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

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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-

Summary

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 and 92 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...
Psoriasis is a chronic, systemic disease that has possible associations with psychiatric, arthritic, cardiometabolic and malignant comorbidities.\textsuperscript{1,2} Most patients treated with biologic agents require continuous long-term treatment to achieve disease control.\textsuperscript{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.\textsuperscript{5}

Risankizumab is a selective interleukin (IL)-23 inhibitor\textsuperscript{6} 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\textsuperscript{5,7–9} and is approved for the treatment of moderate-to-severe plaque psoriasis in over 70 countries, including the USA, Canada, Japan and in Europe.\textsuperscript{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.\textsuperscript{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\textsuperscript{®}) 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-blind 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 recurrence (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 1.0–2.9 events 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...
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)      |                            |                                 |                                 |
| < 65             | 48 (19-85)                 | 48 (18-84)                      | 48-0 (18-85)                    |
| 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\(^{-2}\))\(^c\) |                            |                                 |                                 |
| < 25             | 29-8 (17-0–51-4)           | 29-9 (15-0–67-0)                | 29-3 (15-0–92-7)                |
| 25–30 (overweight) | 62 (20-7)                  | 282 (21-6)                      | 708 (23-1)                      |
| ≥ 30 (obese)     | 91 (30-3)                  | 400 (30-6)                      | 972 (31-7)                      |
|                  | 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. \(^a\)Differences in baseline demographic and clinical characteristics for the short- and long-term analysis sets are the result of pooling data from several different studies. \(^b\)Treatment 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. \(^c\)Missing data for one patient in the long-term cohort.

PSOLAR (0-48–0-84 events per 100 PY)\(^1,4\) and were lower than those in the MarketScan\(^0\) 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\(^0\) 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*                  | Long term*             |
|---------------------|---------------------------|------------------------|
|                     | Placebo (n = 300; 92.0 PY) | RZB 150 mg (n = 1306, 402 PY) | All RZBb (n = 3072; 7927 PY) |
| Overall AEs         | Events (events per 100 PY) |                        |                        |
|                     | 261 (284)                 | 1279 (318)             | 13 548 (171)           |
| Most common AEs‡    |                           |                        |                        |
| Nasopharyngitisd    | 1 (3.6)                   | 7 (1.7)                | 1333 (16.8)            |
| Viral upper respiratory tract infectiond | 14 (1.5) | 86 (21.4) | 62 (0.8) |
| Upper respiratory tract infection | 9 (0.9) | 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 (4.4) | 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‡ | 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 (0.0)                   | 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; < 0.1–1.8)     | 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 (0.0)                   | 0 (0.0)                | 4 (< 0.1; < 0.1–0.1) |

AE, adverse event; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; RZB, risankizumab. A Week 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. Treatment duration and exposure calculations include data from four patients from ongoing trials with erroneous dosing dates that overestimate their treatment duration and exposure. AEs with at least three events per 100 PY in the long-term analysis set. The lower-level symptoms of cold, cold symptoms, common cold syndrome, fever, 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. As assessed by the investigator. One 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 0.2-2 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). Summary of malignancy 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 accidental causes; 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).
could, in theory, impair immune responses to Candida and fungal pathogens. The *IL-23/T helper 17* pathway is involved in mucocutaneous defence against bacteria and in the pathophysiology of psoriasis, 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 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

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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)\textsuperscript{14,18} (ranges shown for ustekinumab, infliximab, other biologics and nonbiologics) and the MarketScan\textsuperscript{16} claims database cohort study.\textsuperscript{17} CI, confidence interval; MACE, major adverse cardiovascular event; NB, nonbiologics arm; NMSC, nonmelanoma skin cancer; PsO, psoriasis cohort.
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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, Bristol Myers Squibb, Daiichi Sankyo, GlaxoSmithKline, Janssen, LEO Pharma, MedImmune, 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, Eli Lilly, Merck, Novartis, Pfizer and UCB. A.B. has served as a scientific advisor and/or clinical study investigator for AbbVie, Abcentra, Aligos, Almirall, Amgen, Arcutis, Arena, Aslan, Avesta, 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, Avilion, 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 Xenopont.

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.

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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.