




Direct comparison of risankizumab and fumaric acid esters in systemic therapy-naïve patients with moderate-to-severe plaque psoriasis: a randomized controlled trial*

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Summary

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Conflicts of interest

See Appendix S1 (Supporting Information).

Data availability statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual- and trial-level data (analysis datasets), 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. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and

Background Fumaric acid esters (FAEs; Fumaderm[®]) are the most frequently prescribed first-line systemic treatment for moderate-to-severe plaque psoriasis in Germany. Risankizumab (Skyrizi[®]) is a humanized IgG1 monoclonal antibody that specifically binds to the p19 subunit of interleukin 23.

Objectives To compare risankizumab treatment to FAEs in patients with psoriasis.

Methods This phase III randomized, active-controlled, open-label study with blinded assessment of efficacy was conducted in Germany. Patients were randomized (1 : 1) to subcutaneous risankizumab 150 mg (weeks 0, 4 and 16) or oral FAEs at increasing doses from 30 mg daily (week 0) up to 720 mg daily (weeks 8–24). Enrolled patients were adults naïve to and candidates for systemic therapy, with chronic moderate-to-severe plaque psoriasis. Phototherapy was not allowed within 14 days before or during the study.

Results Key efficacy endpoints were met at week 24 for risankizumab (n = 60) vs. FAEs (n = 60) (P < 0.001): achievement of a ≥ 90% improvement in Psoriasis Area and Severity Index (PASI; primary endpoint 83.3% vs. 10.0%), ≥ 100% improvement in PASI (50.0% vs. 5.0%), ≥ 75% improvement in PASI (98.3% vs. 33.3%), ≥ 50% improvement in PASI (100% vs. 53.3%) and a Static Physician's Global Assessment of clear/almost clear (93.3% vs. 38.3%). The rates of gastrointestinal disorders, flushing, lymphopenia and headache were higher in the FAE group. One patient receiving risankizumab reported a serious infection (influenza, which required hospitalization). There were no malignancies, tuberculosis or opportunistic infections in either treatment arm.

Conclusions Risankizumab was found to be superior to FAEs, providing earlier and greater improvement in psoriasis outcomes that persisted with continued treatment, and more favourable safety results, which is consistent with the known safety profile. No new safety signals for risankizumab or FAEs were observed.

What is already known about this topic?

- Risankizumab (Skyrizi[®]) is approved as treatment for patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy.
- Risankizumab is a humanized IgG1 monoclonal antibody that specifically binds to the p19 subunit of interleukin 23.

approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement. 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: <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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- Fumaric acid esters (FAEs) are the most frequently prescribed first-line systemic treatment for moderate-to-severe plaque psoriasis in Germany.

What does this study add?

- In patients with psoriasis who were naïve to systemic treatment, risankizumab treatment was superior to FAEs, providing earlier and greater improvement in psoriasis outcomes that persisted to week 24.
- Risankizumab showed more favourable safety results than FAEs and no new safety signals.
- The results support risankizumab treatment for patients with moderate-to-severe plaque psoriasis who are naïve to systemic treatment.

Psoriasis is a chronic inflammatory disease that manifests as raised, well-demarcated and scaly erythematous plaques.¹ It is one of the most prevalent immune-mediated skin diseases, affecting approximately 2% of the world's population.^{2,3} Approximately 25% of patients with psoriasis have moderate-to-severe disease, which has a considerable negative impact on their psychosocial and economic status,^{4,5} and 20–30% experience joint involvement.^{6,7} Moderate-to-severe plaque psoriasis is highly correlated with comorbidities such as obesity, diabetes, depression, metabolic syndrome, nonalcoholic liver disease and cardiovascular risk.^{8–10} Psoriasis is frequently associated with psoriatic arthritis and inflammatory bowel disease.

Successful management of moderate-to-severe psoriasis may require phototherapy or systemic therapy. The most frequently prescribed first-line systemic treatment for psoriasis in Germany is the oral formulation of fumaric acid esters (FAEs), Fumaderm[®]. FAEs are approved in Germany for patients with moderate-to-severe plaque psoriasis¹¹ and reach maximum efficacy after 24 weeks of treatment.^{12,13} They are also recommended by the European S3-Guideline on the systemic treatment of psoriasis vulgaris as a first-line treatment before biologic treatments are considered.¹⁴ In a 2015 controlled study of FAEs in patients with psoriasis from four European countries (including Germany), 40.3% and 22.3% of patients achieved a $\geq 75\%$ (PASI 75) and $\geq 90\%$ (PASI 90) improvement from baseline in Psoriasis Area and Severity Index (PASI), respectively.¹⁵ Adverse events (AEs) commonly occurring after treatment with FAEs have included gastrointestinal disorders and flushing.¹²

Increasingly, psoriasis is being treated with biologic agents, including tumour necrosis factor (TNF)- α inhibitors (adalimumab, etanercept, infliximab and certolizumab pegol),^{16–19} interleukin (IL)-12/23 inhibitors (ustekinumab),^{20,21} IL-17 inhibitors (IL-17A: secukinumab and ixekizumab; IL-17RA: brodalumab)^{22–25} and, more recently, IL-23 p19 inhibitors (risankizumab, guselkumab and tildrakizumab).^{26–29} The most effective anti-TNF and IL-12/23 agents provide approximately 75% improvement in psoriasis for approximately 60–70% of patients, with a general risk for loss of response over time,

especially with TNF inhibitors. In comparison, anti-IL-17 agents may provide better efficacy, but the requirement for monthly injections hampers their long-term use.²² Anti-IL-23 agents may offer improved efficacy over the long term and convenient dosing vs. other biologic agents.

Risankizumab (Skyrizi[®]) is a humanized IgG1 monoclonal antibody that binds to the p19 subunit and specifically inhibits IL-23, a cytokine that plays a pivotal role in the development and maintenance of psoriatic lesions.^{26,30} It is approved for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy (USA, European Union) or phototherapy (USA) and for the treatment of plaque psoriasis, generalized pustular psoriasis, erythrodermic psoriasis and psoriatic arthritis in adults who have an inadequate response to conventional therapies (Japan only).^{31–33} It has also been shown to have superior efficacy and comparable safety to the IL-12/23 inhibitor ustekinumab, the IL-17A inhibitor secukinumab, and the TNF- α inhibitor adalimumab.^{26,27,34}

This study compared the efficacy and safety of subcutaneous (SC) risankizumab with oral FAEs in adult patients in Germany who had moderate-to-severe plaque psoriasis and were naïve to systemic therapy.

Patients and methods

Study design

This phase III randomized, active-controlled, multicentre, open-label study with blinded assessment of efficacy (ClinicalTrials.gov identifier NCT03255382) was conducted at 21 sites in Germany between 22 August 2017 and 6 July 2018. Patients were randomly assigned in a 1 : 1 ratio to receive either risankizumab 150 mg SC at weeks 0, 4 and 16, or oral FAEs at increasing doses from 30 mg daily at week 0 up to a maximum dosage of 720 mg daily at weeks 8–24, if tolerability allowed, to achieve PASI 90 (per local label; Figure 1). Patients were randomly assigned via interactive response/web response technology using block randomization and a randomization schedule

prepared by the statistics department of the sponsor. Randomization was stratified by prior phototherapy exposure.

Patients

Patients eligible for enrolment into this study were aged ≥ 18 and < 80 years, had been diagnosed with chronic plaque psoriasis at least 6 months before enrolment, and were naïve to and candidates for systemic therapy. They were required to have stable, moderate-to-severe plaque psoriasis, defined as a PASI score > 10 , a psoriasis-affected body surface area (BSA) of $> 10\%$ and a Dermatology Life Quality Index (DLQI) score of > 10 , and have an inadequate response, intolerance or contraindication to topical psoriasis treatment. Phototherapy was not allowed 14 days before screening or during participation in the study.

Patients were excluded from the study if they had nonplaque forms of psoriasis, drug-induced psoriasis or active inflammatory diseases other than psoriasis; had received systemic therapy or photochemotherapy for psoriasis; had an active systemic infection within 2 weeks of prescreening; had an active or suspected malignancy or history of malignancy within 5 years of prescreening; or had severe gastrointestinal disease, risk factors for renal toxicity, or a contraindication to Fumaderm.

Assessments

The primary endpoint was the proportion of patients who achieved PASI 90 at week 24. Key secondary efficacy endpoints were determined at multiple patient visits and included achievement of $\geq 50\%$ improvement in PASI from baseline (PASI 50), PASI 75 and $\geq 100\%$ improvement in PASI from baseline (PASI 100); a Static Physician's Global Assessment (sPGA) of 0 or 1 (clear or almost clear of psoriasis, respectively; 'static' refers to the patient's disease state at the time of the assessments without comparison to disease states at baseline or at a previous visit); sPGA 0; mean percentage improvement from baseline in PASI; Palmoplantar Psoriasis Area Severity Index (PPASI) and Psoriatic Scalp Severity Index (PSSI; score ranges for PASI, PPASI and PSSI 0–72; higher scores indicate more severe disease); and Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPSI; range

0–32; higher scores indicate more severe disease). An additional analysis was performed to determine the achievement of mean absolute PASI score categories of < 1 , ≤ 3 and ≤ 5 . Other secondary endpoints have been reported in a separate publication.³⁵ Safety was assessed by monitoring AEs, laboratory values and vital signs throughout the study.

Statistical analysis

Using a two-sided χ^2 -test at a 5% level of significance, the sample size of 110 patients (55 per study arm) was expected to provide 94% power, assuming response rates of the primary endpoint (PASI 90 at week 24) of 70% for risankizumab and 35% for oral FAEs. These assumptions aligned with reported PASI 90 response rates for risankizumab [$n = 63/83$ (76%) at week 24] and oral FAEs [$n = 61/273$ (22.3%) at week 16] from other trials.^{15,36}

Efficacy analyses were performed using the intent-to-treat population (all randomized patients). Safety analyses were performed for all randomized patients who received ≥ 1 dose of the study drug. All comparisons were done with two-sided tests, with a significance level of 0.05 for the primary endpoint. Categorical variables were analysed using the Cochran–Mantel–Haenszel test stratified by prior phototherapy exposure; continuous endpoints for PASI, PPASI, PSSI and NAPSI were analysed using ANCOVA. Missing efficacy data were imputed using nonresponder imputation (NRI) for categorical endpoints and last observation carried forward for continuous endpoints. An as-observed case (OC) analysis was used as a secondary approach in the analysis of continuous endpoints and did not impute values for missing evaluations (e.g. patients who did not have an evaluation at a scheduled visit were excluded from the OC analysis for that visit).

Results

Patient characteristics

The details of the 120 randomized patients who entered the study are shown in Figure 2. No patients in the risankizumab

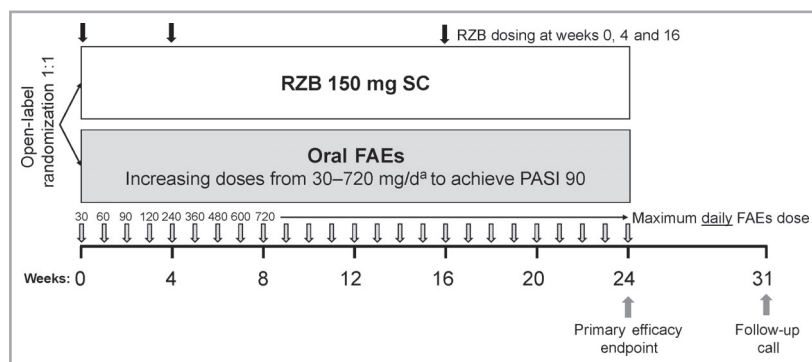


Figure 1 Study design. FAEs, fumaric acid esters (oral formulation); PASI 90, $\geq 90\%$ improvement from baseline in Psoriasis Area and Severity Index; RZB, risankizumab; SC, subcutaneously. ^aIf tolerability allowed.

group discontinued the study or the study drug, compared to 13 patients (21.7%) in the FAE group (three discontinued the study because of an AE and five discontinued the study drug because of an AE).

Baseline demographics and disease characteristics were generally similar between the risankizumab and FAE treatment arms (Table 1). The majority of patients were white men (mean age 42.3 years). Most patients (61.7%) had an above-normal body mass index (BMI; $\geq 25 \text{ kg m}^{-2}$). Disease severity was shown by a mean percentage of involved BSA of 21.2%, a mean DLQI score of 20.3, a mean PASI score of 17.9 and a sPGA at least moderate for 85.8% of patients. Mean time to diagnosis was approximately 15.6 years. PASI scores at baseline were numerically higher for the risankizumab group (mean 19.0, median 18.0) than for the FAE group (mean 16.7, median 14.7), and the proportion of overweight patients (BMI $\geq 25 \text{ kg m}^{-2}$) was higher in the risankizumab group than in the FAEs group (71.7% vs. 53.3%, respectively).

Efficacy

The primary and all-reported secondary efficacy endpoints were achieved. At week 24, significantly more patients randomized to risankizumab achieved PASI 90 compared with patients randomized to FAEs [83.3% vs. 10.0% ($P < 0.001$); Figure 3]. Significantly more patients in the risankizumab group also achieved PASI 50, PASI 75, PASI 100, sPGA 0/1 and sPGA 0 after 24 weeks of treatment compared with patients in the FAE group (all $P < 0.001$).

From weeks 8 to 24, a significantly greater proportion of patients receiving risankizumab achieved clear or almost-clear skin (PASI 100 or PASI 90) compared with patients randomized to FAEs (Figure 3). An even greater proportion of these patients achieved PASI 50 and PASI 75 from weeks 4 to 24.

Significantly more patients randomized to risankizumab achieved sPGA 0/1 starting at week 4 ($P < 0.001$) and sPGA

0 starting at week 8 ($P = 0.048$) compared with patients randomized to FAEs across 24 weeks of treatment (Figure 4).

As shown in Figure 5, the mean percentage improvement in PASI score was statistically significantly higher in the risankizumab group at each time point across 24 weeks. Across weeks 8–24, the rates of achievement of PASI < 1 , ≤ 3 and ≤ 5 increased in the risankizumab group and were significantly greater compared with the FAE group. A significant improvement in PASI score was also observed in the risankizumab group compared with the FAE group at each time point, using OC analysis (Figure S1; see Supporting Information).

Results for the nail, scalp and palmoplantar psoriasis secondary efficacy endpoints show that the mean percentage improvement from baseline for the risankizumab group was significantly higher compared with the FAE group for PSSI and NAPSI scores at weeks 16 and 24 and for PPASI at week 16 and increased slightly from weeks 16 to 24 (Figure 6). Using OC analysis, improvements in PSSI and NAPSI scores also showed significant differences in the risankizumab group compared with the FAE group at weeks 16 and 24. There was no statistically significant difference in PPASI scores for the risankizumab group compared with the FAE group at either time point (Figure S2; see Supporting Information).

Safety

A total of 117 patients were included in the safety analysis (60 in the risankizumab arm and 57 in the FAE arm). The rates of AEs and discontinuations of the study drug because of AEs were lower in the risankizumab group than in the FAE group; rates for AEs related to the study drug were substantially lower in the risankizumab group (Table 2). There were no meaningful differences in the rates of serious or severe AEs between the treatment groups. No patients in the risankizumab group discontinued the study drug because of an AE vs. five patients in the FAE group who discontinued the study drug because of AEs (leukopenia, lymphopenia, upper

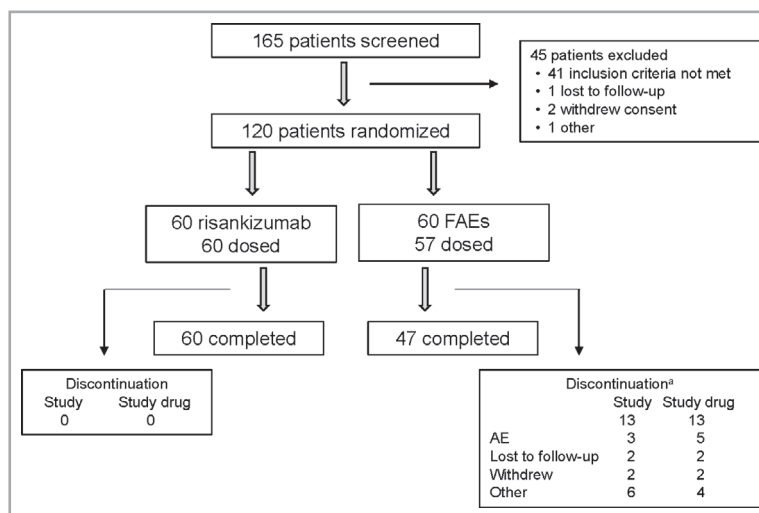


Figure 2 Study flowchart. AE, adverse event; FAEs, fumaric acid esters. ^aPrimary reason.

Table 1 Baseline patient demographics and disease characteristics

Characteristic	RZB (n = 60)	FAEs (n = 60)	All patients (n = 120)
Sex			
Female	27 (45)	22 (36.7)	49 (40.8)
Male	33 (55)	38 (63.3)	71 (59.2)
Mean (SD) age (years)	42.0 (13.75)	42.5 (12.71)	42.3 (13.18)
Median (range) age (years)	40.5 (18.0–73.0)	42.0 (19.0–69.0)	41.5 (18.0–73.0)
Race			
White	59 (98)	60 (100)	119 (99.2)
Asian	1 (1.7)	0	1 (0.8)
Mean (SD) weight (kg) ^a	88.4 (23.0)	85.5 (22.3)	87.0 (22.6)
Median (range) weight (kg) ^a	85.1 (49.0–146.0)	80.0 (48.5–165.0)	81.7 (48.5–165.0)
Mean (SD) BMI (kg m ⁻²) ^{a,b}	29.0 (6.7)	27.7 (6.1)	28.4 (6.5)
Median (range) BMI (kg m ⁻²) ^{a,b}	28.0 (18.7–53.1)	26.5 (18.7–44.8)	27.4 (18.7–53.1)
BMI < 25 (normal)	17 (28)	26 (45)	43 (36.4)
BMI 25 to < 30 (overweight)	24 (40)	17 (29)	41 (34.7)
BMI ≥ 30 (obese)	19 (32)	15 (26)	34 (28.8)
Mean (SD) time since PsO diagnosis (years)	15.8 (12.2)	15.5 (13.6)	15.7 (12.9)
Median (range) time since PsO diagnosis (years)	14 (0–55)	13 (0–61)	13 (0–61)
Mean (SD) BSA (% of PsO-affected area)	23.5 (13.6)	19.0 (8.9)	21.2 (11.7)
Median (range) BSA (% of PsO-affected area)	18.0 (11.0–78.0)	15.0 (11.0–46.0)	16.0 (11.0–78.0)
Mean (SD) PASI (score 0–72) ^c	19.0 (6.9)	16.7 (5.7)	17.9 (6.4)
Median (range) PASI (score 0–72) ^c	18.0 (10.1–39.6)	14.5 (10.2–30.2)	16.0 (10.1–39.6)
sPGA ^a			
Mild (2)	7 (12)	9 (15)	16 (13.4)
Moderate (3)	46 (77)	43 (73)	89 (74.8)
Severe (4)	7 (12)	7 (12)	14 (11.8)
Mean (SD) PPASI (score 0–72) ^{a,c}	0.7 (1.8)	1.5 (3.7)	1.1 (2.9)
Median (range) PPASI (score 0–72) ^{a,c}	0 (0–9)	0 (0–17)	0 (0–17)
Mean (SD) PSSI (score 0–72) ^{a,c}	23.1 (17.6)	20.2 (14.8)	21.6 (16.3)
Median (range) PSSI (score 0–72) ^{a,c}	16 (0–60)	16 (0–60)	16 (0–60)
Mean (SD) NAPSI (score 0–32) ^{a,c}	30.3 (35.0)	22.3 (27.2)	26.3 (31.5)
Median (range) NAPSI (score 0–32) ^{a,c}	14 (0–147)	6 (0–98)	10 (0–147)
Mean (SD) DLQI (score 0–30) ^c	20.0 (5.3)	20.5 (6.0)	20.3 (5.7)
Median (range) DLQI (score 0–30) ^c	20.0 (8.0–30.0)	20.5 (7.0–30.0)	20.0 (7.0–30.0)
Prior phototherapy for PsO	10 (17)	11 (18)	21 (18)

Data are n (%) unless otherwise specified. BMI, body mass index; BSA, body surface area; DLQI, Dermatology Life Quality Index; FAEs, fumaric acid esters (oral formulation); NAPSI, Nail Assessment in Psoriasis and Psoriatic Arthritis; PASI, Psoriasis Area Severity Index; PPASI, Palmoplantar Psoriasis Area Severity Index; PsO, psoriasis; PSSI, Psoriatic Scalp Severity Index; RZB, risankizumab; sPGA, Static Physician's Global Assessment. ^aData missing for FAEs: n = 2 for weight, BMI; n = 1 for sPGA, PPASI, PSSI and NAPSI. Data missing for RZB: n = 2 for NAPSI. ^bBMI categories were defined in the protocol. ^cHigher scores indicate more disability or disease severity.

abdominal pain, drug eruption and flushing). A substantially greater number of patients in the FAE group experienced gastrointestinal disorders, flushing, lymphopenia and headache than in the risankizumab group. There were no deaths and no cases of malignancies, tuberculosis, opportunistic infections, major adverse cardiac events or other cardiovascular events, herpes zoster-related events or serious hypersensitivity for either treatment group in the study.

Discussion

This is the first head-to-head psoriasis trial to compare risankizumab with FAEs in patients naïve to systemic treatment. In summary, the primary endpoint of this trial (i.e. achievement of PASI 90 after 24 weeks of treatment) showed the superiority of risankizumab to FAEs. The PASI 90 endpoint, which

indicates clear to almost-clear skin, has been identified as the current treatment goal for psoriasis.^{37,38} The secondary endpoints in this trial were also achieved at week 24, with significant differences favouring risankizumab (except for PPASI, which numerically favoured risankizumab) also seen across patient visits before week 24. These results support the superiority of risankizumab to FAEs in producing clinically meaningful improvement in the extent and severity of psoriasis over time. The rates of serious and severe AEs were low in both treatment groups.

The treatment populations in this trial were generally similar to populations with moderate-to-severe psoriasis from other phase III trials of risankizumab and trials of FAEs, with respect to entry criteria and baseline characteristics.^{15,26,27,29,33,39–41} In relation to the entry criteria of PASI > 10, affected BSA > 10% and DLQI > 10, patients had a high

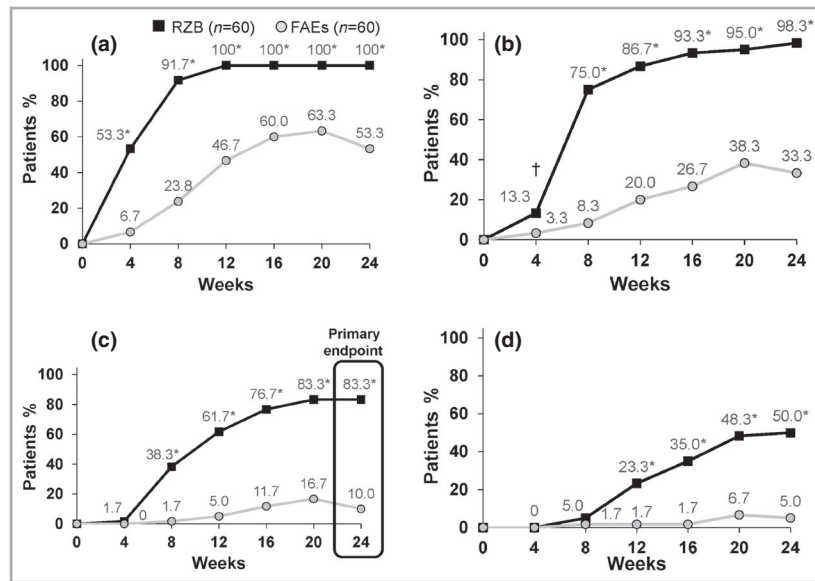


Figure 3 Achievement of Psoriasis Area and Severity Index (PASI) across 24 weeks of treatment. (a) Fifty per cent or more improvement in PASI from baseline (PASI 50), (b) ≥ 75% improvement in PASI from baseline (PASI 75), (c) ≥ 90% improvement in PASI from baseline (PASI 90; primary efficacy endpoint) and (d) 100% improvement in PASI from baseline (PASI 100). Intention-to-treat population, nonresponder imputation. * $P < 0.001$ and † $P < 0.05$ vs. fumaric acid esters (oral formulation; FAEs). RZB, risankizumab.

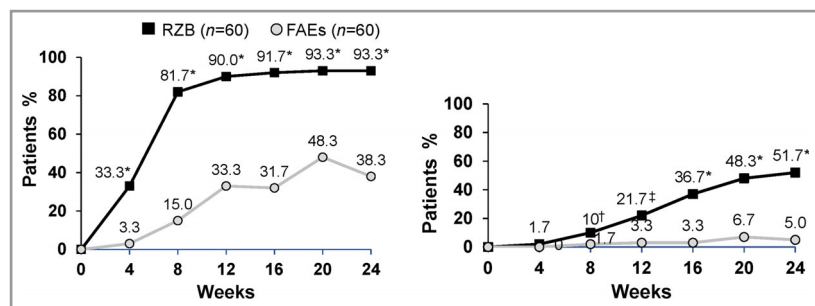


Figure 4 Achievement of static Physician's Global Assessment (sPGA) across 24 weeks of treatment. (a) sPGA 0/1 and (b) sPGA 0. Intention-to-treat population, nonresponder imputation. * $P < 0.001$; † $P < 0.05$ and ‡ $P = 0.01$ vs. fumaric acid esters (oral formulation; FAEs). RZB, risankizumab.

disease burden, as shown by an overall mean PASI score of 17.9, a mean DLQI score of 20.3, a mean percentage of psoriasis-involved BSA of 21.2% and a mean time to disease diagnosis of 15.6 years. The higher disease burden was comparable to that of other phase III randomized, open-label, head-to-head trials of biologics and FAEs in systemic treatment-naïve patients,^{29,40,41} possibly because these patients have a greater perception of impairment to their quality of life. The current trial was conducted in Germany, whereas other phase III trials of risankizumab were conducted across multiple global regions, and some FAE trials were carried out in Europe. Compared with other risankizumab trials, the current risankizumab population was slightly younger with a higher disease burden in terms of mean DLQI score, and any prior systemic therapy in the past was not allowed.

In this trial, the rates of disease improvement – as measured by achievement of PASI 75, PASI 90 and PASI 100, and of a

sPGA 0/1 after 24 weeks of risankizumab treatment – are consistent with rates after 52 weeks of treatment in other phase III trials of risankizumab that evaluated moderate-to-severe plaque psoriasis,^{26,36,39} and were higher for risankizumab in the current trial than rates after 24 weeks of treatment with biologics in the other head-to-head vs. FAE trials.^{29,40,41} Treatment response was more rapid after risankizumab treatment than it was after FAE treatment, which is consistent with the other head-to-head biologics vs. FAE trials. For the FAE group in this study, rates of disease improvement, as measured by PASI 75, PASI 90 and PASI 100 at week 24, are comparable to rates in head-to-head trials with other biologics at week 24. The risankizumab group showed significantly greater mean improvement in PASI score across all six measured time-points compared with the FAE group.

Treatment response when measured using relative PASI (achievement of a 50%, 75%, 90% or 100% improvement in

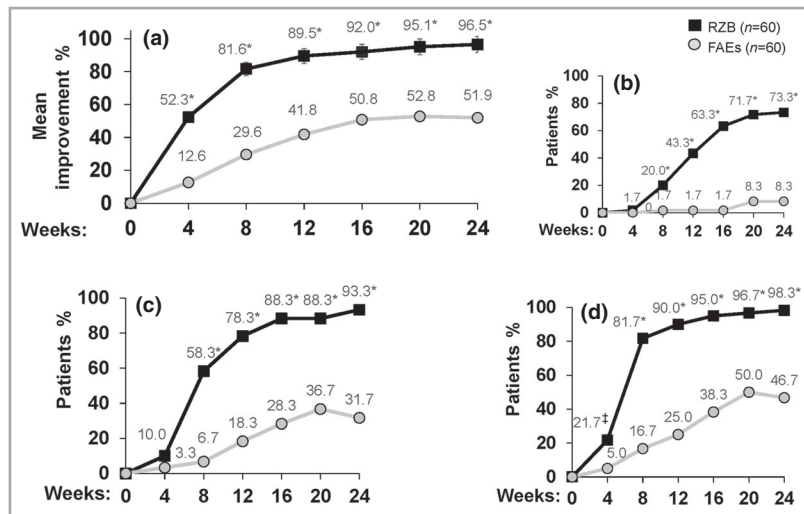


Figure 5 Psoriasis Area and Severity Index (PASI) efficacy outcomes. Intention-to-treat population. * $P < 0.001$ and † $P = 0.01$ vs. fumaric acid esters (oral formulation; FAEs). (a) Mean percentage improvement from baseline in overall PASI (LOCF) and (b–d) proportion of patients achieving PASI < 1 , ≤ 3 and ≤ 5 (NRI), respectively. P-values calculated from ANCOVA with baseline value and treatment in the model. LOCF, last observation carried forward; NRI, nonresponder imputation; RZB, risankizumab.

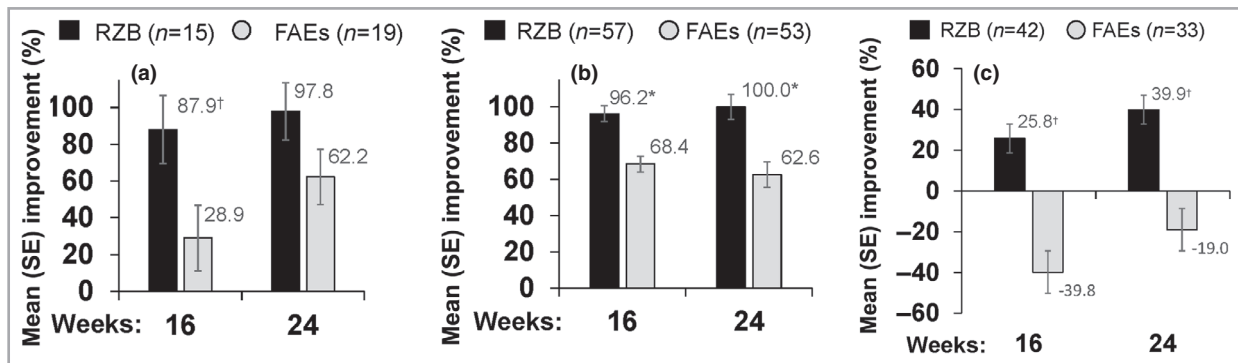


Figure 6 Improvement from baseline in palmoplantar psoriasis, scalp and nail outcomes. Mean percentage improvement from baseline in (a) Palmoplantar Psoriasis Area Severity Index (PPASI), (b) Psoriatic Scalp Severity Index (PSSI) and (c) Nail Assessment in Psoriasis and Psoriatic Arthritis (NAPS). Intention-to-treat population, last observation carried forward (LOCF). * $P < 0.001$ and † $P < 0.05$ vs. fumaric acid esters (oral formulation; FAEs). RZB, risankizumab.

PASI from baseline) can be problematic because the accuracy and relevance of the measurement depend on a baseline PASI measurement, which is not always available in the clinical setting. Thus, absolute PASI is becoming an attractive alternative for evaluating therapeutic response^{42–45}; however, a consensus on definitive, clinically meaningful target scores that can be associated with levels of disease improvement has not yet been reached.^{42,46–48}

Our analysis of absolute PASI < 1 , ≤ 3 and ≤ 5 showed significantly greater achievement rates in the risankizumab group than in the FAE group, starting at week 8 (week 4 for PASI ≤ 5). These rates are consistent with rates at week 24 from a head-to-head trial of guselkumab vs. FAEs; 67% vs. 10% achieved PASI ≤ 1 and 90% vs. 24% achieved PASI ≤ 3 (NRI).²⁹ Achievement rates for risankizumab at week 16 were comparable to rates from the phase III UltIMMA-1 and UltIMMA-2 risankizumab pooled analysis (PASI ≤ 1 : 58.9%; \leq

3: 82.9%),⁴⁹ and higher than rates in other trials of biologic treatment for psoriasis, which included secukinumab [retrospective, real-world study (week 24): 45.5%, 71.2% and 77.0% achieved absolute PASI ≤ 1 , ≤ 3 and ≤ 5 , respectively; NRI],⁵⁰ ustekinumab [phase III TRANSIT study (week 28): 37%, 66% and 83% achieved absolute PASI ≤ 1 , ≤ 3 and ≤ 5 , respectively; observed]⁴³ and ixekizumab [phase III UNCOVER-2 and UNCOVER-3 pooled analysis (week 12): 54.6%, 80.8% and 89.3% achieved absolute PASI ≤ 1 , ≤ 3 and ≤ 5 , respectively; NRI].⁴⁵

Moderate-to-severe psoriasis manifestations in the nails, scalp and palmoplantar areas do not respond as well to therapy as skin psoriasis. This trial is the only trial of risankizumab and the only head-to-head trial of biologics vs. FAEs that evaluated scalp, palmoplantar and nail psoriasis treatment outcomes in systemic treatment-naïve patients with moderate-to-

Table 2 Summary of treatment-emergent adverse events (AEs) over 24 weeks

Event	Treatment	
	RZB (n = 60)	FAEs (n = 57)
AE	49 (82)	57 (100)
SAE ^a	1 (2)	2 (4)
AE leading to discontinuation of study drug ^b	0	5 (9)
AE assessed as related to study drug ^c	15 (25)	52 (91)
SAE assessed as related to study drug ^c	1 (2)	0
Infections	43 (72)	35 (61)
Severe AE	4 (7)	3 (5)
AE rate of > 10% in any group ^d		
Nasopharyngitis	35 (58)	26 (46)
Diarrhoea	4 (7)	32 (56)
Upper abdominal pain	1 (2)	26 (46)
Flushing	0	23 (40)
Headache	5 (8)	7 (12)
Abdominal pain	0	11 (19)
Nausea	0	9 (16)
Lymphopenia	0	8 (14)
Hypersensitivity	1 (2)	6 (11)

Treatment-emergent adverse events (AEs) were defined as any AE with an onset date on or after the first dose of study drug and up to 105 days after the last dose for risankizumab (RZB) and up to 7 days for fumaric acid esters (FAEs; oral formulation). SAE, serious adverse event. ^aInfluenza infection and chronic obstructive pulmonary disease in one patient (RZB) requiring hospitalization. Arthralgia in one patient (FAEs) requiring hospitalization, obesity in one patient (FAEs) hospitalized for elective gastric bypass. ^bLeukopenia, lymphopenia, upper abdominal pain, drug eruption and flushing. ^cInvestigator assessment. ^dMedDRA v21.0 Preferred Term.

severe psoriasis, with the exception of the guselkumab vs. FAE trial, which evaluated scalp psoriasis. Significantly greater improvements were shown in the risankizumab vs. FAE group for nail psoriasis (NAPSI) and scalp psoriasis (PSSI) at both evaluated timepoints. The risankizumab group showed numerically greater improvement in palmoplantar psoriasis (PPASI) at both timepoints. Scalp psoriasis in the guselkumab vs. FAE trial showed a greater improvement in the guselkumab group; however, improvement was measured using the scalp-specific Investigator Global Assessment and is difficult to compare with results from the PSSI used in the current study.²⁹

In this study, the safety profiles for the risankizumab and FAE groups were consistent with the known respective safety profiles,^{12,13,31–33} and no new safety findings were observed. There were few serious AEs in either treatment group. No patients in the risankizumab group discontinued the study. In the FAE group, three of 13 patients who discontinued the study and five who discontinued study drug did so because of an AE; this rate (23%) was much lower than the rates in the other head-to-head trials with FAEs (60–69%).^{29,40,41} Five patients in the FAE group discontinued the study drug because

of an AE vs. no patients in the risankizumab group. The AEs leading to discontinuation of FAEs were mostly related to gastrointestinal tolerability, lymphopenia and flushing, which is consistent with the known safety profile of FAEs.¹¹ Serious infections in both groups (influenza and chronic obstructive pulmonary disease for one risankizumab patient, and arthralgia and obesity for one patient each in the FAE group) were considered serious because they resulted in hospitalization. The rates of overall AEs in this trial for both treatment groups were similar to the rates of biologics and FAEs in the head-to-head trials.^{29,40,41}

The limitations of this study include a smaller number of patients vs. previous risankizumab and FAE trials, the relatively short study duration and that this study was conducted only in Germany, unlike other trials of risankizumab and FAEs that had a more global population.

The superiority of risankizumab to FAEs was consistently shown across all reported endpoints, including skin, scalp, nail and palmoplantar psoriasis. Significantly more patients randomized to risankizumab achieved clear or almost-clear skin earlier than patients randomized to FAEs. A significantly greater improvement in psoriasis from baseline was observed in the risankizumab group compared with the FAE group. The risankizumab safety profile appeared to be more favourable than that of FAEs, and was consistent with the known risankizumab safety profile. No new safety signals were observed.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1 Conflicts of interest.

Figure S1 Psoriasis Area and Severity Index efficacy outcomes (observed case analysis).

Figure S2 Improvement from baseline in palmoplantar psoriasis, scalp and nail outcomes (observed case analysis).