





Long-term safety of risankizumab from 17 clinical trials in patients with moderate-to-severe plaque psoriasis*

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Summary

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Conflicts of interest

Statements can be found in Appendix 1.

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 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 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 the following link: <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information->

Background Risankizumab has demonstrated efficacy and safety in patients with moderate-to-severe plaque psoriasis in randomized clinical trials.

Objectives To evaluate safety data from risankizumab psoriasis phase I–III clinical trials.

Methods Short-term safety (through week 16) was analysed using integrated data from five phase II and III clinical trials. Long-term safety was evaluated using integrated data from 17 phase I–III completed and ongoing trials.

Results Short-term safety analyses included 1306 patients receiving risankizumab 150 mg and 300 patients receiving placebo [402.2 and 92.0 patient-years (PY) of exposure, respectively]. Long-term analyses included 3072 risankizumab-treated patients (exposure: 7927 PY). The median (excluding four outliers) treatment duration was 2.9 years (range 2 days to 5.9 years). Exposure-adjusted adverse event rates did not increase with long-term treatment (318 vs. 171 events per 100 PY for short- and long-term analyses). With long-term risankizumab treatment, rates of serious adverse events were 7.8 per 100 PY, serious infections 1.2 per 100 PY, nonmelanoma skin cancer (NMSC) 0.7 per 100 PY, malignant tumours excluding NMSC 0.5 per 100 PY, and adjudicated major adverse cardiovascular events 0.3 per 100 PY, with no important identified risks. Limitations include that the study inclusion and exclusion criteria varied and that three studies enrolled ≤ 50 patients. **Conclusions** Risankizumab demonstrated a favourable safety profile over short- and long-term treatment in patients with moderate-to-severe psoriasis.

What is already known about this topic?

- In clinical trials of patients with moderate-to-severe plaque psoriasis, risankizumab, a selective interleukin-23 inhibitor, was well tolerated and efficacious.

What does this study add?

- In this comprehensive evaluation of risankizumab safety in patients with moderate-to-severe psoriasis, adverse event rates were comparable between risankizumab ($n = 1306$, 402 patient-years) and placebo ($n = 300$, 92 patient-years) in the

sharing/data-and-information-sharing-with-qualified-researchers.html.

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short-term (16-week) analysis set, and were consistent with those in the long-term analysis ($n = 3072$, 7927 patient-years of risankizumab exposure).

- These findings are consistent with the known safety profile of risankizumab and support its long-term use in moderate-to-severe psoriasis.

Psoriasis is a chronic, systemic disease that has possible associations with psychiatric, arthritic, cardiometabolic and malignant comorbidities.^{1,2} Most patients treated with biologic agents require continuous long-term treatment to achieve disease control.^{3,4} Owing to the immunomodulatory nature of biologics, it has been suggested that patients treated with biologics may be more susceptible to opportunistic and other infections.⁵

Risankizumab is a selective interleukin (IL)-23 inhibitor⁶ that binds to the p19 subunit of IL-23, preventing interaction with the IL-23 receptor. Risankizumab has been shown to be well tolerated and efficacious in patients with moderate-to-severe plaque psoriasis^{3,7–9} and is approved for the treatment of moderate-to-severe plaque psoriasis in over 70 countries, including the USA, Canada, Japan and in Europe.^{10,11} Here we report safety for up to 5.9 years of treatment with risankizumab using integrated data from 17 completed or ongoing clinical trials in plaque psoriasis.

Patients and methods

Patients and study treatment

The long-term safety analysis included all risankizumab data for patients who received at least one risankizumab dose (double-blinded or open-label treatment, dose range 18–180 mg; most patients received 150 mg) in 17 phase I–III trials in patients with moderate-to-severe plaque psoriasis. The database cutoff for the ongoing trials in the long-term analysis set was 25 March 2020. Short-term safety (through week 16) was analysed using integrated data from the placebo-controlled double-blinded period of five of these trials (Table S1; see Supporting Information).

Treatment-emergent adverse events (TEAEs) were defined as events with onset after the first dose of study drug until the end of the placebo-controlled period (i.e. 15 weeks after the dose preceding the week 16 dose) for short-term safety analysis, and as events with onset between the first and last dose of risankizumab plus five risankizumab half-lives (20 weeks) for long-term safety analysis. This difference in monitoring periods was based on recent enhanced understanding of the half-life of risankizumab from phase III pharmacokinetic data.¹²

Patient eligibility criteria for the included trials are provided in Appendix S1 (see Supporting Information). Of note, patients with the following conditions were not excluded: inflammatory bowel disease; suicidal ideation and behaviour; depression; latent tuberculosis (prophylaxis was mandatory only if required for comparator); active, ongoing

cardiovascular or cerebrovascular disease (unless severe); successfully treated nonmelanoma skin cancer (NMSC) or carcinoma in situ; or a history of successfully treated malignancy > 5 years prior to enrolment. Patients with a history of HIV, hepatitis C or acute or chronic hepatitis B were excluded from participation in risankizumab clinical trials. Patients previously treated with IL-12/IL-23 inhibitors, IL-17 inhibitors or tumour necrosis factor inhibitors within 6 weeks to 6 months (depending on drug) or other systemic immunomodulators (within 30 days) prior to study start were excluded. Patients previously treated with IL-23 inhibitors at any time were excluded from phase III trials.

Individual studies were conducted in accordance with the International Conference on Harmonisation guidelines, applicable regulations and the principles of the Declaration of Helsinki that were in place at the time the studies were conducted. Studies and study-related documents were approved by independent ethics committees or institutional review boards, and all patients provided written informed consent.

In all studies, participation was terminated for safety reasons if, in the opinion of the sponsor or the investigator, continued exposure to the study medication represented a significant risk. Other reasons for discontinuation included lack of efficacy, patient withdrawal, other medical reasons [e.g. surgery, adverse events (AEs), other diseases or pregnancy] or loss to follow-up.

Integrated analyses of safety outcomes

Safety data were pooled at the individual patient level. Rates of AEs were expressed as exposure-adjusted event rates (EAERs) per 100 patient-years (PY) for the entire treatment period and were coded using the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (<https://www.meddra.org>), versions 22.1 and 20.0 for long- and short-term analysis, respectively.

Short-term safety (up to 16 weeks) was analysed in the integrated data from the double-blinded placebo- or active-comparator-controlled periods of one phase II and four phase III clinical trials. In addition to these five trials, the long-term safety analysis set also included data from two phase I studies, one phase II extension study, one phase IIb/III study, seven phase III studies and a phase II/III extension study, for a total of 17 studies. The majority of patients in both analysis datasets received the standard 150-mg dose of risankizumab.

The analysis populations for short- and long-term safety consist of different sets of patients, and patients included in the long-term analysis set have varying lengths of treatment

exposure. Any risankizumab safety events included in the short-term analysis set are also included in the long-term analysis set.

Statistical analysis

EAERs with 95% exact Poisson confidence intervals (CIs) were calculated using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). For the displays of rates over 6- or 12-month intervals, the total PY of exposure and number of events in each interval were used to calculate the EAER and 95% CI. The standardized mortality ratio of risankizumab-treated patients was calculated as the ratio of observed (treatment-emergent) to expected deaths using mortality data from the World Health Organization (2015) adjusting for country, sex, age and length of risankizumab exposure.¹³

Results

Baseline characteristics and risankizumab exposure

In total 3072 risankizumab-treated patients were included in the long-term analysis set, representing 7927 cumulative PY of risankizumab exposure. The median risankizumab treatment duration was 2.9 years. The treatment duration (i.e. the time between the first and last doses plus 12 weeks) was ≥ 3 , ≥ 6 , ≥ 12 , ≥ 24 , ≥ 36 and ≥ 48 months in 2942 (96%), 2831 (92%), 2447 (80%), 2019 (66%), 1455 (47%) and 172 (6%) patients, respectively. The short-term analysis set included 1306 patients receiving risankizumab 150 mg (402 PY of exposure). The baseline characteristics were similar between the two analysis sets (Table 1).

General safety overview

The EAER for AEs in the long-term analysis set was 171 events per 100 PY (Table 2). The majority of AEs were mild to moderate in severity, did not require study discontinuation and were considered by the investigators to be unrelated to risankizumab treatment. In the short-term analysis set, EAERs were comparable between risankizumab- and placebo-treated patients (Table 2 and Table S2; see Supporting Information) and were consistent with those in the long-term analysis set. In a post hoc subanalysis of patients ≥ 65 years of age (11.7% of the analysis population), EAERs were consistent with or lower than those in the entire population, with the exception of malignancies excluding NMSC, and deaths – trends typical for this older subgroup of patients (Table S3; see Supporting Information).

Adverse events in areas of safety interest

Areas of safety interest were identified based on their higher prevalence in the population with moderate-to-severe psoriasis, customary concerns with injected immunoglobulin products, or the immunomodulatory activity of risankizumab.

EAERs for TEAEs of safety interest were low for both analysis sets and generally remained consistent or decreased over time (Table 2 and Figure 1).

Infections

EAERs for infection were 90.8 and 56.4 events per 100 PY in the short- and long-term analysis sets, respectively – most commonly nasopharyngitis and upper respiratory tract infection (Table 2 and Table S2). Rates of serious infection were 1.7 and 1.2 events per 100 PY in the short- and long-term analysis sets, respectively, and for long-term analysis were comparable with placebo at 16 weeks (1.1 events per 100 PY; Table 2). Summaries of EAERs over time are provided in Figure 2. Treatment-emergent serious infections with an occurrence of at least two events in the long-term analysis set are summarized in Table S4 (see Supporting Information). Those reported most frequently (sepsis, pneumonia, cellulitis, diverticulitis and appendicitis) are those commonly reported in the general population. Rates of serious infections were consistent with those in the Psoriasis Longitudinal Assessment Registry (PSOLAR; 0.93–2.91 events per 100 PY; Figure 3).¹⁴

Opportunistic infections

The EAER for *Candida* infections in the long-term analysis set was 0.6 events per 100 PY (44 events; Table S5; see Supporting Information) and there were no reports of deep or systemic candidiasis. Among the 37 occurrences of herpes zoster, three were classified as serious; all of these involved a single dermatome and none required treatment discontinuation or recurred (Table S4). The EAER for herpes zoster in the long-term analysis set (0.5 events per 100 PY) was below the PSOLAR reference benchmarks of 1.0 per 100 PY (patients with psoriasis receiving systemic therapy or biologics) and 0.6 per 100 PY (patients with moderate-to-severe psoriasis).^{15,16}

There were no cases of active tuberculosis in this analysis. An earlier data cut (1 September 2017) across the four pivotal phase III psoriasis clinical studies showed no development of active tuberculosis among 72 patients who had positive QuantiFERON Gold tests at baseline and concurrent risankizumab and tuberculosis prophylaxis during a mean follow-up of 61 weeks. In IMMhance, none of the 31 patients with positive QuantiFERON Gold tests at baseline who did not receive prophylaxis developed active tuberculosis during a mean follow-up of 55 weeks.

Malignancies

Rates of NMSC and malignant tumours excluding NMSC over time are summarized in Figure 2. In the long-term analysis set, there were 42 non-NMSCs (0.5 per 100 PY), most commonly those reported in the general population (colorectal, < 0.1 per 100 PY; prostate, < 0.1 per 100 PY; breast, 0.1 per 100 PY; Table 2 and Table S4). Rates were within the reference range for moderate-to-severe psoriasis reported in

Table 1 Baseline demographic and disease characteristics

	Week 16 placebo (n = 300)	Week 16 RZB 150 mg (n = 1306) ^a	Long-term all RZB (n = 3072) ^{a,b}
Sex			
Male	219 (73.0)	908 (69.5)	2129 (69.3)
Female	81 (27.0)	398 (30.5)	943 (30.7)
Age (years)			
Median (range)	48 (19–85)	48 (18–84)	48.0 (18–85)
< 65	261 (87.0)	1165 (89.2)	2712 (88.3)
65–74	35 (11.7)	124 (9.5)	322 (10.5)
≥ 75	4 (1.3)	17 (1.3)	38 (1.2)
Body mass index (kg m ⁻²) ^c			
Median (range)	29.8 (17.0–51.4)	29.9 (15.0–67.0)	29.3 (15.0–92.7)
< 25	62 (20.7)	282 (21.6)	708 (23.1)
25–30 (overweight)	91 (30.3)	400 (30.6)	972 (31.7)
≥ 30 (obese)	147 (49.0)	624 (47.8)	1391 (45.3)
Race			
White	240 (80.0)	1020 (78.1)	2406 (78.3)
Asian	50 (16.7)	216 (16.5)	522 (17.0)
Black/African American	5 (1.7)	49 (3.8)	101 (3.3)
American Indian/Alaska Native	3 (1.0)	11 (0.8)	21 (0.7)
Native Hawaiian/Pacific Islander	2 (0.7)	4 (0.3)	11 (0.4)
Other	0 (0.0)	6 (0.5)	11 (0.4)
Weight (kg) ^c			
≤ 100	211 (70.3)	931 (71.3)	2225 (72.5)
> 100	89 (29.7)	375 (28.7)	846 (27.5)
Hypertension	4 (1.3)	38 (2.9)	266 (8.7)
Hyperlipidaemia	9 (3.0)	53 (4.1)	180 (5.9)
Diabetes	5 (1.7)	23 (1.8)	115 (3.7)
Prior TNFi use			
Yes	83 (27.7)	328 (25.1)	543 (17.7)
No	217 (72.3)	978 (74.9)	2529 (82.3)
Prior biologics			
0	167 (55.7)	736 (56.4)	1889 (61.5)
≥ 1	133 (44.3)	570 (43.6)	1183 (38.5)

The data are presented as n (%) unless stated otherwise. RZB, risankizumab; TNFi, tumour necrosis factor inhibitor. ^aDifferences in baseline demographic and clinical characteristics for the short- and long-term analysis sets are the result of pooling data from several different studies.

^bTreatment duration and exposure calculations include data from four patients from ongoing trials with erroneous dosing dates that overestimate their treatment duration and exposure; the range excluding the four outliers was 2 days to 5.9 years. ^cMissing data for one patient in the long-term cohort.

PSOLAR (0.48–0.84 events per 100 PY)¹⁴ and were lower than those in the MarketScan[®] claims database cohort study (Figure 3).¹⁷ There were no concerning trends in pathological type among malignancies, and no reports of lymphoma or haematological malignancy. Rates of NMSC (54 events, 0.7 per 100 PY) were lower than reported in the MarketScan[®] study (overall psoriasis population, 1.80 events per 100 PY; non-biologic arm, 1.99 events per 100 PY).¹⁷ Basal cell carcinoma (BCC) was reported in 23 patients and cutaneous squamous cell carcinoma (SCC) in 14 patients in the long-term dataset (BCC : SCC ratio of 1.6 : 1).

Two cases of recurrent breast cancer were reported in the long-term analysis set: one patient continued in the study, the other withdrew. No other recurrence of malignancy was reported. A summary of serious AEs in the 10 patients with a history of malignancy excluding NMSC is provided in Table S6 (see Supporting Information).

Depression and suicidality

Rates of depression were 1.0 and 0.7 per 100 PY in the short- and long-term analysis sets, respectively. Most were not serious, and none resulted in study drug discontinuation (Table 2). Rates of suicidal ideation and behaviour were 0.5 and < 0.1 per 100 PY in the short- and long-term analysis sets, respectively (Table 2). All patients had multiple confounding factors (prior history of depression, bipolar disorder, suicidal ideation). There were no cases of completed suicide.

Serious hypersensitivity

Serious hypersensitivity was reported by four patients in the long-term analysis set (< 0.1 events per 100 PY; Table 2). All were considered unrelated to risankizumab and none led to

Table 2 Treatment-emergent adverse events (TEAEs) overall and TEAEs in areas of safety interest per 100 person-years (PY): 16-week and long-term analyses

	Week 16 ^a		Long term ^a
	Placebo (n = 300; 92.0 PY)	RZB 150 mg (n = 1306; 402 PY)	All RZB ^b (n = 3072; 7927 PY)
Overall AEs	Events (events per 100 PY)		
	261 (284)	1279 (318)	13 548 (171)
Most common AEs^c			
Nasopharyngitis ^d	1 (1.1)	7 (1.7)	1333 (16.8)
Viral upper respiratory tract infection ^d	14 (15.2)	86 (21.4)	62 (0.8)
Upper respiratory tract infection	9 (9.8)	63 (15.7)	724 (9.1)
Arthralgia	10 (10.9)	35 (8.7)	284 (3.6)
Headache	6 (6.5)	46 (11.4)	275 (3.5)
Injection-site reaction	5 (5.4)	26 (6.5)	256 (3.2)
Hypertension	6 (6.5)	15 (3.7)	236 (3.0)
Serious AEs	16 (17.4)	40 (9.9)	617 (7.8)
Serious AEs related to study drug ^e	1 (1.1)	6 (1.5)	82 (1.0)
AEs leading to discontinuation	9 (9.8)	11 (2.7)	136 (1.7)
AEs leading to death	0	1 (0.2)	17 (0.2)
AEs in areas of safety interest	Events (events per 100 PY; 95% confidence interval)		
Serious infections	1 (1.1; < 0.1–6.1)	7 (1.7; 0.7–3.6)	97 (1.2; 1.0–1.5)
Depression	2 (2.2; 0.3–7.9)	4 (1.0; 0.3–2.6)	56 (0.7; 0.5–0.9)
NMSC	1 (1.1; < 0.1–6.1)	3 (0.7; 0.2–2.2)	54 (0.7; 0.5–0.9)
Malignant tumours excluding NMSC	0 (0; 0–3.3)	3 (0.7; 0.2–2.2)	42 (0.5; 0.4–0.7)
Adjudicated MACE	1 (1.1; < 0.1–6.1)	1 (0.2; < 0.1–1.4)	20 (0.3; 0.2–0.4)
Suicidal ideation and behaviour	1 (1.1; < 0.1–6.1)	2 (0.5; < 0.1–1.8)	7 (< 0.1; < 0.1–0.2)
Serious hypersensitivity	0	0	4 (< 0.1; < 0.1–0.1) ^f

AE, adverse event; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; RZB, risankizumab. ^aWeek 16 (five-study pool) and long term (17-study pool) represent different pools of patients with varying lengths of treatment exposure included in the long-term set. RZB events counted in the week 16 column are also included in the long-term column. ^bTreatment duration and exposure calculations include data from four patients from ongoing trials with erroneous dosing dates that overestimate their treatment duration and exposure. ^cAEs with at least three events per 100 PY in the long-term analysis set. ^dThe lower-level symptoms of cold, cold symptoms, common cold syndrome, febrile cold including influenza-like illness, head cold and pyrexial cold were coded to the preferred term 'viral upper respiratory tract infection' in MedDRA version 20.0 in the 16-week analysis and to 'nasopharyngitis' using MedDRA version 22.1 in the long-term analysis. ^eAs assessed by the investigator. ^fOne case each of erythema multiforme (attributed to an antibiotic), Stevens–Johnson syndrome (chlorpromazine), hypersensitivity (hair dye application) and eczema.

study drug discontinuation. There were no reports of anaphylaxis or serum-sickness-like reactions.

Injection-site reactions

All injection-site reactions in the long-term analysis set (256 events; 3.2 events per 100 PY) were of mild to moderate severity; none led to study drug discontinuation.

Inflammatory bowel disease

One patient reported worsening (moderate severity) of pre-existing ulcerative colitis on day 468. This resolved within 7 days with treatment and was not considered to be related to risankizumab.

Major adverse cardiovascular events

Rates of adjudicated major adverse cardiovascular events (MACE) were 0.2 and 0.3 events per 100 PY in the short-

and long-term analysis sets, respectively, and were consistent with reference rates in PSOLAR (0.51–0.64 events per 100 PY; Figure 3).^{14,18} Summaries of MACE over time intervals are shown in Figure 2; further details are provided in Tables S4 and S7 (see Supporting Information).

Mortality

In total, 17 deaths, including 16 treatment-emergent deaths, were reported: two each due to sudden cardiac death, myocardial infarction and cardiac arrest; and one each due to intestinal adenocarcinoma/hepatic metastatic cancer, pancreatitis, epilepsy, seizures (subsequently clarified as death due to drug overdose), congestive heart failure, hepatic cirrhosis, and accident; the causes of the remaining four deaths were not determined (Table S7). One, death due to congestive heart failure in a 64-year-old man with multiple cardiovascular risk factors, was assessed by the investigator as possibly related to treatment. The standardized mortality ratio for treatment-emergent deaths was 0.32 (95% CI 0.18–0.53).

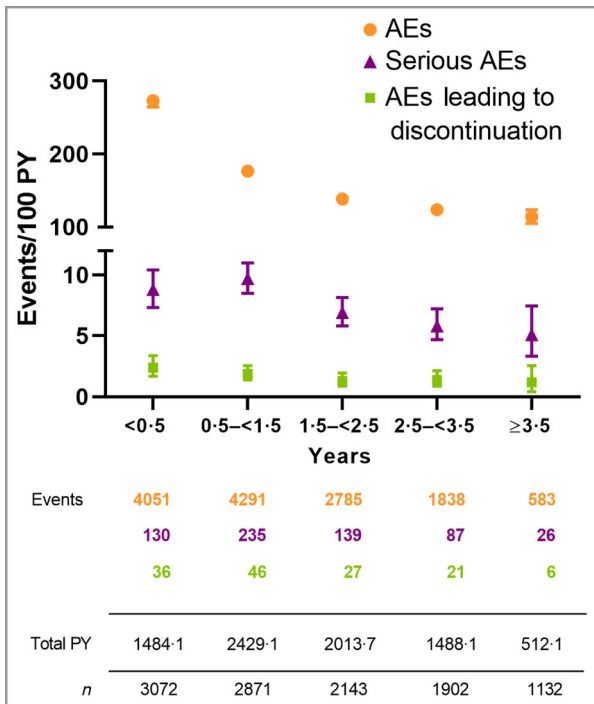


Figure 1 Plaque psoriasis. Rates of adverse events (AEs), serious AEs and AEs leading to discontinuation over 6-month to 1-year intervals, calculated by events in each interval divided by total patient-years (PY) of risankizumab exposure. The error bars show the 95% confidence interval.

Discussion

This integrated analysis of safety included data from 17 completed or ongoing clinical trials of risankizumab for moderate-to-severe psoriasis (3072 patients, 7927 PY of risankizumab exposure and treatment duration up to 5.9 years). The findings showed that the event rates for AEs and AEs of safety interest were consistent with the known safety profile of risankizumab and confirm its suitability for longer-term use.^{3,19,20}

The EAER for serious infections in the long-term analysis set was 1.2 events per 100 PY, within the range reported in the PSOLAR study.^{14,18} Evidence for the association between immunomodulating therapies and an increased risk of serious infection in psoriasis is inconclusive.²¹⁻²⁴ In addition to a role in the pathophysiology of psoriasis, the IL-23/T helper 17 pathway is involved in mucocutaneous defence against bacterial and fungal pathogens.²⁵⁻²⁷ Thus use of risankizumab could, in theory, impair immune responses to *Candida* infection, increasing the risk of invasive infection. The EAER for *Candida* infections in the long-term analysis set was 0.6 events per 100 PY (Table S5) and there were no cases of deep or systemic candidiasis. These data are consistent with a recently performed comprehensive review of the literature, in which no evidence of an increased rate of systemic or deep *Candida* infections was found with inhibition of the p19 subunit of IL-23.²⁸ Furthermore, rates of two other opportunistic infections during long-term risankizumab treatment, herpes zoster

(0.5 events per 100 PY) and tuberculosis (no incidences), are reassuring.

Patients with psoriasis may have higher rates of malignancy than the general population, regardless of treatment,²¹ and the balance of IL-23 and IL-12 has been shown to affect the development of both antitumour and protumour immune responses.²⁹ In this integrated analysis of 7927 PY of risankizumab exposure, the EAERs of NMSC and non-NMSC malignant tumours were 0.7 events per 100 PY and 0.5 events per 100 PY, respectively, consistent with the rates reported in PSOLAR and lower than those in the MarketScan[®] psoriasis and nonbiologic-treated cohorts. Among patients with a prior history of cancer (n = 10), two patients experienced a recurrence of malignancy. These data suggest that risankizumab does not increase the risk of malignancy over that already associated with the pathophysiology of psoriasis, but that patients should be evaluated for risks of malignancy both before and during treatment.³⁰

Patients with psoriasis are known to be at increased risk of other chronic health conditions as well, including cardiovascular and metabolic disorders.³¹⁻³⁴ Additionally, reports of MACE during phase II and III clinical trials of the anti-IL-12/23 antibody briakinumab in patients with psoriasis and in the setting of a large real-life database of patients who had received ustekinumab raised concerns about the short- and long-term cardiovascular safety of biologic therapies.^{35,36} In this integrated analysis of risankizumab studies, the EAER of adjudicated MACE was low in both analysis sets (0.2 and 0.3 events per 100 PY in the short- and long-term analysis sets, respectively) and compares favourably with the range in the PSOLAR study for other biologic therapies (Figure 3).^{14,18} Conversely, it has been shown recently that anti-IL biologics have a positive effect on lipid-rich atherosclerosis in patients with psoriasis.³⁷

The treatment-emergent mortality rate in this integrated analysis was 0.5% (16 deaths, 0.2 events per 100 PY), with a standardized mortality ratio for treatment-emergent deaths of 0.32 (95% CI 0.18-0.53), suggesting that the risk of mortality was not increased in risankizumab-treated patients compared with the general population.

Limitations of this analysis include the lack of long-term comparators, possible selection of healthier patients to clinical trials in general, and that the EAER estimations were not adjusted for heterogeneity between trials. In addition, attrition over time might result in the population becoming more selected (healthy-user bias). Future analyses from these ongoing psoriasis trials are needed to confirm these results, as well as data from real-world, long-term registries.

In conclusion, this comprehensive analysis of more than 7000 PY of exposure to risankizumab supports the favourable safety profile of risankizumab in patients with moderate-to-severe psoriasis. Indeed, these data do not identify any new potential safety signals for risankizumab. These reassuring results should inform decisions that practitioners make regarding long-term treatment options for their patients with moderate-to-severe psoriasis.

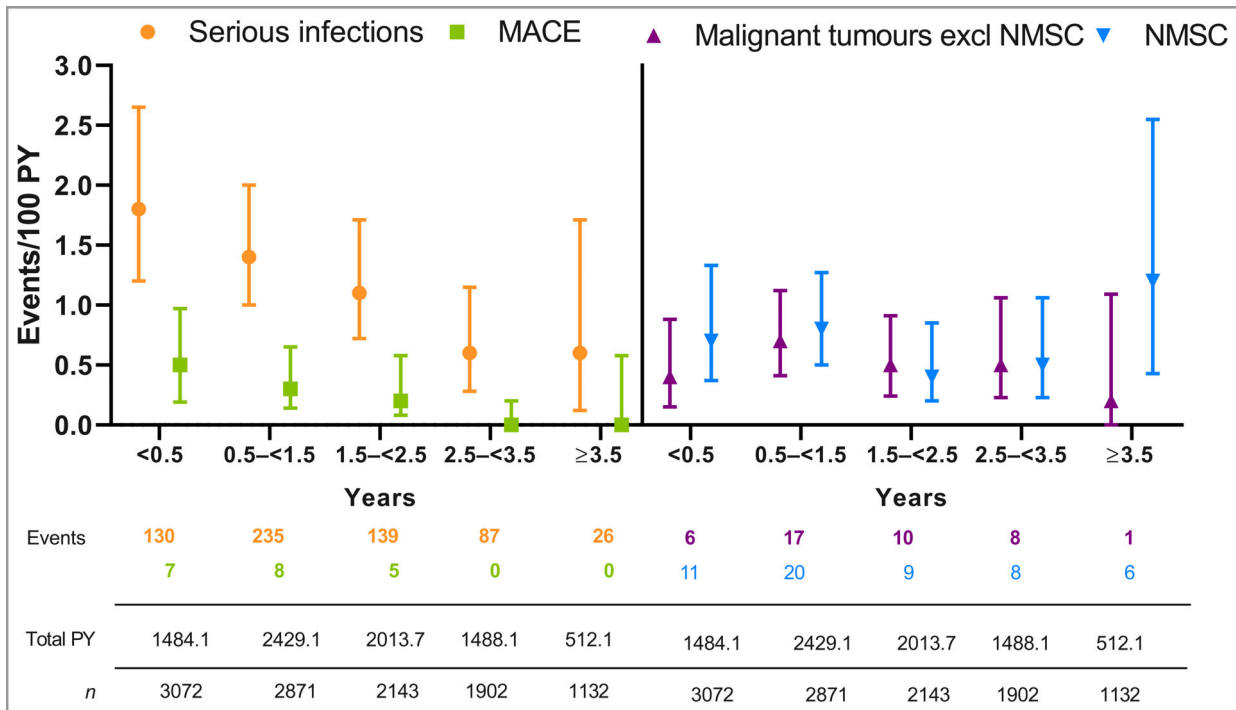


Figure 2 Plaque psoriasis. Rate of serious infections, malignant tumours excluding nonmelanoma skin cancer (NMSC), NMSC and major adverse cardiovascular events (MACE) over 6-month to 1-year intervals, calculated by events in each interval divided by total patient-years (PY) of risankizumab exposure. The error bars show the 95% confidence interval.

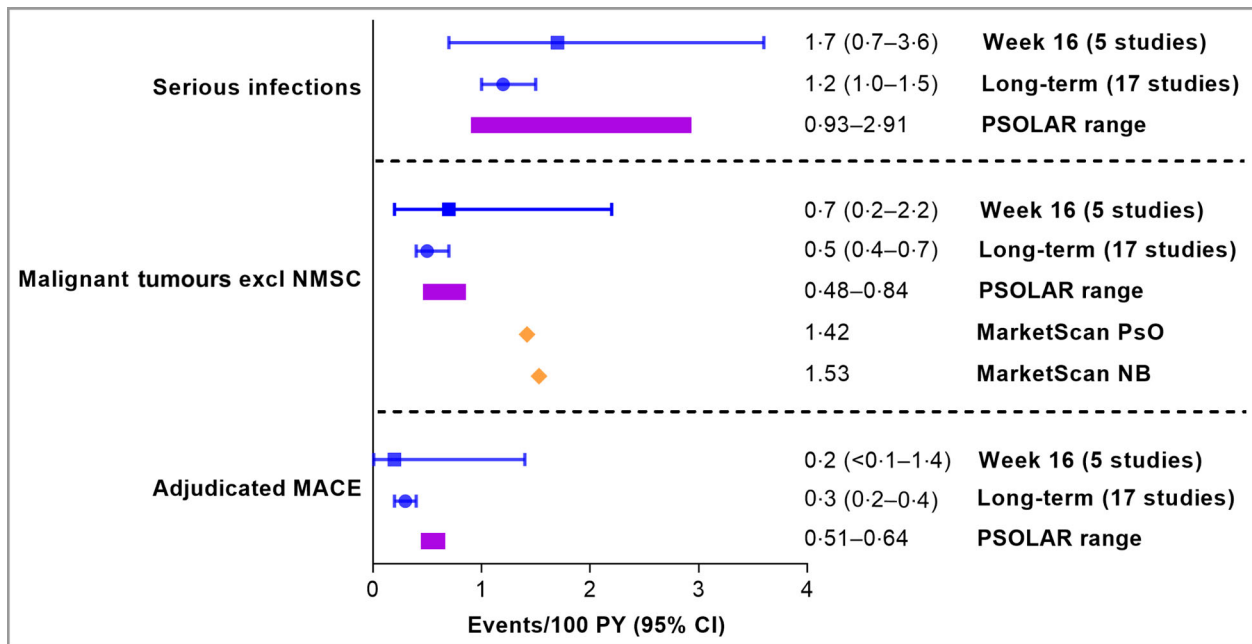


Figure 3 Plaque psoriasis. Treatment-emergent adverse events of safety interest per 100 patient-years (PY) in the 16-week and long-term risankizumab analyses. The week 16 (n = 1306; 402 PY) and long-term (n = 3072; 7927 PY) risankizumab analysis sets represent different pools of patients with varying lengths of treatment exposure included in the long-term set. Events counted in the week 16 data are also included in the long-term data. Reference data are from the Psoriasis Longitudinal Assessment Registry (PSOLAR)^{14,18} (ranges shown for ustekinumab, infliximab, other biologics and nonbiologics) and the MarketScan® claims database cohort study.¹⁷ CI, confidence interval; MACE, major adverse cardiovascular event; NB, nonbiologics arm; NMSC, nonmelanoma skin cancer; PsO, psoriasis cohort.

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References

- Chiesa Fuxench ZC, Shin DB, Ogdie Beatty A *et al.* The risk of cancer in patients with psoriasis: a population-based cohort study in the Health Improvement Network. *JAMA Dermatol* 2016; **152**:282–90.
- Lonnberg AS, Skov L. Co-morbidity in psoriasis: mechanisms and implications for treatment. *Expert Rev Clin Immunol* 2017; **13**:27–34.
- Blauvelt A, Leonardi CL, Gooderham M *et al.* Efficacy and safety of continuous risankizumab therapy vs treatment withdrawal in patients with moderate to severe plaque psoriasis: a phase 3 randomized clinical trial. *JAMA Dermatol* 2020; **156**:649–58.
- Gordon KB, Armstrong AW, Foley P *et al.* Guselkumab efficacy after withdrawal is associated with suppression of serum IL-23-regulated IL-17 and IL-22 in psoriasis: VOYAGE 2 study. *J Invest Dermatol* 2019; **139**:2437–46.e1.
- Siegel SAR, Winthrop KL. In the real world: infections associated with biologic and small molecule therapies in psoriatic arthritis and psoriasis. *Curr Rheumatol Rep* 2019; **21**:36.
- Singh S, Kroe-Barrett RR, Canada KA *et al.* Selective targeting of the IL23 pathway: generation and characterization of a novel high-affinity humanized anti-IL23A antibody. *MAbs* 2015; **7**:778–91.
- Papp KA, Blauvelt A, Bukhalo M *et al.* Risankizumab versus ustekinumab for moderate-to-severe plaque psoriasis. *N Engl J Med* 2017; **376**:1551–60.
- Gordon KB, Strober B, Lebwohl M *et al.* Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet* 2018; **392**:650–61.
- Reich K, Gooderham M, Thaçi D *et al.* Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. *Lancet* 2019; **394**:576–86.
- Saeki H, Nakagawa H, Nakajo K *et al.* Efficacy and safety of ixekizumab treatment for Japanese patients with moderate to severe plaque psoriasis, erythrodermic psoriasis and generalized pustular psoriasis: results from a 52-week, open-label, phase 3 study (UNCOVER-J). *J Dermatol* 2017; **44**:355–62.
- Takeshita J, Grewal S, Langan SM *et al.* Psoriasis and comorbid diseases: epidemiology. *J Am Acad Dermatol* 2017; **76**:377–90.
- Pang Y, Khatri A, Suleiman AA *et al.* Clinical pharmacokinetics and pharmacodynamics of risankizumab in psoriasis patients. *Clin Pharmacokinet* 2020; **59**:311–26.
- Torres T. Selective interleukin-23 p19 inhibition: another game changer in psoriasis? Focus on risankizumab. *Drugs* 2017; **77**:1493–503.
- Papp K, Gottlieb AB, Naldi L *et al.* Safety surveillance for ustekinumab and other psoriasis treatments from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Drugs Dermatol* 2015; **14**:706–14.
- Levandoski KA, Quesenberry CP, Tsai AL *et al.* Herpes zoster rates in a large cohort of patients with systemically treated psoriasis. *JAMA Dermatol* 2018; **154**:218–19.
- Takeshita J, Shin DB, Ogdie A *et al.* Risk of serious infection, opportunistic infection, and herpes zoster among patients with psoriasis in the United Kingdom. *J Invest Dermatol* 2018; **138**:1726–35.
- Kimball AB, Schenfeld J, Accortt NA *et al.* Cohort study of malignancies and hospitalized infectious events in treated and untreated patients with psoriasis and a general population in the United States. *Br J Dermatol* 2015; **173**:1183–90.
- Papp KA, Langholff W. Safety surveillance for ustekinumab and other psoriasis treatments from the Psoriasis Longitudinal Assessment and Registry (PSOLAR) Errata. *J Drugs Dermatol* 2020; **19**:571–2.
- Ohtsuki M, Fujita H, Watanabe M *et al.* Efficacy and safety of risankizumab in Japanese patients with moderate to severe plaque psoriasis: results from the SustaIMM phase 2/3 trial. *J Dermatol* 2019; **46**:686–94.
- Warren RB, Blauvelt A, Poulin Y *et al.* Efficacy and safety of risankizumab vs. secukinumab in patients with moderate-to-severe plaque psoriasis (IMMerge): results from a phase III, randomized, open-label, efficacy-assessor-blinded clinical trial. *Br J Dermatol* 2021; **184**:50–9.
- Kimball AB, Schenfeld J, Accortt NA *et al.* Incidence rates of malignancies and hospitalized infectious events in patients with psoriasis with or without treatment and a general population in the U.S.A.: 2005–09. *Br J Dermatol* 2014; **170**:366–73.
- Wakkee M, de Vries E, van den Haak P *et al.* Increased risk of infectious disease requiring hospitalization among patients with psoriasis: a population-based cohort. *J Am Acad Dermatol* 2011; **65**:1135–44.
- Dommasch ED, Abuabara K, Shin DB *et al.* The risk of infection and malignancy with tumour necrosis factor antagonists in adults with psoriatic disease: a systematic review and meta-analysis of randomized controlled trials. *J Am Acad Dermatol* 2011; **64**:1035–50.
- Baddley JW, Winthrop KL, Chen L *et al.* Non-viral opportunistic infections in new users of tumour necrosis factor inhibitor therapy: results of the Safety Assessment of Biologic Therapy (SABER) study. *Ann Rheum Dis* 2014; **73**:1942–8.
- Zelante T, De Luca A, Bonifazi P *et al.* IL-23 and the Th17 pathway promote inflammation and impair antifungal immune resistance. *Eur J Immunol* 2007; **37**:2695–706.
- Nur S, Sparber F, Lemberg C *et al.* IL-23 supports host defense against systemic *Candida albicans* infection by ensuring myeloid cell survival. *PLOS Pathog* 2019; **15**:e1008115.
- Blauvelt A, Lebwohl MG, Bissonnette R. IL-23/IL-17A dysfunction phenotypes inform possible clinical effects from anti-IL-17A therapies. *J Invest Dermatol* 2015; **135**:1946–53.
- Yang K, Oak ASW, Elewski BE. Use of IL-23 inhibitors for the treatment of plaque psoriasis and psoriatic arthritis: a comprehensive review. *Am J Clin Dermatol* 2021; **22**:173–92.
- Yan J, Smyth MJ, Teng MWL. Interleukin (IL)-12 and IL-23 and their conflicting roles in cancer. *Cold Spring Harb Perspect Biol* 2018; **10**:a028530.
- Smith CH, Anstey AV, Barker JN *et al.* British Association of Dermatologists' guidelines for biologic interventions for psoriasis 2009. *Br J Dermatol* 2009; **161**:987–1019.
- Mehta NN, Yu Y, Pinnelas R *et al.* Attributable risk estimate of severe psoriasis on major cardiovascular events. *Am J Med* 2011; **124**:775.e1–6.
- Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. *J Am Heart Assoc* 2013; **2**:e000062.
- Raaby L, Ahlehoff O, de Thurah A. Psoriasis and cardiovascular events: updating the evidence. *Arch Dermatol Res* 2017; **309**:225–8.

- 34 Masson W, Lobo M, Molinero G. Psoriasis and cardiovascular risk: a comprehensive review. *Adv Ther* 2020; **37**:2017–33.
- 35 Gordon KB, Langley RG, Gottlieb AB *et al.* A phase III, randomized, controlled trial of the fully human IL-12/23 mAb briakinumab in moderate-to-severe psoriasis. *J Invest Dermatol* 2012; **132**:304–14.
- 36 Poizeau F, Nowak E, Kerbrat S *et al.* Association between early severe cardiovascular events and the initiation of treatment with the anti-interleukin 12/23p40 antibody ustekinumab. *JAMA Dermatol* 2020; **156**:1208–15.
- 37 Choi H, Uceda DE, Dey AK *et al.* Treatment of psoriasis with biologic therapy is associated with improvement of coronary artery plaque lipid-rich necrotic core: results from a prospective, observational study. *Circ Cardiovasc Imaging* 2020; **13**:e011199.

Appendix 1

Conflicts of interest

K.B.G. has received honoraria for serving as a consultant for and/or grants as an investigator from AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dermira, Eli Lilly, GlaxoSmithKline, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi-Aventis, Sun and UCB Pharma. M.L. is an employee of Mount Sinai and has received grants as an investigator from AbbVie, Amgen, Arcutis, Avotres Therapeutics, Boehringer Ingelheim, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development LLC, Ortho Dermatologics, Regeneron and UCB Inc.; and is a consultant for Aditum Bio, Almirall, AltruBio Inc., AnaptysBio, Arcutis Inc., Aristeia Therapeutics, Arrive Technologies, Avotres Therapeutics, BiomX, Boehringer Ingelheim, Bristol Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Dr. Reddy's Laboratories, Evelo Biosciences, Evommune Inc., Facilitation of International Dermatologic Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Helsinn Therapeutics, Hexima Ltd., LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy and Verrica. K.A.P. has received honoraria or fees for serving on advisory boards from AbbVie, Amgen, Bausch Health, Baxalta, Baxter, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galderma, Janssen, LEO Pharma, Merck Serono, Merck Sharp & Dohme, Novartis, Pfizer, Sanofi Genzyme, Stiefel, Sun Pharma, UCB and Valeant; has received honoraria or fees as a speaker for AbbVie, Amgen, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Kyowa Hakko Kirin, LEO Pharma, Merck Serono, Novartis, Pfizer, Sanofi Genzyme, UCB and Valeant; has received honoraria or fees as a consultant for AbbVie, Amgen, Arcutis, Astellas, Avillion, Bausch Health, Baxalta, Baxter, Boehringer Ingelheim, Botanix, Bristol Myers Squibb, Celgene, Coherus, Dermavant, Dermira, Eli Lilly, Forward Pharma, Galderma, Genentech, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, LEO Pharma, Meiji Sika Pharma, MedImmune, Merck Serono, Merck Sharp & Dohme, Mitsubishi, Novartis, Pfizer, Regeneron, Roche, Samsung Bioepis, Sanofi Genzyme, Stiefel, Sun Pharma, Takeda, UCB and Valeant; and has received grants as principal investigator from

AbbVie, Amgen, Arcutis, Astellas, Avillion, Bausch Health, Baxalta, Baxter, Boehringer Ingelheim, Botanix, Bristol Myers Squibb, Celgene, Coherus, Dermavant, Dermira, Eli Lilly, Galderma, Genentech, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, LEO Pharma, MedImmune, Meiji Sika Pharma, Merck Serono, Merck Sharp & Dohme, Mitsubishi, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Stiefel, Sun Pharma, Takeda, UCB and Valeant. H.B. has received honoraria or fees for serving on advisory boards or as a speaker or consultant, and grants as an investigator from AbbVie, Almirall, Amgen, AnaptysBio, Avillion, Biocad, Boehringer Ingelheim, Celgene, Dermavant, Eli Lilly, Innovaderm, Janssen, Kyowa Kirin, LEO Pharma, Mylan, Novartis, Pfizer, Sun Pharmaceuticals and UCB. J.J.W. is or has been an investigator, consultant or speaker for AbbVie, Almirall, Amgen, Arcutis, Aristeia Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Dr. Reddy's Laboratories, Eli Lilly, Galderma, Janssen, LEO Pharma, Mindera, Novartis, Regeneron, Sanofi Genzyme, Solius, Sun Pharma, UCB, Valeant Pharmaceuticals North America LLC and Zerigo Health. R.G.L. has served as principal investigator, served on the scientific advisory board or provided a lecture for AbbVie, Amgen, Boehringer Ingelheim, Celgene, LEO, Lilly, Merck, Novartis, Pfizer and UCB. A.B. has served as a scientific adviser and/or clinical study investigator for AbbVie, Abcentra, Aligos, Almirall, Amgen, Arcutis, Arena, Aslan, Athenex, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Eli Lilly and Company, Evommune, Forte, Galderma, Incyte, Janssen, Landos, LEO, Novartis, Pfizer, Rapt, Regeneron, Sanofi Genzyme, Sun Pharma and UCB Pharma. B.K., M.S., Y.Z. and R.S. are full-time salaried employees of AbbVie and may own stock or options. K.R. has served as an adviser and/or paid speaker for and/or participated in clinical trials sponsored by AbbVie, Affibody, Almirall, Amgen, Avillion, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Centocor, Covagen, Dermira, Forward Pharma, Fresenius Medical Care, Galapagos, Galderma, GlaxoSmithKline, Janssen-Cilag, Kyowa Kirin, LEO, Lilly, Medac, Merck Sharp & Dohme, Miltenyi Biotec, Novartis, Ocean Pharma, Pfizer, Regeneron, Samsung Bioepis, Sanofi, Sun Pharma, Takeda, UCB, Valeant and Xenoport.

Supporting Information

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

Appendix S1 Inclusion and exclusion criteria, study treatment, adjudication of major adverse cardiovascular events, and benchmark reference ranges for adverse events of safety interest.

Table S1 Risankizumab clinical trials in patients with moderate-to-severe psoriasis that enrolled patients studied in the 16-week and long-term safety analyses.

Table S2 Patients with treatment-emergent adverse events (TEAEs) overall and TEAEs in areas of safety interest: 16-week and long-term analyses.

Table S3 Overview of treatment-emergent adverse events per 100 patient-years in patients aged ≥ 65 years (all-risankizumab population).

Table S4 Treatment-emergent serious infections, malignancies and major adverse cardiovascular events that were observed two or more times during the long-term evaluation (at least two events).

Table S5 *Candida* infection treatment-emergent adverse events per 100 patient-years: 16-week and long-term analyses.

Table S6 Serious adverse events in patients with a history of malignancy (excluding nonmelanoma skin cancer) at baseline.

Table S7 All-cause deaths.