TNF-α inhibitor exposure[a]	150 (36.9)	35 (35.0)	37 (33.3)	75 (33.3)
Prior IL-17 inhibitor exposure[b]	106 (26.0)	26 (26.0)	30 (27.0)	56 (24.9)
Prior IL-12/IL-23 inhibitor exposure[c]	88 (21.6)	20 (20.0)	18 (16.2)	48 (21.3)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by meters squared); BSA, body surface area; IL-17, interleukin 17; IL-23, interleukin 23; IQR, interquartile range; PASI, Psoriasis Area and Severity Index; sPGA, static Physician's Global Assessment; TNF-α, tumor necrosis factor α.

[a] Stratification factors at randomization.

[b] Including brodalumab, ixekizumab, and secukinumab.

[c] Including ustekinumab and briakinumab.

Table 2. Primary, Secondary, and Additional End Points in Part A and Part B[a]

Study Part	No. (%) of Patients		Risk difference (95% CI), %
Part A1			
Treatment	Risankizumab	Placebo	Risankizumab vs placebo
No. of patients per group	407	100	
PASI 90 at week 16	298 (73.2)	2 (2.0)	70.8 (65.7-76.0)[b]
sPGA 0/1 at week 16	340 (83.5)	7 (7.0)	76.5 (70.4-82.5)[b]
PASI 75 at week 16	361 (88.7)	8 (8.0)	80.6 (74.5-86.6)[b]
PASI 100 at week 16	192 (47.2)	1 (1.0)	45.5 (40.3-50.8)[b]
sPGA 0 at week 16	189 (46.4)	1 (1.0)	44.8 (39.5-50.0)[b]
DLQI 0/1 at week 16	266 (65.4)	3 (3.0)	62.1 (56.4-67.9)[b]
Part B			
Treatment	Risankizumab/ risankizumab[c]	Risankizumab/ placebo[d]	Risankizumab/risankizumab vs risankizumab/placebo
No. of patients per group	111	225	
sPGA 0/1 at week 52	97 (87.4)	138 (61.3)	25.9 (17.3, 34.6)[e]
sPGA 0/1 at week 104	90 (81.1)	16 (7.1)	73.9 (66.0, 81.9)[e]
PASI 75 at week 52	103 (92.8)	161 (71.6)	21.2 (13.7, 28.7)[f]
PASI 90 at week 52	95 (85.6)	118 (52.4)	33.1 (24.0, 42.2)[f]
PASI 100 at week 52	71 (64.0)	68 (30.2)	33.7 (23.2, 44.2)[f]

Abbreviations: DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index; sPGA, sPGA, static Physician's Global Assessment.

[a] Categorical variables were analyzed using Cochran-Mantel-Haenszel risk difference estimates stratified by baseline weight and prior exposure to a tumor necrosis factor α inhibitor. Missing data were imputed as nonresponders.

[b] $P < .001$ compared with placebo.

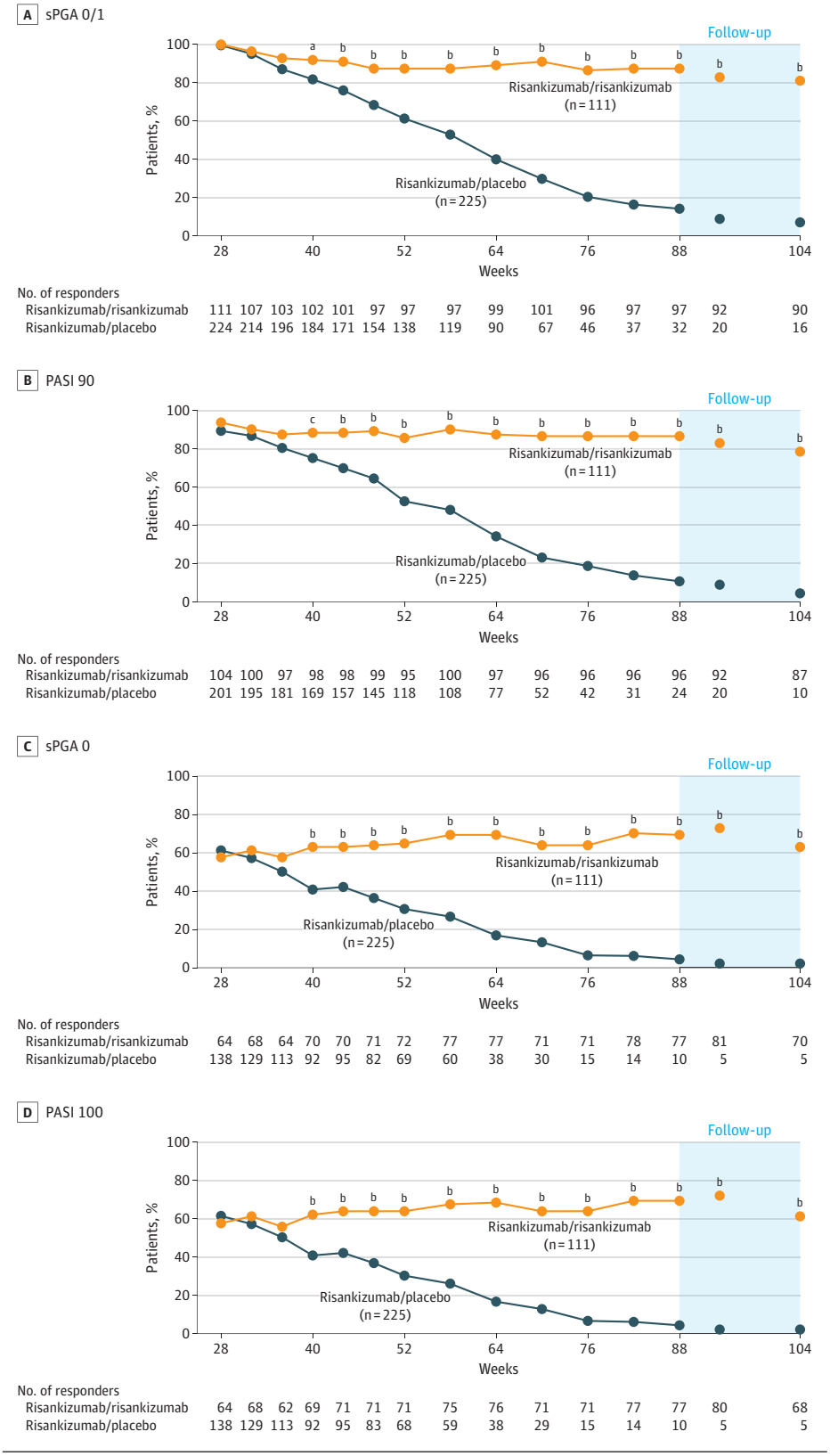
[c] Continuous risankizumab therapy.

[d] Treatment withdrawal to placebo.

[e] $P < .001$ compared with risankizumab/placebo.

[f] $P < .001$ compared with risankizumab/placebo nominal P value.

Figure 2. Patients Response With Nonresponder Imputation After Rerandomization in Part B



Proportion of patients achieving static Physician's Global Assessment (sPGA) 0/1, indicating clear or almost clear (A), Psoriasis Area and Severity Index (PASI) 90, indicating greater than or equal to 90% improvement in the PASI from baseline (B), sPGA 0, indicating clear (C), and PASI 100, indicating 100% improvement in the PASI from baseline (D).

[a] $P = .005$ vs placebo based on nominal P value.

[b] $P < .001$ vs placebo based on nominal P value except for sPGA 0/1 at weeks 52 and 104.

[c] $P < .002$ vs placebo based on nominal P value.

risankizumab achieved sPGA 0/1 at week 52 vs 136 (61.5%) receiving placebo (eTable 7 in Supplement 2).

In part A1, significantly higher percentages of patients receiving risankizumab vs placebo achieved sPGA 0/1 (32.9% vs 0.0%) (eFigure 2A in Supplement 2), PASI 90 (7.1% vs 0.0%) (eFigure 2B in Supplement 2), and PASI 75 (27.0% vs 1.0%) (eFigure 3 in Supplement 2) at week 4 and all subsequent time points ($P < .001$ for all). Similarly, significantly higher percentages of patients receiving risankizumab (2.2% and 2.2%) vs placebo (0.0% and 0.0%) achieved complete clearance of psoriatic lesions (PASI 100 and sPGA 0, respectively) starting at week 4 ($P = .046$ at week 4 for both) (eFigure 2C and 2D in Supplement 2). For patient-reported outcomes, significantly higher percentages of patients receiving risankizumab achieved DLQI 0/1 starting at week 12 (first measured time point after initiating therapy) than those treated with placebo (59.7% vs 2.0%, respectively; $P < .001$) (eFigure 2E in Supplement 2).

In part B, significantly higher percentages of patients rerandomized to continuous risankizumab achieved sPGA 0/1 (91.9%; $P = .005$) (Figure 2A) and PASI 90 (88.3%; $P = .002$) (Figure 2B) vs those rerandomized to placebo (withdrawal of therapy) starting at week 40 (81.8% vs 75.1%, respectively). Similarly, significantly higher percentages of patients rerandomized to continuous risankizumab vs placebo achieved PASI 75 (eFigure 4 in the Supplement 2) (95.5% vs 89.8%, $P = .046$), PASI 100 (62.2% vs 40.9%, $P < .001$), and sPGA 0 (63.1% vs 40.9%, $P < .001$) starting at week 40 (Figure 2C and D) and sPGA 0/1 (last observation carried forward analysis) starting at week 36 (95.5% vs 88.8%, $P = .022$) (eFigure 5 in Supplement 2). The median time to sPGA greater than or equal to 3 (relapse) was significantly different between patients rerandomized to placebo (295 days; IQR, 211-428 days) vs continuous risankizumab (not determinable owing to the low number of relapses in this group [5/111; 4.5%]; log-rank $P < .001$; hazard ratio [HR], 0.028; 95% CI, 0.011-0.068) (eFigure 6 in Supplement 2). Similarly, the median time to loss of PASI 90 was significantly different between patients rerandomized to placebo (210 days; IQR, 113-296 days) vs continuous risankizumab (not determinable in this group owing to the low number who lost their PASI 90 response [23/104; 22.1%]; log-rank $P < .001$; HR, 0.108; 95% CI, 0.069-0.168) (eFigure 7 in Supplement 2).

For the 153 patients who achieved sPGA 0/1 at week 28 and experienced relapse (sPGA ≥3) after treatment withdrawal, 128 patients (83.7%) regained their sPGA 0/1 response at 16 weeks after retreatment (eFigure 8 in Supplement 2). Complete clearance (PASI 100 or sPGA 0) was achieved by 65 patients (42.5%) and 64 patients (41.8%), respectively, who experienced relapse during withdrawal at 16 weeks after retreatment (eFigure 8 in Supplement 2). PASI 75 and PASI 90 responses were also achieved by more patients after 16 weeks of retreatment (PASI 75: from 30 [19.6%] to 146 [95.4%]; PASI 90: from 6 [3.9%] to 116 [75.8%]) (eFigure 8 and eFigure 9 in Supplement 2).

In part A1, AEs were reported in 186 patients (45.7%) and serious AEs were reported in 8 patients (2.0%) receiving risankizumab; in the placebo group, AEs occurred in 49 patients (49.0%) and serious AEs developed in 8 patients (8.0%) (**Table 3**). The most frequently reported AEs occurring in 5% or more of the patients in either group were nasopharyngitis (risankizumab, 21 [5.2%]; placebo, 6 (6.0%]), upper respiratory tract infection (risankizumab, 6 [1.5%]; placebo, 5 (5.0%]), and psoriasis (risankizumab, 2 [0.5%]; placebo, 5 [5.0%]) (eTable 8 in Supplement 2). No events of active tuberculosis, serious hypersensitivity, opportunistic infections, or death (including non-treatment-emergent deaths) were observed dur-

Table 3. Treatment-Emergent AEs During Part A1 and Part B

Treatment-emergent AE	No. (%) of Patients	
Part A1		
Treatment	Risankizumab (n = 407)	Placebo (n = 100)
Adverse event		
Any	186 (45.7)	49 (49.0)
Serious	8 (2.0)	8 (8.0)
Severe	7 (1.7)	4 (4.0)
Leading to drug discontinuation	2 (0.5)	4 (4.0)
Infections	70 (17.2)	18 (18.0)
Serious	1 (0.2)	1 (1.0)
Tuberculosis[a]		
Active	0	0
Latent	0	0
Adjudicated major adverse cardiovascular event	0	1 (1.0)
Cancers	3 (0.7)	0
Excluding nonmelanoma skin cancer	2 (0.5)	0
Serious hypersensitivity	0	0
Deaths (including non-treatment emergent)	0	0
Part B		
Treatment	Risankizumab/ risankizumab (n = 111)	Risankizumab/ placebo (n = 225)
Adverse event		
Any	91 (82.0)	155 (68.9)
Serious	13 (11.7)	17 (7.6)
Severe	9 (8.1)	16 (7.1)
Leading to drug discontinuation	4 (3.6)	4 (1.8)
Infections	66 (59.5)	105 (46.7)
Serious	2 (1.8)	2 (0.9)
Tuberculosis[a]		
Active	0	0
Latent	0	0
Adjudicated major adverse cardiovascular event	2 (1.8)[b]	0
Cancers	2 (1.8)	6 (2.7)
Excluding nonmelanoma skin cancer	0	4 (1.8)
Serious hypersensitivity	0	0
Deaths (including nontreatment emergent)	2 (1.8)[c]	0

Abbreviation: AE, adverse event.

[a] Tuberculosis testing was performed at screening and at the end of treatment using interferon-gamma release assay or purified protein derivative skin test.

[b] One event of stroke and death of unknown cause.

[c] One death due to epileptic seizures and 1 death of unknown cause.

ing part A1 (Table 3). Serious infections were similar between arms (eTable 9 in Supplement 2). Both cancers and hepatic events were reported in 3 patients (0.7%) receiving risankizumab, all of which were nonserious (eTable 9 in Supplement 2). One patient (1.0%) receiving placebo experienced a major adverse cardiovascular event (stroke).

In part B, AEs were reported in 91 patients (82.0%) and serious AEs were reported 13 patients (11.7%) rerandomized to continuous risankizumab therapy and 155 (68.9%) and 17 (7.6%), respectively, patients rerandomized to placebo (Table 3). The most frequently reported AEs occurring in 5% or more of the patients in part B were nasopharyngitis (risankizumab, 24 [21.6%]; placebo, 45 [20.0%]), upper respiratory tract infection (risankizumab, 16 [14.4%]; placebo, 23 [10.2%]), arthralgia (risankizumab, 10 [9.0%]; placebo, 13 [5.8%]), headache (risankizumab, 8 [7.2%]; placebo, 7 [3.1%]), influenza (risankizumab, 7 [6.3%]; placebo, 8 [3.6%]), and back pain (risankizumab, 4 [3.6%]; placebo, 12 [5.3%]) (eTable 8 in Supplement 2). The AE profile was similar in the other treatment arms in parts A2 and B (eTable 10 in Supplement 2) and during retreatment in patients who experienced relapse (eTable 11 in Supplement 2). No events of active tuberculosis or serious hypersensitivity among rerandomized patients were observed during part B (Table 3). Serious infections were similar between arms (eTable 9 in Supplement 2). Cancers were reported in 2 patients (1.8%) receiving continuous risankizumab and 6 patients (2.7%) receiving placebo (eTable 9 in Supplement 2); 5 patients (2 receiving risankizumab; 3, placebo) discontinued treatment because of these AEs. Hepatic events were reported in 8 patients (7.2%) receiving continuous risankizumab and 5 patients (2.2%) receiving placebo (eTable 9 in Supplement 2); no rerandomized patients discontinued the study drug owing to hepatic events in part B. Major adverse cardiovascular events were reported in 2 patients (1.8%) receiving continuous risankizumab therapy (stroke and death of unknown cause, neither considered related to risankizumab). Death occurred in 2 patients (1.8%) receiving continuous risankizumab therapy (epileptic seizure and unknown cause), both of which were considered not related to risankizumab.

Among the 500 patients receiving risankizumab at any point throughout the trial, 426 patients (85.2%) reported 1792 AEs (259.7 AEs/100 patient-years) (eTable 12 in Supplement 2). Serious AEs were reported in 55 patients (11.0%) (93 serious AEs; 13.5 AEs/100 patient-years). The most frequently reported AEs occurring in 5% or more of the patients were nasopharyngitis (117 [23.4%]), upper respiratory tract infection (77 [15.4%]), headache (34 [6.8%]), and back pain (28 [5.6%]). There were no events of active tuberculosis or serious hypersensitivity among patients receiving risankizumab throughout the trial. Serious infections (1.4 events/100 patient-years) were reported in 9 patients (1.8%) and 15 cancers (2.2 events/100 patient-years) were reported in 13 patients (2.6%). Hepatic events were reported in 23 patients (4.6%), of which 1 patient (0.2%) had a serious event (hepatic cirrhosis). Six major adverse cardiovascular events (3 strokes, 2 myocardial infarctions, and 1 cardiovascular death [unknown cause]; 0.9 events/100 patient-years, none considered related to risankizumab) were reported in 4 patients (0.8%). Death occurred in 4 patients (0.8%) patients (epileptic seizure, metastatic hepatic cancer, and 2 of unknown cause), all of which were considered not related to risankizumab.

Discussion

In this phase 3 trial, risankizumab demonstrated superior efficacy to placebo and treatment withdrawal in adults with moderate to severe plaque psoriasis, as evidenced by achievement of all primary and ranked secondary end points. In the placebo-controlled part of the trial, efficacy rates were significantly higher in risankizumab-treated patients starting at week 4 vs placebo. In part B, efficacy rates were significantly higher in responders rerandomized to continuous risankizumab vs those rerandomized to treatment withdrawal starting at week 40, or the equivalent of a single missed dose at week 28. Most patients retreated with risankizumab for 16 weeks regained their clinical response after experiencing relapse during treatment withdrawal.

During the placebo-controlled portion of the trial, treatment-emergent AEs were similar with risankizumab and placebo. Beyond week 16, treatment-emergent AEs remained stable over time with risankizumab, and no additional safety concerns were identified in patients for 2 years. Altogether, the efficacy and safety observed in this trial were consistent with the findings reported in 3 other phase 3 trials, further supporting the benefit-risk profile of risankizumab.[15,16]

In clinical practice, treatment gaps are frequently observed in patients with psoriasis treated with biologic agents, thereby necessitating the assessment of maintenance of response without the drug and the ability to regain the response once relapse occurs.[23-26] Following a single missed dose at week 28, significant differences were observed in efficacy thresholds starting at week 40 for continuous risankizumab-treated patients vs treatment withdrawal. Yet, median times to loss of response (PASI 90) and relapse (sPGA ≥3) were 30 weeks (210 days; 42 weeks from last dose) and 42 weeks (295 days; 54 weeks from the last dose), respectively, demonstrating significant durability of risankizumab response following withdrawal. Other clinical trials in patients with plaque psoriasis assessed time to loss of response after withdrawal from biologic treatments,[27-31] including a trial with guselkumab wherein patients with an initial response to treatment who were withdrawn from the study drug to placebo had a median time to loss of PASI 90 response of 15 weeks (23 weeks after the last guselkumab dose).[14] Most patients who experienced relapse during treatment withdrawal regained their response after 16-week risankizumab retreatment, consistent with a report of retreatment with guselkumab after loss of response during treatment withdrawal.[32] Additional studies are needed to evaluate potential predictors of response following risankizumab withdrawal. Regardless, data from 2 years of continuous risankizumab therapy clearly support every-12-week dosing to maintain optimal skin clearance.

Limitations and Strengths

An important limitation of the trial was the lack of quality-of-life measurements during part B and follow-up to correlate loss of efficacy response with changes in quality of life. Because a previous report demonstrated that there was a correlation between loss of efficacy and decreased quality of life after withdrawal from an IL-23 inhibitor, this association would have been an important finding to confirm with risankizumab.[14] Another limitation relates to the timing of the last treatment dose and the last assessment. Throughout the study, risankizumab was administered according to its label-recommended loading dose and subsequent every 12-week maintenance dosing; however, there was a prolonged interval (16 weeks) between the final dose at week 88 to the final efficacy assessment at week 104. This prolonged interval potentially resulted in slightly diminished sPGA and PASI responses at week 104 compared with week 88, as evidenced by the higher and more stable sPGA 0/1 response rates by last observation carried forward (eFigure 5 in Supplement 2).

Some strengths of this study were inclusion of a high percentage of patients with previous exposure to biologic therapy (55.4%), inclusion of 55 patients without active tuberculosis who had positive interferon-gamma release assay test results (24 with and 31 without tuberculosis prophylaxis treatment), and inclusion of patients from several geographic locations, permitting generalization to a larger population. Moreover, this trial included 2-year, double-blind efficacy and safety data with risankizumab, providing further support for the durability of response with risankizumab and extending the benefit-risk profile to 2 years—a year longer than previous reports.

Conclusions

Selective inhibition of IL-23 with risankizumab demonstrated high and durable efficacy that was maintained with every-12-week dosing during 2 years of therapy. The overall safety profile of risankizumab was comparable with that of placebo at week 16 and remained stable over time with no new safety findings. Together, these findings support the use of 12-week risankizumab dosing as an efficacious and safe regimen for maintenance of clinical efficacy in patients with moderate to severe plaque psoriasis.

ARTICLE INFORMATION

Accepted for Publication: February 20, 2020.

Published Online: April 8, 2020. doi:10.1001/jamadermatol.2020.0723

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Conflict of Interest Disclosures: Dr Blauvelt has served as a scientific adviser and/or clinical study investigator for AbbVie, Aclaris, Almirall, Arena, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Dermira, Eli Lilly and Company, FLX Bio, Forte, Galderma, Janssen, Leo, Novartis, Ortho, Pfizer, Regeneron, Sandoz, Sanofi Genzyme, Sun Pharma, and UCB Pharma, and as a paid speaker for AbbVie. Dr Leonardi has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, as well as grants as an investigator from AbbVie, Actavis, Amgen, Celgene, Coherus, Dermira, Eli Lilly, Galderma, Janssen, Leo, Merck, Novartis, Pfizer, Sandoz, Stiefel, UCB, and Wyeth. Dr Gooderham has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, as well as grants as an investigator from AbbVie, Amgen, Akros, Arcutis, Boehringer Ingelheim, BMS, Celgene, Coherus, Dermavant, Dermira, Eli Lilly, Galderma, GSK, Janssen, Kyowa Hakko Kirin Pharma, Leo Pharma, MedImmune, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Sun Pharma, Takeda, UCB, and Valeant. Dr Papp has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, as well as grants as principal investigator from AbbVie, Amgen, Astellas, Baxalta, Baxter, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Coherus, Dermira, Eli Lilly, Forward Pharma, Galderma, Genentech, GlaxoSmithKline, Janssen, Kyowa-Hakko Kirin, Leo Pharma, MedImmune, Merck-Serono, Merck Sharp & Dohme, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Stiefel, Sun Pharma, Takeda, UCB, and Valeant. Dr Philipp has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, as well as grants as an investigator from AbbVie, Almirall, Amgen, Biogen, BMS GmbH, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, GSK, Hexal, Janssen Cilag, Leo Pharma, Maruho, MSD, Merck, Mundipharma, Novartis, Pfizer, UCB Pharma, and VBL Therapeutics. Dr J. J. Wu has been an investigator for AbbVie, Amgen, Eli Lilly, Janssen, and Novartis; a paid consultant for AbbVie, Almirall, Amgen, Bristol-Myers Squibb, Celgene, Dermira, Dr Reddy's Laboratories, Eli Lilly, Janssen, LEO Pharma, Novartis, Promius Pharma, Regeneron, Sun Pharmaceutical, UCB, and Valeant Pharmaceuticals North America LLC; and a speaker for AbbVie, Amgen, Celgene, Novartis, Regeneron, Sanofi Genzyme, Sun Pharmaceutical, UCB, and Valeant Pharmaceuticals North America LLC. Dr Igarashi has received honoraria or fees for serving on advisory boards, as a speaker, and as a consultant, as well as grants as an investigator from AbbVie, Celgene, Eli Lilly, Kyowa Kirin, Janssen, Maruho and Novartis. Dr Flack is a full-time employee of Boehringer Ingelheim. Drs Geng, T. Wu, and Williams are full-time employees of AbbVie and may own stock/options. Dr Camez is a former full-time employee of AbbVie and may own stock/options. Dr Langley has served as principal investigator for and is a paid member of the scientific advisory board or served as a speaker for AbbVie, Amgen, Celgene, Janssen, Leo, Lilly, Merck, Novartis, Pfizer, and Boehringer Ingelheim.

Funding/Support: Funding for the study was provided by AbbVie and Boehringer Ingelheim.

Role of the Funder/Sponsor: Boehringer Ingelheim contributed to the design of the study and participated in data collection. AbbVie participated in data analysis and interpretation of the data. AbbVie and Boehringer Ingelheim participated in writing, review, and approval of the manuscript. All authors had full access to the data, reviewed and

approved the final version, and were responsible for the decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 3.

Additional Contributions: AbbVie and Boehringer Ingelheim funded the IMMhance study; Boehringer Ingelheim contributed to its design and participated in data collection. AbbVie participated in data analysis and interpretation of the data, and in writing, review, and approval of the abstract. All authors had access to relevant data. Medical writing support was provided by Daniel O'Brien, PhD (AbbVie), and editorial assistance was provided by Maria Hovenden, PhD (Complete Publication Solutions, LLC), and was funded by AbbVie.

Additional Information: Dr Blauvelt was the coordinating investigator for IMMhance.

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