ORIGINAL ARTICLE

Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis

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ABSTRACT

BACKGROUND

Interleukin-23 is thought to be critical to the pathogenesis of psoriasis. We compared risankizumab (BI 655066), a humanized IgG1 monoclonal antibody that inhibits interleukin-23 by specifically targeting the p19 subunit and thus prevents interleukin-23 signaling, and ustekinumab, an interleukin-12 and interleukin-23 inhibitor, in patients with moderate-to-severe plaque psoriasis.

METHODS

We randomly assigned a total of 166 patients to receive subcutaneous injections of risankizumab (a single 18-mg dose at week 0 or 90-mg or 180-mg doses at weeks 0, 4, and 16) or ustekinumab (45 or 90 mg, according to body weight, at weeks 0, 4, and 16). The primary end point was a 90% or greater reduction from baseline in the Psoriasis Area and Severity Index (PASI) score at week 12.

RESULTS

At week 12, the percentage of patients with a 90% or greater reduction in the PASI score was 77% (64 of 83 patients) for risankizumab (90-mg and 180-mg groups, pooled), as compared with 40% (16 of 40 patients) for ustekinumab ($P<0.001$); the percentage of patients with a 100% reduction in the PASI score was 45% in the pooled 90-mg and 180-mg risankizumab groups, as compared with 18% in the ustekinumab group. Efficacy was generally maintained up to 20 weeks after the final dose of 90 or 180 mg of risankizumab. In the 18-mg and 90-mg risankizumab groups and the ustekinumab group, 5 patients (12%), 6 patients (15%), and 3 patients (8%), respectively, had serious adverse events, including two basal-cell carcinomas and one major cardiovascular adverse event; there were no serious adverse events in the 180-mg risankizumab group.

CONCLUSIONS

In this phase 2 trial, selective blockade of interleukin-23 with risankizumab was associated with clinical responses superior to those associated with ustekinumab. This trial was not large enough or of long enough duration to draw conclusions about safety. (Funded by Boehringer Ingelheim; ClinicalTrials.gov number, NCT02054481).

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Psoriasis is a chronic immune-mediated inflammatory skin disease that occurs in 2% of adults; it has a substantial effect on quality of life and is associated with obesity, hypertension, diabetes mellitus, hypercholesterolemia, and the metabolic syndrome.[1-4] The proinflammatory cytokine interleukin-23 is thought to play a pivotal role in the pathogenesis of psoriasis by inducing and maintaining T helper (Th) 17 cells, Th22 cells, innate lymphoid cells, and the effector cytokines interleukin-17, interleukin-22, and tumor necrosis factor (TNF) α.[5-9] Interleukin-23 is composed of two subunits, p19 and p40. The p19 subunit is unique to interleukin-23, whereas the p40 subunit is common to interleukin-12 and interleukin-23. Ustekinumab targets the p40 subunit, thereby blocking both interleukin-12 and interleukin-23, and has been shown to have significant efficacy and safety in the treatment of psoriasis.[10,11] However, evidence from some studies suggests that the inhibition of interleukin-23 is primarily responsible for the efficacy of ustekinumab and similar drugs.[12-14] These studies, however, did not include direct comparisons between drugs that target interleukin-23 specifically and ustekinumab to test the relative efficacy of selective interleukin-23 inhibition versus inhibition of both interleukin-12 and interleukin-23 at doses used in clinical practice.

Risankizumab (BI 655066) is a humanized IgG1 monoclonal antibody that selectively inhibits interleukin-23 by specifically targeting p19. Risankizumab was shown to produce rapid and durable clearing of skin lesions in a phase 1 trial involving patients with moderate-to-severe psoriasis.[15] This 48-week phase 2 trial of risankizumab versus ustekinumab in patients with moderate-to-severe chronic plaque psoriasis assessed the magnitude, onset, and duration of clinical response, as well as safety, after selective interleukin-23 inhibition.

Methods

Trial Design

This 48-week, multicenter, randomized, dose-ranging, phase 2 trial was conducted at 32 sites across North America and Europe. Patients were randomly assigned in a 1:1:1:1 ratio to receive, as subcutaneous injections, either one of three dosages of risankizumab (a single 18-mg dose at week 0 or a 90-mg or 180-mg dose at weeks 0, 4, and 16) or ustekinumab (45 mg for patients with body weight ≤100 kg or 90 mg for patients with body weight >100 kg, at weeks 0, 4, and 16); randomization was stratified according to body weight (≤100 kg vs. >100 kg) and whether treatment with two or more TNF inhibitors had failed previously. The trial was double blind within the risankizumab dose groups and single blind (to patients) with regard to drug (ustekinumab or risankizumab). All efficacy assessments were conducted by an assessor who was unaware of the treatment assignments. Patients were followed up to 32 weeks after the final injection (additional details regarding the trial design are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org).

Patients

Patients 18 to 75 years of age were eligible for participation in the trial if they had stable (for >6 months) moderate-to-severe chronic plaque psoriasis (with or without psoriatic arthritis) involving 10% or more of the body-surface area, with a Psoriasis Area Severity Index (PASI) score of 12 or higher (the PASI is a composite evaluation of erythema, induration, scaling, and percentage of body-surface area affected; scores range from 0 [no disease] to 72 [maximal disease]),[16] and a static Physician's Global Assessment (sPGA) score of 3 or higher (clinician assessment of overall psoriasis severity; scores range from 0 [clear skin] to 5 [severe disease]).[17] Patients were required to be candidates for systemic psoriasis treatment or phototherapy and eligible for ustekinumab therapy in accordance with local approved labeling.

Patients were excluded if they had previously received treatment with ustekinumab or any other agent targeting interleukin-12 or interleukin-23. Additional exclusion criteria included treatment with other biologic agents within 12 weeks before enrollment, treatment with systemic antipsoriatic medications or phototherapy in the previous 4 weeks, or treatment with topical antipsoriatic medications in the previous 2 weeks. The use of low-potency topical glucocorticoids (U.S. class 6 or 7) was permitted on the face, axillae, or genitalia, if required (see the Supplementary Appendix for additional exclusion criteria).

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TRIAL OVERSIGHT

The trial was funded by Boehringer Ingelheim and designed by the first author and the authors who are employees of Boehringer Ingelheim, as well as by other Boehringer Ingelheim personnel. All patients provided written informed consent. The study-site investigators collected the data, and data analyses were conducted by Boehringer Ingelheim. All the authors had full access to the trial data and vouch for the accuracy and completeness of the data and analyses and the fidelity of the trial to the protocol, available at NEJM.org. Agreements between Boehringer Ingelheim and the authors included the confidentiality of the trial data. All the authors collaborated on writing the manuscript (with the assistance of a professional medical writer funded by Boehringer Ingelheim) and made the decision to submit the manuscript for publication.

EFFICACY AND SAFETY ASSESSMENTS

The primary end point was a 90% or greater reduction from baseline in the PASI score (PASI90) at week 12. Secondary efficacy end points included PASI score reductions from baseline of 50% or more (PASI50), 75% or more (PASI75), and 100% (PASI100), at week 12; PASI75 and PASI100 at week 24; an sPGA score of 0 (clear) or 1 (almost clear) and percentage PASI reduction at week 12; and the time to loss of PASI50 response. Other prespecified end points included PASI50, PASI75, PASI90, and PASI100, over time; an sPGA score of 0 or 1 over time; and the time to onset of a PASI50 response. Additional assessments included the Psoriasis Scalp Severity Index (PSSI; scores range from 0 to 72, with higher scores indicating greater severity), palmoplantar PASI (PPASI; scores range from 0 to 72, with higher scores indicating greater severity), and Nail Psoriasis Severity Index (NAPSI [hands only]; scores range from 0 to 80, with higher scores indicating greater severity) in patients with scalp, palmoplantar, or fingernail disease, respectively; patient's global assessment rank (PGAR); patient's assessment of itching (PAI); patient's assessment of pain on a visual analogue scale (pain VAS) in patients with psoriatic arthritis; Dermatology Life Quality Index (DLQI; scores range from 0 to 30, with higher scores indicating more severe impairment of quality of life)[18]; EuroQol 5 dimensions (EQ-5D) VAS and EQ-5D index; and time to onset and loss of PASI90 (time to loss of PASI90 was prespecified in the statistical analysis plan). Additional details on these measures are provided in the Supplementary Appendix.

Safety end points included adverse events (coded with the use of the *Medical Dictionary for Drug Regulatory Activities*, version 18.1) and serious adverse events, with severity grading based on the Rheumatology Common Toxicity Criteria (version 2.0),[19] discontinuation of therapy because of adverse events, side-effect profile, vital signs, physical examination, and laboratory assessments. Immunogenicity assessments are described in the Supplementary Appendix.

Skin biopsies were performed as an optional procedure at baseline and at week 4; a total of 60 patients had a biopsy performed. Psoriasis and interleukin-23 pathway biomarkers were assessed in skin-biopsy samples by immunohistochemical analysis, as previously described by Krueger et al.[15] Biopsy results were classified as excellent, good, slight, no change, or worsening (see Table S1 in the Supplementary Appendix for classification criteria). In addition, transcriptome-wide RNA sequencing was performed on biopsy samples, as described previously[15] and summarized briefly in the Supplementary Appendix.

STATISTICAL ANALYSIS

The estimated sample size (160 patients) was based on 120 patients undergoing randomization in a 2:1 ratio between risankizumab (90 and 180 mg, pooled) and ustekinumab to provide greater than 80% power with the use of a two-sided test and a type I error of 0.10, under the assumption of a 70% PASI90 response rate for risankizumab and a 45% response rate for ustekinumab. Primary and other end points were analyzed on an intention-to-treat basis. Differences in pairwise comparisons were analyzed with the use of the Cochran–Mantel–Haenszel risk difference estimate, and nominal P values are provided. No adjustments for multiplicity were performed. Kaplan–Meier estimates were used for time-to-event analyses for each treatment group, and comparisons and their associated P values were calculated by the stratified log-rank test with the use of the randomization strata. Median changes in DLQI total scores were analyzed by the van Elteren test.

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In the primary analyses, last observation carried forward was prespecified in the trial protocol as the method of handling missing data; a sensitivity analysis with nonresponse imputation was also performed. Safety analyses included patients who received at least one dose of a study drug. Frequencies of adverse events were summarized for all patients for the 48-week duration of the trial.

RESULTS

PATIENTS

Of the 231 patients screened, 166 patients at 32 study sites underwent randomization; 43 patients were assigned to 18 mg of risankizumab, 41 patients to 90 mg of risankizumab, 42 patients to 180 mg of risankizumab, and 40 patients to ustekinumab (see the Supplementary Appendix for recruitment figures according to site). Baseline demographic data and disease characteristics were generally well balanced among the treatment groups, apart from the 18-mg risankizumab group, which had slightly fewer men, fewer patients with concomitant psoriatic arthritis, and slightly more patients from Europe (Table 1). A total of 161 patients (97%) completed the trial up to week 24, with 157 patients (95%) receiving all doses of the trial medication. A total of 139 patients (84%) completed the trial, including 107 patients (77%) who completed the follow-up period through week 48 and 32 patients who entered the open-label extension early because of nonresponse (i.e., <50% decrease in the PASI score); 27 patients discontinued participation in the trial (5 discontinued because of adverse events, 3 were lost to follow-up, 11 withdrew, 1 had a protocol violation, and 7 discontinued for other reasons) (Fig. S1 in the Supplementary Appendix).

EFFICACY

Primary and Secondary Efficacy End Points

Risankizumab (90 and 180 mg, pooled) was superior to ustekinumab with regard to the prespecified primary end point, PASI90 at week 12 (77% vs. 40%, P<0.001) (Table 2); this is the only comparison for which the type I error rate was controlled; all other P values reported are nominal, and no adjustments for multiplicity were performed in these analyses. PASI90 was achieved in 73% of the patients in the 90-mg risankizumab group and 81% of the patients in the 180-mg risankizumab group, as compared with 40% of the patients who received ustekinumab. The percentages of patients in whom at least PASI75 was achieved were 63% in the 18-mg risankizumab group, 98% in the 90-mg risankizumab group, and 88% in the 180-mg risankizumab group, as compared with 72% in the ustekinumab group. The percentages of patients in whom complete clearance of lesions (PASI100) was achieved were 14% in the 18-mg risankizumab group, 41% in the 90-mg risankizumab group, and 48% in the 180-mg risankizumab group, as compared with 18% in the ustekinumab group. The percentages of patients in whom at least PASI50 was achieved were 86% in the 18-mg risankizumab group, 100% in the 90-mg risankizumab group, and 93% in the 180-mg risankizumab group, as compared with 82% in the ustekinumab group. An sPGA score of 0 or 1 was achieved in 58%, 90%, and 88% of the patients in the 18-mg, 90-mg, and 180-mg risankizumab groups, respectively, as compared with 62% of the patients in the ustekinumab group. Data at week 12 were missing for six patients (three in the 18-mg risankizumab group, one in 180-mg risankizumab group, and two in the ustekinumab group). Efficacy results were similar when missing data were handled with the use of either last observation carried forward or nonresponse imputation (Table 2, and the Supplementary Appendix).

At week 24, the percentages of patients in whom at least PASI75 was achieved were 53% in the 18-mg risankizumab group, 90% in the 90-mg risankizumab group, and 88% in the 180-mg risankizumab group, as compared with 70% in the ustekinumab group. In addition, at week 24, the percentages of patients in whom at least PASI90 was achieved were 28% in the 18-mg risankizumab group, 63% in the 90-mg risankizumab group, and 81% in the 180-mg risankizumab group, as compared with 55% in the ustekinumab group (Table S3 in the Supplementary Appendix).

Time Course of Response

Decreases in the PASI score were seen as early as week 2 (Fig. 1, and Fig. S2 in the Supplementary Appendix). By week 8, PASI75 or greater was achieved in approximately 80% of the patients in the 90-mg and 180-mg risankizumab groups, as compared with 60% in the ustekinumab group

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Table 1. Demographic and Disease Characteristics at Baseline.*

Characteristic	Risankizumab			Ustekinumab (N=40)	Total (N=166)
	18 mg (N=43)	90 mg (N=41)	180 mg (N=42)		
Age — yr	44±14	49±13	45±14	45±12	46±14
Male sex — no. (%)	23 (53)	30 (73)	29 (69)	27 (68)	109 (66)
White race — no. (%)†	39 (91)	38 (93)	40 (95)	34 (85)	151 (91)
Weight — kg	92±19	89±18	87±19	90±19	90±19
Previous TNF inhibitor treatment — no. (%)	12 (28)	11 (27)	12 (29)	9 (22)	44 (27)
≥2 TNF inhibitor treatment failures — no. (%)	2 (5)	0	1 (2)	2 (5)	5 (3)
Body-surface area — %‡	25.8±18.5	21.8±14.7	26.3±16.7	24.6±13.2	24.6±15.9
PASI score§	19±7	19±7	20±8	20±6	20±7
sPGA score — no. (%)¶					
3	27 (63)	26 (63)	26 (62)	18 (45)	97 (58)
≥4	16 (37)	15 (37)	16 (38)	21 (52)	68 (41)
Psoriatic arthritis — no.‖	7	13	12	14	46
Pain VAS	65±33	48±23	55±26	59±22	56±25
DLQI**	14±7	12±7	14±8	16±7	14±7
Scalp psoriasis — no.	41	40	39	36	156
PSSI††	19±13	19±16	23±16	22±15	21±15
Fingernail psoriasis — no.	24	23	27	22	96
NAPSI‡‡	26±21	29±19	29±20	29±23	28±21
Palmoplantar psoriasis — no.	13	13	9	7	42
PPASI§§	5±3	5±5	9±13	9±9	7±8

* Plus–minus values are means ±SD. The differences among the treatment groups were not significant. TNF denotes tumor necrosis factor.
† Race was reported by the patient.
‡ This variable indicates the percentage of the body-surface area affected by psoriasis.
§ Psoriasis Area and Severity Index (PASI) scores range from 0 to 72, with higher scores indicating greater severity of psoriasis.
¶ Static Physician's Global Assessment (sPGA) scale scores are 0 (clear), 1 (almost clear), 2 (mild), 3 (moderate), 4 (marked), and 5 (severe).
‖ Psoriatic arthritis was either previously diagnosed by a rheumatologist or suspected by the trial investigator. Pain visual analogue scale (VAS) scores range from 0 to 100, with higher scores indicating greater pain, and are reported for the subgroup of patients with psoriatic arthritis.
** Dermatology Life Quality Index (DLQI) scores range from 0 to 30, with higher scores indicating a greater effect on quality of life.
†† Psoriasis Scalp Severity Index (PSSI) scores range from 0 to 72, with higher scores indicating greater severity, and are reported for the subgroup of patients with scalp psoriasis.
‡‡ Nail Psoriasis Severity Index (NAPSI) scores range from 0 to 80 (hands only), with higher scores indicating worse disease, and are reported for the subgroup of patients with fingernail psoriasis.
§§ Palmoplantar Psoriasis Area Severity Index (PPASI) scores range from 0 to 72, with higher scores indicating greater severity, and are reported for the subgroup of patients with palmoplantar psoriasis.

(Fig. 1A), and an sPGA score of 0 or 1 was achieved in 73% of the patients in the 90-mg risankizumab group and 88% of the patients in 180-mg risankizumab group, as compared with 53% in the ustekinumab group (see the Supplementary Appendix). By week 16, PASI90 was achieved in 80% of the patients who received risankizumab (90-mg and 180-mg groups, pooled) and 43% of the patients who received ustekinumab (Fig. 1B), and PASI100 was achieved in 55% of the patients in the 180-mg risankizumab group and 20% of the patients in the ustekinumab group (see the Supplementary Appendix). Decreases in the PASI score were generally maintained for up to 20 weeks after the final dose of risankizumab (week 36). Complete clearing was maintained in 29% of the patients in the 90-mg risankizumab group and 26% of the patients in the 180-mg risankizumab group for up to 32 weeks after the final administration of study

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Table 2. Clinical Response at Week 12.*

Response Measure	Risankizumab				Ustekinumab (N=40)
	18 mg (N=43)	90 mg (N=41)	180 mg (N=42)	Pooled 90 mg+180 mg (N=83)	
PASI90					
Last observation carried forward					
No. of patients (%)	14 (33)	30 (73)	34 (81)	64 (77)	16 (40)
Difference vs. ustekinumab — percentage points	−7	33†	40†	36‡	
Nonresponse imputation					
No. of patients (%)	13 (30)	30 (73)	33 (79)	63 (76)	16 (40)
Difference vs. ustekinumab — percentage points	−10	33†	37†	35†	
PASI75 at week 12§					
No. of patients (%)	27 (63)	40 (98)	37 (88)	77 (93)	29 (72)
Difference vs. ustekinumab — percentage points	−10	23‡	14	19‡	
PASI100 at week 12§					
No. of patients (%)	6 (14)	17 (41)	20 (48)	37 (45)	7 (18)
Difference vs. ustekinumab — percentage points	−4	23‡	29‡	26‡	
PASI50§					
No. of patients (%)	37 (86)	41 (100)	39 (93)	80 (96)	33 (82)
Difference vs. ustekinumab — percentage points	4	17‡	10	14‡	
sPGA§					
Score of 0 or 1 — no. (%)	25 (58)	37 (90)	37 (88)	74 (89)	25 (62)
Difference vs. ustekinumab — percentage points	−4	27‡	24‡	25‡	
Change in PASI score from baseline — %§					
Median	−83	−95	−99	−98	−89
Interquartile range	−71 to −92	−89 to −100	−91 to −100	−91 to −100	−76 to −97
DLQI¶					
Score of 0 or 1 — no./total no. (%)	17/40 (42)	29/41 (71)	30/41 (73)	59/82 (72)	19/36 (53)
Change in score from baseline — %					
Median	−81	−100	−100	−100†	−91
Interquartile range	−65 to −100	−77 to −100	−81 to −100	−79 to −100	−60 to −100
Change in pain VAS score from baseline — %¶‖					
Median	−32	−70	−58	−68	−57
Interquartile range	−20 to −69	−45 to −91	−3 to −93	−3 to −91	−24 to −98

* For the primary analyses, last observation carried forward was prespecified for the handling of missing data; the sensitivity analysis with nonresponse imputation is also shown for the primary end point and additional end points. The analyses in which last observation carried forward was used for the additional end points are provided in Table S2 in the Supplementary Appendix. For percentage changes in scores from baseline, differences in pairwise comparisons of the primary and secondary end points were analyzed with the use of the Cochran–Mantel–Haenszel risk difference estimate, and nominal P values are provided. No adjustments for multiplicity were performed in these analyses.

† Nominal P<0.05 versus ustekinumab. With 39 comparisons and a type I error of 0.05, two comparisons would be expected to be significant by chance.

‡ P<0.001 versus ustekinumab.

§ Nonresponse imputation was used in this analysis.

¶ Observed data (no imputation) were used in this analysis.

‖ Pain VAS was evaluated in patients with psoriatic arthritis. Psoriatic arthritis was either previously diagnosed by a rheumatologist or suspected by the trial investigator; pain VAS scores were available for 7 patients in the 18-mg group and 11 patients in each of the other three treatment groups.

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drug (week 48). In contrast, we found reductions in responses with ustekinumab from week 24 (8 weeks after the last dose) with no patients having complete clearing at 48 weeks. This time course was confirmed by the analysis of the PASI score reduction from baseline over time (Fig. S2 in the Supplementary Appendix). The rapid onset of effect with risankizumab is supported by Kaplan–Meier plots of the first onset of PASI50 and PASI90, and analysis of the time to loss of PASI50 and PASI90 indicates a longer duration of effect with risankizumab than with ustekinumab (Fig. S3 in the Supplementary Appendix).

Patient-Reported Outcomes

At week 12, the median reduction in DLQI score from baseline was 100% in the risankizumab group (90-mg and 180-mg groups pooled) and 91% in the ustekinumab group (Table 2, and Fig. S4 in the Supplementary Appendix). A DLQI score of 0 or 1 was achieved in 72% of the patients who received 90 mg or 180 mg of risankizumab, as compared with 53% of the patients who received ustekinumab (Table 2). Overall, the percentage of patients in whom a DLQI score of 0 or 1 was achieved was correlated with decreases in the PASI score and sPGA score, with 94% of the patients in whom PASI100 was achieved having a DLQI score of 0 or 1 (Fig. S5 in the Supplementary Appendix). Among patients with psoriatic arthritis, 69% of those who received 90 mg of risankizumab and 83% of those who received 180 mg of risankizumab had a decrease in pain of more than 50% at week 24, as compared with 50% of the patients who received ustekinumab (Fig. S6 in the Supplementary Appendix). The changes from baseline in EQ-5D VAS and EQ-5D index were consistent with decreases in the DLQI score (Table S3 in the Supplementary Appendix). Tables showing changes in PGAR and PAI over time are provided in the Supplementary Appendix.

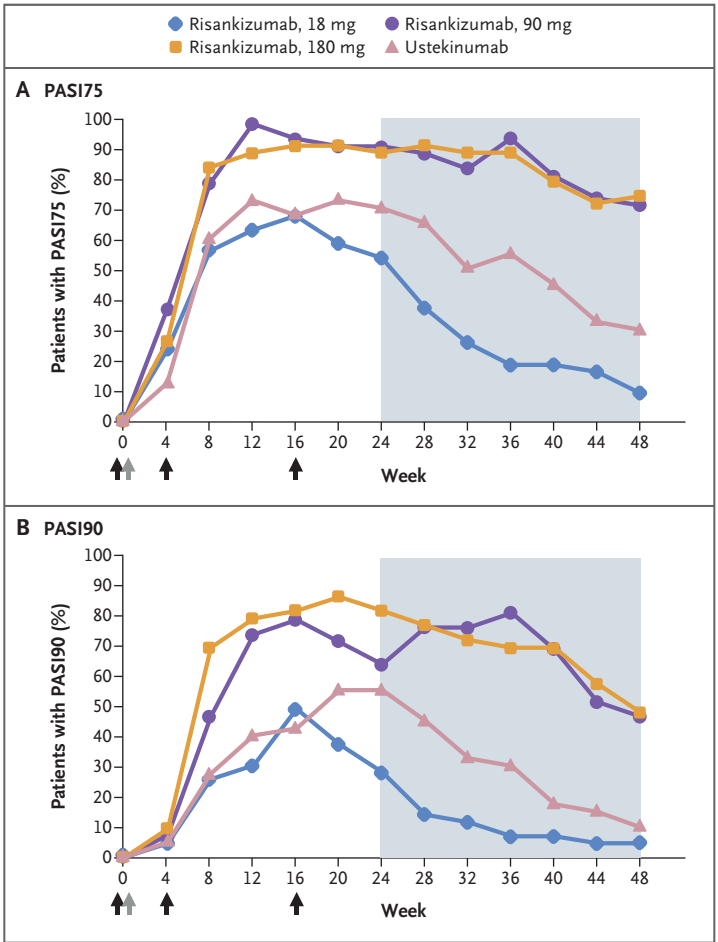

Figure 1. PASI75 and PASI90 Response Rates through Week 48.

Changes in the rates of clinical response, measured as the Psoriasis Area Severity Index (PASI) score, are shown; Panel A shows the percentages of patients in whom a decrease in the PASI score of 75% or greater (PASI75) was achieved, and Panel B shows the percentages of patients in whom a decrease of 90% or greater (PASI90) was achieved. Patients were randomly assigned to receive either a single dose of 18 mg of risankizumab at week 0 (gray arrow); 90 or 180 mg of risankizumab at weeks 0, 4, and 16 (black arrows); or ustekinumab (45 or 90 mg) at weeks 0, 4, and 16 (black arrows). The treatment period ended at week 24, with patients entering the follow-up period through week 48 (indicated by gray shading). The analysis includes all patients who underwent randomization and received at least one dose of the assigned therapy during the trial, with nonresponse imputation of missing data.

Scalp, Fingernail, and Palmoplantar Disease

The mean reductions in the PSSI score (a measure of scalp disease) at week 12 were 90% in the 90-mg risankizumab group and 94% in the 180-mg risankizumab group and were sustained over time, as compared with an 82% reduction in the ustekinumab group that was not sustained over time (Fig. S7A in the Supplementary Appendix). Fingernail improvement was slower, with the mean reduction in the NAPSI score at week 12 being approximately 40% in the 90-mg and 180-mg risankizumab groups and increasing to 61% and 73%, respectively, at week 48. Patients in the ustekinumab group had a mean 20% increase in the NAPSI score at week 12 and an 18% decrease by week 48 (Fig. S7B in the Supplementary Appendix). In the small number of

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patients who had palmoplantar psoriasis, reductions in the PPASI score from baseline occurred in all treatment groups by week 12 (ranging from 75% with ustekinumab to 97% with 90 mg of risankizumab) and were sustained through the end of the trial (Fig. S7C in the Supplementary Appendix).

SAFETY

Through 48 weeks, adverse events occurred in 81% of the patients in the 18-mg risankizumab group, 80% of the patients in the 90-mg risankizumab group, 69% of the patients in the 180-mg risankizumab group, and 72% of the patients in the ustekinumab group (Table 3). One patient each in the 18-mg and 90-mg risankizumab groups and the ustekinumab group discontinued treatment because of an adverse event. The most commonly reported adverse event (occurring in >10% of the patients) in all treatment groups was nasopharyngitis. In the 18-mg, 90-mg, and 180-mg risankizumab groups and the ustekinumab group, 5 (12%), 6 (15%), 0, and 3 (8%) patients, respectively, had serious adverse events, including 2 patients with basal-cell carcinoma, 1 patient with myocardial infarction, and 1 patient who had a cerebrovascular accident on the day after elective surgery for preexisting cerebral aneurysm (Table 3; narratives regarding these patients are provided in the Supplementary Appendix). Antidrug antibodies were detected during treatment in 14% of the patients receiving risankizumab (17 of 124 patients). In most patients, these were transient, low titer (<32), or both. Neutralizing antidrug antibodies were found in 3 patients in the multiple-dose risankizumab groups.

SKIN TISSUE ANALYSES

Skin-biopsy samples were obtained from 60 patients; for 8 patients, the results of one or both biopsies were either not assessable or missing, and thus these patients were excluded. In the 90-mg and 180-mg risankizumab groups, 54% and 69% of the patients, respectively, had global histopathologic assessments graded as indicating "excellent improvement," as compared with 29% of the patients in the ustekinumab group (Table S6 in the Supplementary Appendix). Treatment with risankizumab, but not ustekinumab, also resulted in decreased expression of selected genes from baseline to week 4 (Table S7 in the Supplementary Appendix); these genes were associated with the interleukin-23 pathway and psoriatic disease and included *IL23R*, *DEFB4B* (encoding β-defensin 4B), type I interferon pathway–related genes, and late cornified envelope genes.

DISCUSSION

In this phase 2 head-to-head comparison, PASI90 was achieved in nearly twice as many patients receiving 90 mg or 180 mg of risankizumab as patients receiving ustekinumab. For the first 16 weeks, a single dose of 18 mg of risankizumab was similar in efficacy to the induction dosing of ustekinumab. The onset of activity with risankizumab was faster, and the duration of effect longer. Moreover, clinical responses with risankizumab correlated well with increased quality of life, less joint pain in patients with psoriatic arthritis, and improvements in scalp, palmoplantar, and fingernail psoriasis — three body areas that are generally considered difficult to treat.[20] Basal-cell carcinoma developed in two patients who were treated with risankizumab, and one patient had a major adverse cardiac event. Because this was a phase 2 trial, it was not large enough or of long enough duration to assess the safety profile of risankizumab.

Although these findings are preliminary, the data suggest that selective blockade of interleukin-23 through the inhibition of the p19 subunit rather than p40 provides a more complete inhibition of interleukin-23 activity, potentially resulting in greater efficacy in the treatment of plaque psoriasis at the doses used. However, differences in binding affinity or in potency between risankizumab and ustekinumab may have contributed to the differences in efficacy we found in this trial.

The extended duration of the PASI response that was observed in patients receiving risankizumab supports previously published phase 1 results[15] that indicated that the expression of selected genes associated with psoriasis pathogenesis (genes encoding proteins involved in the interleukin-23–interleukin-17 axis, keratinocyte and epithelial-cell differentiation, tissue inflammation, and type I interferon) was reduced in lesional skin at 8 weeks.

In the current trial, immunohistochemical

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Table 3. Adverse Events through Week 48.*

Adverse Event	Risankizumab			Ustekinumab (N=40)
	18 mg (N=43)	90 mg (N=41)	180 mg (N=42)	
	number of patients (percent)			
Any adverse event	35 (81)	33 (80)	29 (69)	29 (72)
Severe adverse event	4 (9)	4 (10)	1 (2)	4 (10)
Investigator-defined drug-related adverse event	7 (16)	10 (24)	6 (14)	8 (20)
Adverse event leading to discontinuation of treatment	1 (2)	1 (2)	0	1 (2)
Serious adverse event†	5 (12)	6 (15)	0	3 (8)
Death	0	0	0	0
Common adverse events‡				
Nasopharyngitis	15 (35)	14 (34)	11 (26)	5 (12)
Headache	6 (14)	2 (5)	3 (7)	4 (10)
Sinusitis	1 (2)	0	1 (2)	4 (10)
Gastroenteritis	1 (2)	4 (10)	0	0
Back pain	2 (5)	4 (10)	1 (2)	1 (2)
Serious adverse events				
Infection or infestation	1 (2)	0	0	3 (8)
Bronchitis	0	0	0	1 (2)
Diverticulitis	0	0	0	1 (2)
Urinary tract infection	0	0	0	1 (2)
Perineal abscess	1 (2)	0	0	0
Benign, malignant, or unspecified neoplasm	1 (2)	2 (5)	0	0
Basal-cell carcinoma	1 (2)	1 (2)	0	0
Salivary gland neoplasm	0	1 (2)	0	0
Nervous system disorder	2 (5)	1 (2)	0	0
Cerebrovascular accident§¶	0	1 (2)	0	0
Headache	1 (2)	0	0	0
Transient ischemic attack	1 (2)	0	0	0
Cardiac disorder§	0	2 (5)	0	0
Acute myocardial infarction	0	1 (2)	0	0
Chronic coronary artery occlusion	0	1 (2)	0	0
Other serious adverse event‖	4 (9)	2 (5)	0	0

* Adverse events were coded with the use of the *Medical Dictionary for Drug Regulatory Activities*, version 18.1. The severity of adverse events was graded according to the Rheumatology Common Toxicity Criteria, version 2.0.

† A serious adverse event was defined as any adverse event that results in death, is immediately life-threatening, results in persistent or significant disability or incapacity, requires or prolongs hospitalization, is a congenital anomaly or birth defect, or is characterized on the basis of appropriate medical judgment as an important medical event that may jeopardize the patient and may require medical or surgical intervention.

‡ Common adverse events were those reported in at least 10% of the patients in any treatment group; see Table S8 in the Supplementary Appendix for a listing of adverse events reported in at least 5% of the patients in any treatment group.

§ See the Supplementary Appendix for narratives regarding these patients.

¶ The event was not deemed to be a major adverse cardiovascular event by an independent adjudication committee.

‖ A list of the other serious adverse events is provided in Table S9 in the Supplementary Appendix.

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biomarkers associated with the interleukin-23–interleukin-17 axis were reduced by week 4, as was the expression of selected genes linked to the underlying mechanisms associated with psoriatic disease. This was observed only in patients receiving risankizumab, which suggests a unique mechanism of action for selective interleukin-23 p19 inhibition. In most, but not all, patients who had biopsies performed at week 4, the gene profile found in skin-biopsy samples from areas previously affected with psoriasis resembled that published for nonlesional skin from patients with psoriasis[21]; however, further characterization of the cellular and molecular profile of psoriatic lesions over a longer period with risankizumab is needed to support these preliminary findings.

The efficacy findings in this phase 2, 48-week, head-to-head trial need to be confirmed in larger studies with both placebo and active comparators. In addition, the safety of risankizumab needs to be further assessed.

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