Long-Term Safety of Risankizumab in Patients with Psoriatic Disease: Findings from Integrated Analyses of 17 Clinical Trials in Psoriasis and 4 in Psoriatic Arthritis

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OBJECTIVE

To describe the occurrence of adverse events (AEs) of safety interest during long-term risankizumab treatment in patients with moderate to severe plaque psoriasis and in patients with active psoriatic arthritis

CONCLUSIONS

Rates of AEs of safety interest remained low in this largest and longest safety reporting for risankizumab treatment of psoriasis to date, supporting the safety of risankizumab for the long-term treatment of patients with psoriatic disease

Safety data for patients with psoriatic arthritis are generally consistent with those for psoriasis

The rate of AEs, serious AEs, serious infections, MACE, and malignancies in the psoriasis population over 6-month or 1-year intervals remained stable

Rates of AEs of safety interest among patients with psoriasis and patients with psoriatic arthritis were within the reference rates for the respective populations

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INTRODUCTION

- Interleukin (IL)–23 plays a role in the development and maintenance of psoriatic lesions[1]
- Risankizumab, an IL-23 inhibitor, has been shown to be efficacious and well tolerated in phase 2 and 3 clinical studies in plaque psoriasis[2–5] and active psoriatic arthritis[6–9]

METHODS

- We compiled integrated all-risankizumab safety data sets (data cutoff March 25, 2021) from 17 completed or ongoing phase 1–3 risankizumab clinical trials in plaque psoriasis and 4 completed or ongoing phase 2–3 risankizumab clinical trials in psoriatic arthritis
- For all patients who received ≥1 dose of risankizumab (all administered doses, 18 mg to 180 mg), AEs and AEs of safety interest were assessed and recorded through the end of exposure (last dose – first dose + 5 half-lives [20 weeks])
- Treatment-emergent AEs were defined as any event with an onset after the first dose of risankizumab and within 20 weeks after the last dose of risankizumab during the analysis period
- A standardized mortality ratio of risankizumab-treated patients with psoriasis from the 17 pooled trials was calculated as the ratio of observed (treatment emergent) to expected deaths using mortality data from the World Health Organization (2019) and adjusting for country, sex, age, and length of exposure[10]
- Data are reported as number of patients with AEs and events (E) per 100 patient-years (PY); 95% CIs are provided for grouped events

RESULTS

Patient Demographic and Clinical Characteristics

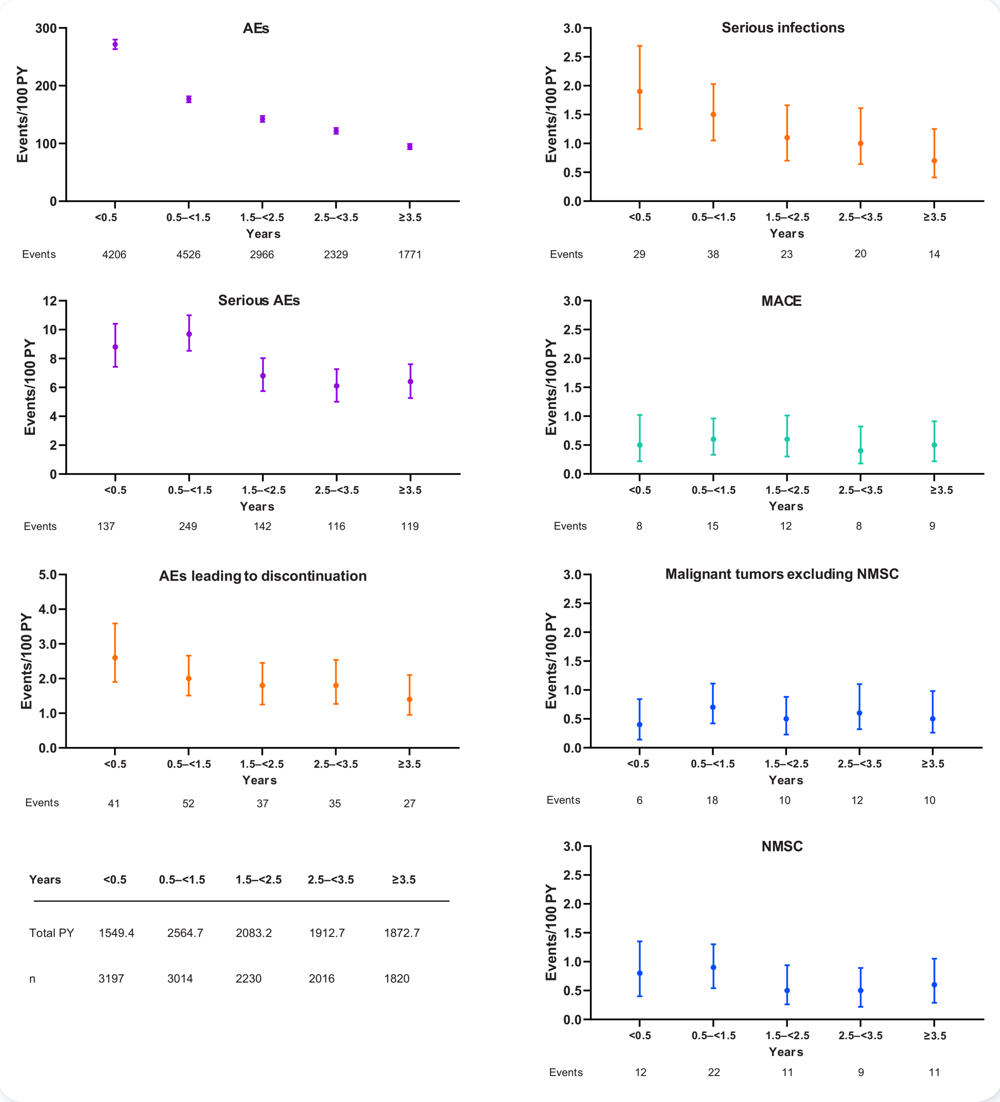
- The analyses included 3197 patients with psoriasis and 1542 patients with psoriatic arthritis, representing 9982.6 PY and 1594.9 PY of risankizumab exposure, respectively
- Baseline demographic and disease characteristics are shown in **Table 1**
- Among the psoriasis population, median treatment duration was 3.7 years (range 1 day to 6.9 years)
  - Treatment duration was ≥6 months in 2978 patients (93.1%), ≥1 year in 2555 patients (79.9%), ≥2 years in 2078 patients (65.0%), ≥3 years in 1929 patients (60.3%), ≥4 years in 1385 patients (43.3%), ≥5 years in 177 patients (5.5%), and ≥6 years in 73 patients (2.3%)
- Among the psoriatic arthritis population, median treatment duration was 1.0 years (range 84 days to 2.0 years)
  - Treatment duration was ≥6 months in 1423 patients (92.3%), ≥1 year in 811 patients (52.6%), and ≥1.5 years in 135 patients (8.8%), and ≥2 years in 2 patients (0.1%)

Table 1. Baseline Demographic and Disease Characteristics

Characteristic, n (%)*	Patients with PsO (n = 3197, 9982.6 PY)	Patients with PsA (n = 1542, 1594.9 PY)
Sex		
Male	2220 (69.4)	765 (49.6)
Female	977 (30.6)	777 (50.4)
Age, years		
<65	2825 (88.4)	1295 (84.0)
65–74	331 (10.4)	213 (13.8)
≥75	41 (1.3)	34 (2.2)
Race		
White	2512 (78.6)	1443 (93.9)
Asian	535 (16.7)	60 (3.9)
Black/African American	103 (3.2)	10 (0.7)
Other	46 (1.4)	24 (1.6)
BMI, mean (SD), kg/m²	30.4 (7.0)	30.6 (6.6)
Prior TNFi use	652 (20.4)	190 (12.3)
Concomitant methotrexate use	<0.1	924 (59.9)

BMI, body mass index; NA, not applicable; PsA, psoriatic arthritis; PsO, psoriasis; TNFi, tumor necrosis factor inhibitor.
*Data are n (%) unless otherwise indicated.

Figure 1. Rate of AEs Over 6-Month to 1-Year Intervals in Patients with Psoriasis



AE; adverse event; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PY, patient-years.

Overall Safety

- Rates of treatment-emergent AEs in the psoriasis and psoriatic arthritis populations (158.3 and 160.8 E/100 PY, respectively), serious AEs (7.6 and 8.4 E/100 PY, respectively) and AEs leading to discontinuation (1.9 and 2.3 E/100 PY, respectively) were similar **(Table 2)**
- The rate of AEs, serious AEs, and AEs leading to discontinuation in the psoriasis population over 6-month or 1-year intervals remained stable **(Figure 1)**

Table 2. TEAEs and TEAEs of Safety Interest in the Psoriasis and Psoriatic Arthritis Populations

	Patients with PsO (n = 3197, 9982.6 PY) E (E/100 PY) [95% CI]	Patients with PsA (n = 1542, 1594.9 PY) E (E/100 PY) [95% CI]
AEs	15,798 (158.3) [155.8–160.7]	2565 (160.8) [154.7–167.2]
Serious AEs	763 (7.6) [7.1–8.2]	134 (8.4) [7.0–10.0]
AEs leading to discontinuation	192 (1.9) [1.7–2.2]	37 (2.3) [1.6–3.2]
Infections		
Most common infections		
Nasopharyngitis	1448 (14.5)	126 (7.9)
Upper respiratory infection	777 (7.8)	89 (5.6)
Serious infections	124 (1.2) [1.0–1.5]	44 (2.8) [2.0–3.7]
Pneumonia	14 (0.1)	4 (0.3)
Sepsis	12 (0.1)	1 (<0.1)
*COVID-19**	7 (<0.1)	6 (0.4)
Opportunistic infections†	9 (<0.1) [0.0–0.2]	2 (0.1) [0.0–0.5]
Tuberculosis	0	0
Candida	54 (0.5) [0.4–0.7]	8 (0.3) [0.2–1.0]
Oral candidiasis	14 (0.1)	4 (0.3)
Vulvovaginal candidiasis	12 (0.1)	2 (0.1)
Skin candida	9 (<0.1)	—
Candida infection	7 (<0.1)	—
Esophageal candidiasis	5 (<0.1)	—
Genital candidiasis	3 (<0.1)	—
Balanitis candida	1 (<0.1)	—
Candida urethritis	1 (<0.1)	—
Gastrointestinal candidiasis	1 (<0.1)	—
Oropharyngeal candidiasis	1 (<0.1)	1 (<0.1)
Anal candidiasis	—	1 (<0.1)
Malignant tumors	121 (1.2) [1.0–1.5]	12 (0.8) [0.4–1.3]
NMSC	65 (0.7) [0.5–0.8]	7 (0.4) [0.2–0.9]
Basal cell carcinoma	41 (0.4)	4 (0.3)
Squamous cell carcinoma	21 (0.2)	3 (0.2)
Malignant tumors excluding NMSC‡	56 (0.6) [0.4–0.7]	5 (0.3) [0.1–0.7]
Breast cancer	13 (0.1)	1 (<0.1)
Prostate cancer	8 (<0.1)	0
Pancreatic carcinoma	5 (<0.1)	0
Colon cancer	5 (<0.1)	1 (<0.1)
Malignant melanoma in situ	4 (<0.1)	1 (<0.1)
Rectal cancer	3 (<0.1)	0
Bladder cancer	2 (<0.1)	0
Papillary thyroid cancer	1 (<0.1)	2 (0.1)
Adjudicated MACE	52 (0.5) [0.4–0.7]	7 (0.4) [0.2–0.9]
Serious hypersensitivity	6 (<0.1) [0.0–0.1]	1 (<0.1) [0.0–0.4]
Injection site reaction	308 (3.1) [2.8–3.5]	25 (1.6) [1.0–2.3]

AE, adverse event; E, event; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; PsA, psoriatic arthritis; PsO, psoriasis; PY, patient-years; TEAEs, treatment-emergent adverse events.
*Clinical trial data for patients with psoriasis mostly pre-dated the onset of the COVID-19 pandemic. †Excluding tuberculosis and herpes zoster. ‡≥2 E/100 PY.

Treatment-Emergent Adverse Events of Safety Interest

Infections

- The most common infectious AEs in the psoriasis and psoriatic arthritis populations were nasopharyngitis (14.5 and 7.9 E/100 PY) and upper respiratory tract infection (7.8 and 5.6 E/100 PY)
- The most frequent serious infections in psoriasis patients were pneumonia and sepsis (both 0.1 E/100 PY), whereas in the psoriatic arthritis population the most frequent serious infections were COVID-19 (0.4 E/100 PY), COVID-19 pneumonia (0.3 E/100 PY), and pneumonia (0.3 E/100 PY, **Table 2**). This is to be expected given the conduct of the psoriatic arthritis trials during the COVID-19 pandemic
- The rates of serious infections with risankizumab remained stable over time **(Figure 1)** and were within the reference rates for serious infections reported for psoriasis (PSOLAR: 0.93–2.91 E/100 PY, **Figure 2**)[11] and psoriatic arthritis (PSOLAR: 1.00–3.01 E/100 PY)[12]
- No cases of active tuberculosis were reported

Malignancies

- Rates of malignancies in the psoriasis (1.2 E/100 PY) and psoriatic arthritis (0.8 E/100 PY) populations were within the reference benchmarks (psoriasis; PSOLAR: range, 0.48–0.84 E/100 PY; and psoriatic arthritis; 0.64 [95% CI, 0.48–0.83] E/100 PY from a recent systematic review of observational cohort studies in patients with psoriatic arthritis)[11,13]
- The most commonly reported cancers in the US general population are breast, lung, colon, uterine, and melanoma in women, and prostate, lung, colon, bladder, and melanoma in men.[14] There was no unexpected trend in malignancies observed with risankizumab treatment

NMSC

- The rate of NMSC in the psoriasis population (0.7 E/100 PY) was lower than reported in the MarketScan® claims database cohort study of 40,788 US patients with psoriasis of varying severity (overall psoriasis population, 1.80 E/100 PY; non-biologic arm, 1.99 E/100 PY)[15]
- The rate of NMSC in the psoriatic arthritis population (0.4 E/100 PY) was lower than that reported in a recent systematic review (0.61 [95% CI, 0.18–1.30] E/100 PY)[13]
- The ratio of patients with basal cell carcinoma (BCC): squamous cell carcinoma (SCC) was 1.6:1 in the psoriasis population and 2:1 in the psoriatic arthritis population

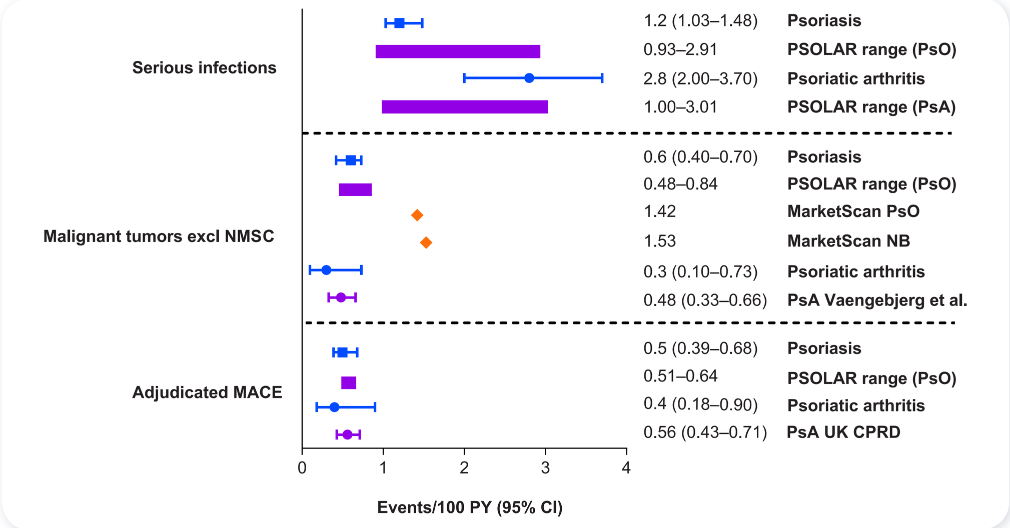
Malignant Tumors Excluding NMSC

- The rate of malignant tumors excluding NMSC in the psoriasis population (0.6 E/100 PY) was within the reference range for moderate to severe psoriasis reported in PSOLAR (0.48–0.84 E/100 PY)[11] and lower than that in the MarketScan® study (overall psoriasis population, 1.42 E/100 PY; non-biologic arm, 1.53 E/100 PY; **Figure 2**)[15]
  - The most common malignant tumors excluding NMSC were breast cancer (0.1 E/100 PY), and prostate cancer, pancreatic carcinoma, colon cancer, and malignant melanoma *in situ* (<0.1 E/100 PY each), malignancies common in the general population or identified in dermatology clinical practices
- The rate of malignant tumors excluding NMSC in the psoriatic arthritis population (0.3 E/100 PY) was slightly lower than that reported in a recent systematic review (0.48 [95% CI, 0.33–0.66] E/100 PY; **Figure 2**)[13]
  - Malignant tumors excluding NMSC included breast cancer, colon cancer, and malignant melanoma *in situ* (<0.1 E/100 PY each), and papillary thyroid cancer (0.1 E/100 PY)

Major Adverse Cardiovascular Events (MACE)

- In the psoriasis population 52 adjudicated MACE (0.5 E/100 PY) were reported in 49 patients: 23 (0.2 E/100 PY) non-fatal myocardial infarctions, 18 (0.2 E/100 PY) non-fatal strokes, 9 (<0.1 E/100 PY) cardiovascular deaths, and 2 (<0.1 E/100 PY) undetermined deaths
  - The rate of MACE remained stable over time **(Figure 1)**
- Among patients with psoriatic arthritis, 7 adjudicated MACE (0.4 E/100 PY) were reported in 7 patients: 4 (0.3 E/100 PY) non-fatal myocardial infarctions and 3 (0.2 E/100 PY) non-fatal strokes
- Patients experiencing a MACE had multiple cardiovascular disease risk factors, including hypertension, hyperlipidemia, diabetes, and a history of coronary artery disease and/or intervention
- The rates of MACE with risankizumab over the long term in both populations (psoriasis 0.5 E/100 PY, psoriatic arthritis 0.4 E/100 PY) were consistent with or slightly lower than reference rates for MACE reported in PSOLAR (psoriasis range, 0.51–0.64 E/100 PY)[16] and the United Kingdom Clinical Practice Research Datalink (UK CPRD), a large, longitudinal, UK general population-based electronic medical database (psoriatic arthritis, 0.56 [95% CI, 0.43–0.71] E/100 PY in patients receiving disease-modifying antirheumatic drugs/biologics)[17]

Figure 2. TEAEs of Safety Interest per 100 Patient-Years in Psoriasis and Psoriatic Arthritis Patients



E, events; MACE, major adverse cardiovascular event; NB, non-biologics arm; NMSC, non-melanoma skin cancer; PsA, psoriatic arthritis population; PsO, psoriasis population; PSOLAR, Psoriasis Longitudinal Assessment Registry; PY, patient-years; TEAE, treatment-emergent adverse event; UK CPRD, the United Kingdom Clinical Practice Research Datalink. Reference data from PSOLAR[11,12,16] (range for ustekinumab, infliximab, other biologics, and non-biologics presented), MarketScan® claims database cohort study,[15] Vaengebjerg et al,[13] and UK CPRD.[17]

Other Adverse Events of Safety Interest

Depression and suicidal ideation and behavior

- A total of 66 episodes of depression (0.7 E/100 PY) were reported among 58 patients with psoriasis; none resulted in discontinuation of risankizumab
  - Suicidal ideation occurred in 2 patients (<0.1 E/100 PY) and 3 patients with multiple risk factors attempted suicide (<0.1 E/100 PY); there were no cases of completed suicide
- In the psoriatic arthritis population there were 14 episodes of depression (0.9 E/100 PY) reported in 14 patients
  - Suicidal ideation occurred in 1 patient (<0.1 E/100 PY) and 1 patient attempted suicide (<0.1 E/100 PY); this patient had pre-existing bipolar disorder, a history of worsening bipolar disorder, and a previous suicide attempt); there were no cases of completed suicide

Hepatic Events and Labs in the Psoriatic Arthritis Population

- Rates of hepatic events in the psoriatic arthritis population were 11.6 E/100 PY; none of these hepatic events were serious. Notably, a majority of psoriatic arthritis patients (59.9%) received concomitant methotrexate
- In the psoriatic arthritis population, most hepatic events were constituted of laboratory abnormalities such as ALT (3.5 E/100 PY) and AST (2.5 E/100 PY) increases, the majority of which were grade 1 elevations
- Considering laboratory data in addition to the AE data, among psoriatic arthritis patients treated with concomitant methotrexate, during the placebo-controlled period patients who received placebo vs risankizumab had similar rates of grade 1 elevations of ALT (89/413 [21.5%] vs 91/422 [21.6%]) and AST (56/413 [13.5%] vs 67/422 [15.9%]), respectively; placebo and risankizumab-treated patients with no concomitant methotrexate had lower rates of grade 1 elevations of ALT (40/280 [14.3%] vs 39/282 [13.8%]) and AST (28/280 [10.0%] vs 34/282 [12.1%]), respectively

Serious hypersensitivity

- Six (<0.1 E/100 PY) patients with psoriasis developed serious hypersensitivity (reports of erythema multiforme attributed to the antibiotic given for an arthropod bite, Stevens-Johnson syndrome attributed to addition of chlorpromazine, drug hypersensitivity resulting from hair dye application, worsening of eczema, facial angioedema, and swollen tongue); there were no reported anaphylactic reactions. None of these events was considered to be related to study drug by the sponsor
  - One case of serious hypersensitivity in the psoriatic arthritis population (<0.1 E/100 PY) occurred in a phase 2 study. This was considered to have a reasonable possibility of being related to study drug by the investigator, and study drug was permanently discontinued. This event was not considered by the sponsor to be consistent with an immunoglobulin-E–mediated reaction

Inflammatory bowel disease

- There was a single report of inflammatory bowel disease in the psoriasis population (worsening of ulcerative colitis in a patient with a history of the disease)

Mortality

- In the psoriasis population, 25 (0.3 E/100 PY; 23 treatment-emergent [0.2 E/100 PY]) deaths were reported, none of which were considered by the sponsor to be related to risankizumab; 1 death due to worsening of congestive heart failure in a 64-year-old man who had multiple cardiovascular risk factors was considered to have a reasonable possibility of being treatment-related by the investigator
- In the psoriatic arthritis population, 1 treatment-emergent death (<0.1 E/100 PY) occurred in an elderly patient, who was hospitalized for pneumonia, and subsequently developed urosepsis and other complications resulting in death. The event of urosepsis was assessed by the investigator and sponsor as having no reasonable possibility of being related to study drug and was adjudicated by the Cardiovascular Adjudication Committee as a non-cardiovascular death
- Using data from the World Health Organization (2015),[10] the standardized mortality ratio for treatment-emergent deaths was 0.37 (95% CI, 0.23–0.55) in the psoriasis population