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ORIGINAL RESEARCH

Long-Term Safety and Efficacy of Risankizumab in Patients with Moderate-to-Severe Chronic Plaque Psoriasis: Results from a Phase 2 Open-Label Extension Trial

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ABSTRACT

Introduction: Although many biologic therapies are effective for clearing skin of patients with psoriasis, some lose effectiveness over time. This phase 2 open-label extension (OLE) trial was designed to investigate the long-term safety and efficacy of risankizumab.

Methods: In the phase 2, double-blind, active comparator, predecessor trial (NCT02054481), patients with moderate-to-severe chronic plaque psoriasis were treated for 24 weeks with subcutaneous (SC) risankizumab or ustekinumab, followed by a 24-week follow-up without treatment administration. Patients could enroll in the OLE (NCT02203851) when they experienced loss of treatment response (< 50% improvement in the Psoriasis Area Severity Index [PASI 50]) during follow-up) or at the end of follow-up if treatment response was ongoing. In the OLE, patients were treated every 12 weeks for at least 48 weeks with SC risankizumab 90 or 180 mg, beginning at week 12 (OLE visit 2), if the patient had not achieved PASI 90. Efficacy endpoints included the proportions of patients who achieved PASI 50/75/90/100 and static Physician's Global Assessment (sPGA) of clear or almost clear skin at week 48 (sPGA 0/1; OLE visit 5).

Results: Of the 110 enrolled patients, 99 (90.0%) completed the OLE. No patients discontinued the study because of adverse events. At week 48, 74.1% of patients achieved PASI 90, whereas 98.1, 91.7, 53.7, and 67.6% achieved PASI 50/75/100 and sPGA 0/1, respectively. All efficacy results were consistent or slightly increased at OLE week 48 compared with week 12. No new safety findings were observed.

Conclusion: Risankizumab treatment was well tolerated with sustained clinical efficacy for at least 48 weeks.

Trial Registration: ClinicalTrials.gov identifier; NCT02203851.

Keywords: Biologic therapy; Interleukin-23; Open-label extension; Psoriasis; Risankizumab

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Key Summary Points

Why carry out this study?

Psoriasis is associated with increased risk of morbidity, mortality, disability, negative psychological stress, and reduced quality of life.

The identification of new therapeutic targets has led to the discovery of several new compounds effective at clearing skin lesions in patients with psoriasis; however, many patients experience loss of treatment response over time.

This phase 2 open-label extension (OLE) trial investigated whether risankizumab, a humanized immunoglobulin G1 monoclonal antibody that inhibits the proinflammatory cytokine interleukin-23 by binding to its p19 subunit, is effective for long-term treatment of moderate-to-severe plaque psoriasis.

What was learned from the study?

Risankizumab 90 or 180 mg treatment administered every 12 weeks resulted in sustained clinical efficacy over 48 weeks following a 48-week predecessor study (24 weeks of active treatment plus up to 24 weeks of follow-up without treatment).

Over 48 weeks, risankizumab was well tolerated, with only 10% of patients discontinuing the study, none of whom discontinued because of adverse events, and no new or unexpected safety signals observed.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13582640.

INTRODUCTION

Psoriasis is a chronic, immune-mediated, inflammatory skin disease with a global prevalence range of 1–4% [1–3]. Patients with psoriasis are at greater risk of morbidity, mortality, disability, negative psychological stress, and reduced quality of life than are unaffected individuals [4–6].

The identification of specific immune pathways that are involved in psoriasis have provided important therapeutic targets and led to the discovery of several new compounds with clinical efficacy in clearing skin lesions in people with psoriasis [7]; however, many patients experience loss of treatment response over time, often resulting in stopping or switching treatment [8–11]. The proinflammatory cytokine interleukin-23 (IL-23) plays an important role in the pathogenesis of psoriasis because it stimulates the production of inflammatory cytokines, such as IL-17, by T-helper 17 (Th17) and innate immune cells [12–14]. Targeting upstream mediators in the IL-23/IL-17 axis, such as IL-23, may translate into prolonged efficacy because of reduced Th17 cell survival or changes in phenotype, restoration of regulatory T (Treg) cell function, or inhibition of IL-22 production [13].

Risankizumab is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that inhibits IL-23 activity by binding to its p19 subunit [15, 16]. Risankizumab was investigated as a treatment for moderate-to-severe plaque psoriasis in four phase 3 multicenter, randomized, double-blind studies (UltIMMa-1, UltIMMa-2, IMMhance, and IMMvent [17–19]) and was subsequently approved for this indication in the USA and several other countries in 2019 [20]. In a 48-week, phase 2 study, treatment with risankizumab led to superior clinical responses compared with ustekinumab [21].

The study reported here is an open-label extension (OLE) trial of the phase 2 study designed to investigate the long-term safety and efficacy of risankizumab for the treatment of patients with moderate-to-severe chronic plaque psoriasis.

METHODS

Study Design and Treatment

This was a phase 2, multicenter OLE trial (Clinicaltrials.gov identifier: NCT02203851) for patients with moderate-to-severe chronic plaque psoriasis who had successfully completed the 48-week, phase 2, double-blind, active comparator trial of subcutaneous (SC) risankizumab versus ustekinumab (Clinicaltrials.gov identifier: NCT02054481). The full details of the predecessor study have been published elsewhere [21] and are summarized in Fig. 1. Briefly, during a 24-week treatment period, patients received double-blind risankizumab as a single 18 mg dose at week 0, or as fixed doses of 90 or 180 mg at weeks 0, 4, and 16; in contrast, patients in the active comparator arm received open-label ustekinumab at doses of 45 or 90 mg, based on body weight (< 100 vs. ≥ 100 kg, respectively), at weeks 0, 4, and 16. At the end of the treatment period, patients were monitored for another 24 weeks without treatment administration [21]. Any patient who demonstrated a loss of response (< 50% improvement from baseline in the Psoriasis Area Severity Index [PASI 50]) during the follow-up period could immediately switch to the OLE, whereas any patient who maintained a clinical response (≥ PASI 50) could enter the OLE at week 48. After completion of this OLE study, patients

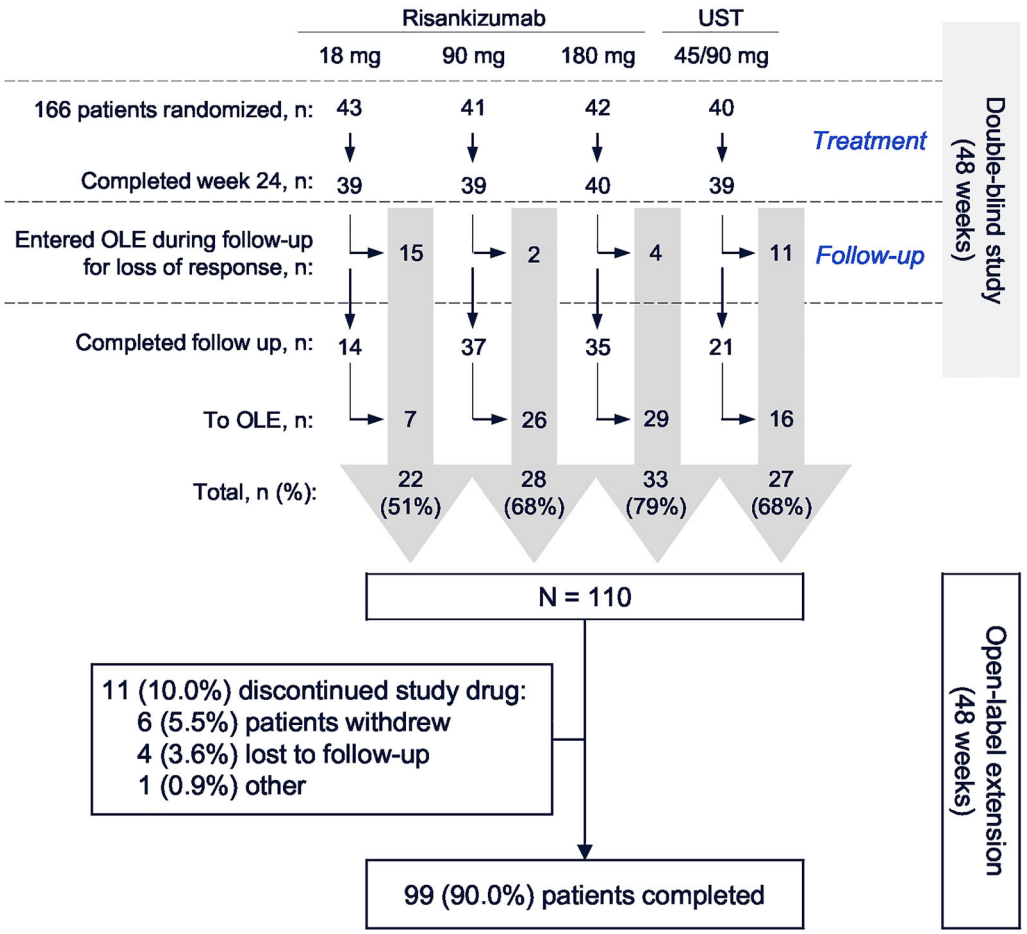

Fig. 1 Patient disposition. *OLE* Open-label extension, *UST* ustekinumab. Full details on patient disposition in the double-blind portion have been published elsewhere [21]

who chose to continue treatment were transferred to a phase 3 OLE study (Clinicaltrials.gov identifier: NCT03047395).

In the OLE, patients were treated with SC risankizumab 90 mg every 12 weeks (q12w) for at least 48 weeks. If at week 12 (OLE visit 2) a patient demonstrated an inadequate response (< PASI 90), the dose could be increased to 180 mg q12w for the remainder of the trial.

This study was conducted in accordance with the Good Clinical Practice Guideline as defined by the International Conference on Harmonisation, the Declaration of Helsinki, and/or all applicable federal and local regulations and the following institutional review boards: Institutional Review Board Services, Aurora, Ontario, Canada; Research Review Board Inc., Richmond Hill, Ontario, Canada; CPP- Ile de France IV, Hôpital Saint-Louis, Paris, France; Ethikkommission des Landes Berlin, Landesamt fur Gesundheit und Soziales, Berlin, Germany; Chesapeake IRB, Columbia, Maryland, USA. All patients provided informed consent and signed approved consent forms prior to any study procedures in accordance with Good Clinical Practice and local legislation.

Patients

To enroll in the predecessor study, patients were required to have moderate-to-severe plaque psoriasis for at least 6 months prior to screening (including ≥ 10% body surface area [BSA] affected by psoriasis; PASI ≥ 12; and static Physician Global Assessment [sPGA] ≥ 3) and had to be a candidate for systemic psoriasis treatment or phototherapy. To enroll in the OLE, patients were required to have completed the double-blind predecessor study, defined as completing the full 48 weeks or demonstrating a loss of response during the follow-up period. Patients could not enroll in the OLE if they had experienced any drug-related serious adverse events (SAEs) or developed guttate, erythrodermic, pustular, or drug-induced psoriasis during the predecessor study or had any other condition that may have compromised safety or data quality.

Assessments

The key efficacy endpoints were the proportions of patients who achieved PASI 50, PASI 75, PASI 90, and PASI 100 (as measured from baseline in the predecessor study) and sPGA scores of clear (0) or almost clear skin (1) at week 48 (OLE visit 5).

Safety assessments were based on treatment-emergent adverse events (TEAEs), which were monitored from the first day of study drug administration in the OLE through 105 days after the last dose in the analysis period. Clinical laboratory parameters, local tolerability, and vital sign measurements were also recorded.

Statistical Analysis

All efficacy and safety analyses were performed for patients who received at least one dose of study drug (intent-to-treat/safety population). Since this was a single-arm OLE study, no statistical tests were performed, and only summary statistics (number, percentage, mean, standard deviation [SD], median, 95% confidence interval, and range) are provided. All efficacy results are based on observed cases and no imputation for missing data was applied.

RESULTS

Patients

Of the 166 patients who were initially randomly assigned to the treatment group in the double-blind predecessor study, 110 (66.3%) entered the OLE. A total of 78 (70.9%) patients across all treatment groups completed the initial study without a loss of clinical response during the follow-up period (Fig. 1). Of the 83 patients who entered the OLE following risankizumab treatment, 62 (74.7%) completed the predecessor study follow-up period without losing clinical response and therefore had initiated risankizumab treatment at least 48 weeks prior to entering the OLE.

Of the 110 patients who entered the OLE, 99 (90.0%) completed the study. The reasons for

discontinuation were withdrawal of consent (n = 6; 5.5%), loss to follow-up (n = 4; 3.6%) and other (n = 1; 0.9%). A total of 23 patients switched to 180 mg risankizumab at week 12 (OLE visit 2) because of a lack of PASI 90 response. The mean (SD) duration of study drug exposure for the combined predecessor and OLE studies was 3.69 (0.66) years and the range was 48.1 weeks–4.34 years.

Most patients were white (91.8%) and male (60%), with a mean (SD) age of 49.0 (13.0) years at OLE baseline (Table 1). Key disease characteristics at baseline included a mean (SD) BSA affected by psoriasis of 23.9 (16.2) m^2, mean PASI of 19.4 (7.2), and mean sPGA of 3.4 (0.5) (Table 1).

Efficacy

The overall proportion of patients with PASI 90 responses at week 48 (OLE visit 5) was 74.1%, which was greater than that observed at the first OLE efficacy assessment at week 12 (OLE visit 2), 67.0% (Fig. 2a). PASI 90 response rates at week 48 (OLE visit 5) were similar for all patients, regardless of which treatment they had received in the predecessor study (range 71.9–77.8%). The proportions of patients who achieved PASI 50/75/100 and sPGA 0/1 were also similar between all the patient groups, regardless of the initial treatment they received (Fig. 2b–e). Responder rates for all endpoints were slightly increased at week 48 (OLE visit 5) compared with week 12 (OLE visit 2), except for sPGA, whose responder rates remained consistent between week 48 (OLE visit 5) and week 12 (OLE visit 2).

Safety

A total of 85 (77.3%) patients reported at least one TEAE during the OLE study (Table 2). The most frequently reported TEAEs were nasopharyngitis (n = 19; 17.3%), upper respiratory tract infection (n = 15; 13.6%), and arthralgia (n = 11; 10.0%). Overall, most TEAEs were mild or moderate, and most were not considered to be related to the study drug. No deaths occurred during the study.

Table 1 Demographics and baseline characteristics

Patient baseline characteristics	Risankizumab (N = 110)
Male sex, n (%)	66 (60.0)
Age (years), mean (SD)	49.0 (13.0)
Age group, n (%)	
< 40 years	31 (28.2)
40 to < 65 years	67 (60.9)
≥ 65 years	12 (10.9)
Race, n (%)	
White	101 (91.8)
Black or African American	2 (1.8)
Asian	3 (2.7)
Native Hawaiian or Other Pacific Islander	2 (1.8)
American Indian or Alaska Native	1 (0.9)
Multiple	1 (0.9)
Not Hispanic or Latino, n (%)	92 (83.6)
Weight (kg), mean (SD)	88.6 (18.0)
Weight category, n (%)	
≤ 100 kg	79 (71.8)
> 100 kg	31 (28.2)
BMI (kg/m^2), mean (SD)	30.3 (5.4)
BSA (%)	
Mean (SD)[a]	23.9 (16.2)
Median (range)	17.0 (10–85)
PASI	
Mean (SD)	19.4 (7.2)
Median (range)	16.60 (12.0–52.0)
sPGA	
Mean (SD)	3.4 (0.5)
Median (range)	3.0 (3–5)

BMI Body mass index, *BSA* body surface area, *PASI* Psoriasis Area Severity Index, *SD* standard deviation, *sPGA* static Physician Global Assessment

[a] n = 109

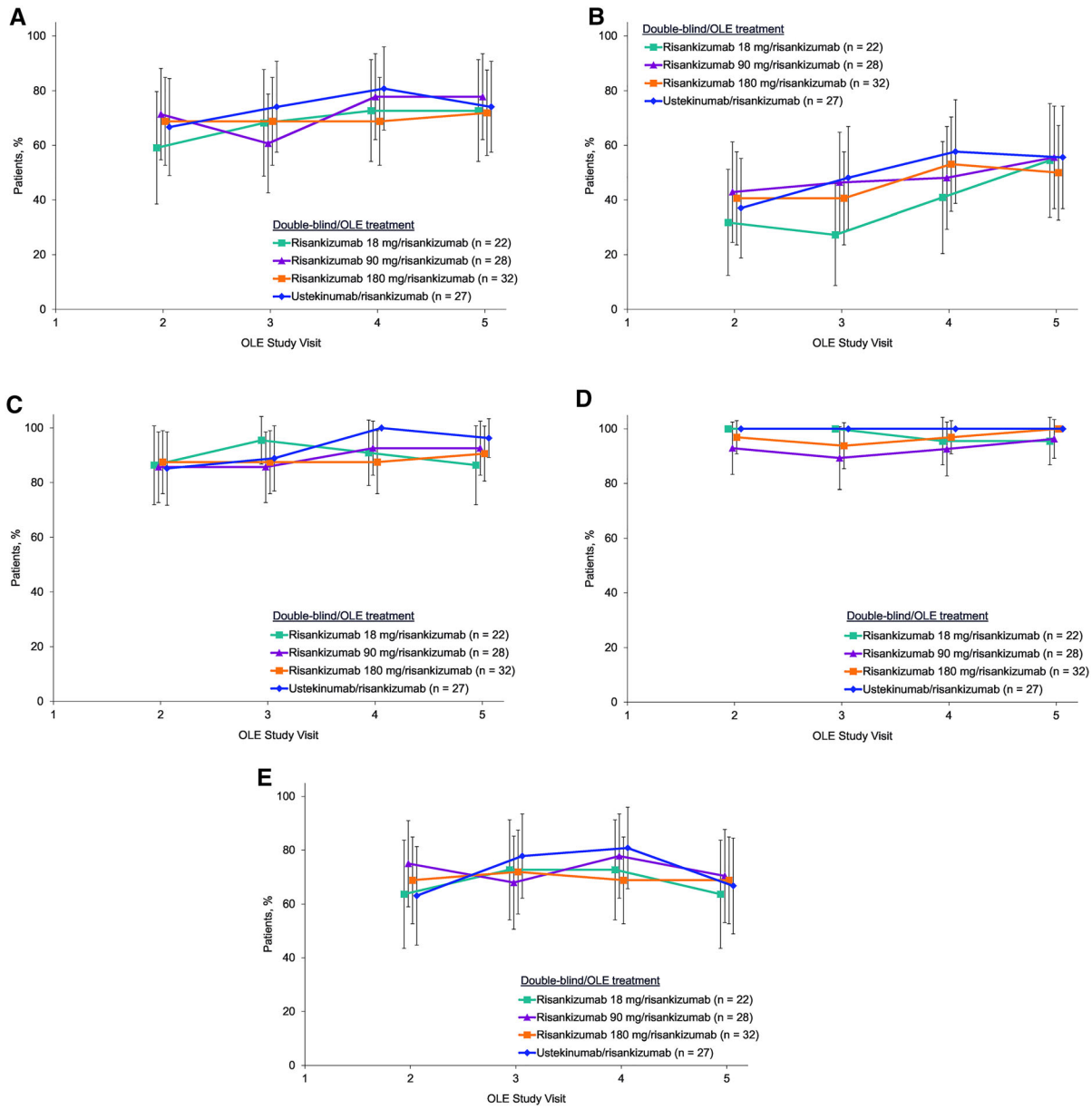

Fig. 2 Efficacy outcomes. Graphs show results for PASI 90 (**a**), PASI 100 (**b**), PASI 75 (**c**), PASI 50 (**d**), and sPGA of clear or almost clear skin (sPGA 0/1) (**e**) over time and by treatment received in the predecessor study. *PASI 50, 75, 90, 100* Psoriasis Area and Severity Index $\geq$ 50, 75, 90 and 100%, respectively, improvement from baseline, *sPGA* static Physician's Global Assessment. Of the 110 patients, 23 switched to risankizumab 180 mg at week 12 (OLE visit 2)

The SAEs reported by more than one patient were basal cell carcinoma and transient ischemic attack (each $n = 2$; 1.8%). The SAEs that were considered possibly related to the study drug were basal cell carcinoma and mild squamous cell carcinoma in one patient and moderate cystitis, moderate pyelonephritis, and moderate sepsis in another patient. Neither patient discontinued the study treatment because of these events.

Two patients (1.8%) reported serious infections during the study: one patient had cystitis,

Table 2 Summary of treatment-emergent adverse events

Treatment-emergent adverse events[a]	Risankizumab	
	Patients (N = 110), n (%)	**Events, n (events/100 PYs)[b]**
Any TEAE	85 (77.3)	457 (134.0)
Serious TEAEs	14 (12.7)	27 (7.9)
Severe (Grade ≥ 3) TEAEs	12 (10.9)	18 (5.3)
TEAEs possibly related to study drug	15 (13.6)	43 (12.6)
TEAEs leading to treatment discontinuation	0	0
Deaths	0	0
TEAEs in ≥ 5 patients		
Nasopharyngitis	19 (17.3)	41 (12.0)
Upper respiratory tract infection	15 (13.6)	21 (6.2)
Arthralgia	11 (10.0)	12 (3.5)
Urinary tract infection	9 (8.2)	10 (2.9)
Bronchitis	7 (6.4)	8 (2.3)
Influenza	7 (6.4)	7 (2.1)
Sinusitis	6 (5.5)	8 (2.3)
Tooth abscess	6 (5.5)	6 (1.8)
Pain in extremity	6 (5.5)	6 (1.8)
Hypertension	6 (5.5)	6 (1.8)
Contact dermatitis	5 (4.5)	5 (1.5)
TEAEs of clinical interest		
Infections and infestations by SOC	58 (52.7)	147 (43.1)
Serious infections	2 (1.8)	4 (1.2)
Fungal infections	5 (4.5)	5 (1.5)
Herpes zoster	1 (0.9)	1 (0.3)
Hypersensitivity reactions	13 (11.8)	17 (5.0)
Serious hypersensitivity reaction	0	0
MACE	1 (0.9)	1 (0.3)
Hepatic events[c]	5 (4.5)	6 (1.8)
Malignancies	2 (1.8)	3 (0.9)
Malignancies excluding non-melanoma skin cancer	0	0

MACE Major adverse cardiac event, *PYs* patient-years, *SOC* system organ class,*TEAE* treatment-emergent adverse event

[a] TEAEs are defined as any event that occurred from the first day of study drug administration in the open-label extension (OLE) to 105 days after the last dose of treatment in the analysis period

[b] Incidence PYs = 341.0

[c] Included increases in alanine aminotransferase, blood bilirubin, hepatic enzyme, and liver function test results and hepatic steatosis

pyelonephritis, and sepsis, all of which were considered serious and possibly related to the study treatment, whereas the other patient had serious pneumonia that was not considered to be related to the study drug. A total of five fungal infections were reported, only one of which (vaginal mycosis) was considered possibly related to the study drug. Although 13 (11.8%) patients reported hypersensitivity reactions, none of the reactions were considered to be serious and no anaphylactic reactions were reported.

No notable changes in laboratory, vital sign, or local tolerability assessments were detected during the study.

DISCUSSION

The results of this phase 2, multicenter OLE trial confirm that risankizumab administered q12w resulted in sustained clinical efficacy and tolerability in patients with moderate-to-severe chronic plaque psoriasis over 48 weeks in addition to 24 weeks of active treatment (plus up to 24 weeks of follow-up without treatment administration) in the predecessor study. The proportions of patients who achieved PASI 50/75/90/100 were slightly greater at week 48 (OLE visit 5) than at week 12 (OLE visit 2). Only 10% of patients discontinued the trial, none of whom reported AEs as the cause.

The availability of biologic therapies was a major advancement for patients seeking safe and effective treatment for moderate-to-severe plaque psoriasis; however, over the nearly two decades since the first biologic treatment was approved for this condition, evidence has revealed that although such biologics are initially effective, many lose effectiveness over time [9–11]. This has been attributed to several causes, including the development of anti-drug antibodies [22]. Additionally, some treatments are intolerable for some patients, resulting in discontinuation [23]. Therefore, there has been an ongoing unmet need for treatments that provide sustained efficacy and are well tolerated for an extended duration. The results from this study indicate that risankizumab provided sustained efficacy over 48 weeks with few patient withdrawals, none of which were due to TEAEs. It is also important to note that half of the patients who entered the OLE had been treated with risankizumab 90 or 180 mg for 24 weeks in the double-blind predecessor study and had sustained treatment responses over the 24-week follow-up period prior to re-starting treatment with risankizumab in the OLE. In sequence, these studies covered a period of up to almost 2 years of treatment with risankizumab (96 weeks, less the follow-up period when the study drug was not administered), during which the clinical efficacy demonstrated an overall trend toward improvement over time. Notably, 25% of the patients in the OLE had been treated with ustekinumab during the predecessor study, and this group's improvements in efficacy endpoints over time were similar to those of the patients who received risankizumab during the initial trial. These findings are similar to those from a recent report showing a mean (SD) improvement in PASI from 11.9 (5.5) to 3.3 (1.7) after 16 weeks of risankizumab treatment in a study of 8 patients who failed anti–IL-17, anti–IL-12/-23, or anti–IL-23 therapy [24].

These results are supported by data from other recent trials in patients with moderate-to-severe plaque psoriasis and are consistent with findings from phase 3 studies assessing the efficacy and safety of 150 mg risankizumab treatment for up to 88 weeks [19, 25, 26]. During a randomized, open-label, efficacy assessor-blinded study in 164 patients treated with risankizumab 150 mg q12w, clinical efficacy was sustained through 52 weeks, during which only two (1.2%) patients discontinued treatment because of an AE [25]. In a double-blind, placebo-controlled, phase 2/3 trial in 113 Japanese patients, treatment with risankizumab 75 or 150 mg q12w resulted in sustained efficacy over 52 weeks, during which only three (2.7%) patients discontinued treatment with risankizumab due to AEs [26]. In a multinational, phase 3, double-blind, placebo-controlled trial, 111 patients treated with risankizumab 150 mg q12w for 88 weeks displayed sustained clinical efficacy and only 4 (3.6%) patients discontinued because of AEs [19]. Finally, in the predecessor to the current trial, only one patient in each of the 18 mg

(single-dose) and 90 mg (q12w) risankizumab groups (2.3 and 2.4%, respectively), and no patients in the 180 mg q12w group, discontinued treatment because of AEs through 48 weeks of treatment [21].

The major strength of this study was the long duration (48 weeks), resulting in up to 96 weeks of observation when considering the predecessor study. However, the results are limited by the open-label design, the lack of a control group for comparisons, and the relatively small sample size. Additionally, patients in this study were not treated with risankizumab doses that are currently approved for clinical use.

CONCLUSION

In conclusion, the results from this 48-week OLE trial reveal that risankizumab provides sustained clinical efficacy during long-term treatment, with clinical outcomes that indicate sustained efficacy over time and a trend toward continued improvement over time. These results also demonstrate that risankizumab has good tolerability when used as a long-term therapy as no new safety signals were observed and no patients discontinued treatment because of AEs.

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Compliance with Ethics Guidelines. This study was conducted in accordance with the Good Clinical Practice Guideline as defined by

the International Conference on Harmonisation, the Declaration of Helsinki, and/or all applicable federal and local regulations and the following institutional review boards: Institutional Review Board Services, Aurora, Ontario, Canada; Research Review Board Inc., Richmond Hill, Ontario, Canada; CPP- Ile de France IV, Hôpital Saint-Louis, Paris, France; Ethikkommission des Landes Berlin, Landesamt fur Gesundheit und Soziales, Berlin, Germany; Chesapeake IRB, Columbia, Maryland, USA. All patients provided informed consent and signed approved consent forms prior to any study procedures in accordance with Good Clinical Practice and local legislation.

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 set 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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