RHEUMATOLOGY

Rheumatology 2020;59:3834–3844
doi:10.1093/rheumatology/keaa189
Advance Access publication 25 May 2020

Original article

Safety of ixekizumab in adult patients with plaque psoriasis, psoriatic arthritis and axial spondyloarthritis: data from 21 clinical trials

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Abstract

Objectives. The aim of this integrated analysis is to evaluate the long-term safety and tolerability of ixekizumab in adults with psoriasis, PsA and axial SpA.

Methods. Integrated safety data from 21 clinical trials are presented by indication in patients who received at least one dose of ixekizumab. Adverse events (AEs) and treatment-emergent adverse events (TEAEs) adjusted incidence rates (IRs) per 100 patient-years (PY) up to 5 years' exposure are reported.

Results. A total of 8228 patients with an ixekizumab exposure of 20 895.9 PY were included in this analysis. The most common TEAEs were nasopharyngitis, upper respiratory tract infection and injection-site reactions. Across populations, IRs were low for AEs leading to discontinuation (IRs $\leq$5.1 per 100 PY), serious AEs (IRs $\leq$6.0 per 100 PY) and death (IRs $\leq$0.3 per 100 PY). The most reported TEAEs of special interest were infections (IRs $\leq$35.8 per 100 PY). Patients rarely reported malignancies (IR $\leq$0.8), IBD including ulcerative colitis and Crohn's disease (IR $\leq$0.8) and major adverse cardiovascular events (IR $\leq$0.5). TEAEs were most commonly reported the first 2 years of exposure with ixekizumab and IR decreased over the years (infections, injection-site reactions and depression) or remained constant over the entire treatment period (serious infections, major adverse cardiovascular events, malignancies and IBD).

Conclusion. This long-term analysis on the safety of ixekizumab was consistent with previously published reports and did not show any new safety signals. The safety profile and tolerability reported in this integrated analysis remained consistent with the known safety profile for ixekizumab.

Key words: ixekizumab, IL-17, safety, psoriasis, psoriatic arthritis, axial spondyloarthritis

CLINICAL SCIENCE

Rheumatology key messages

- Ixekizumab safety profile in 8228 (20 895.9 patient-years) patients with up to 5 years' of exposure.
- Safety data are consistent across adult patients with psoriasis, PsA and axial SpA indications for ixekizumab.
- These data are consistent with the known safety profile of ixekizumab.

Introduction

Psoriasis (PsO), PsA and axial SpA (axSpA) are potentially disabling chronic inflammatory diseases associated with substantial comorbidities [1–3]. Current pharmacological treatments for these inflammatory diseases include conventional synthetic DMARDs (csDMARDs), biologic DMARDs such as TNF inhibitors, IL-12/23 p40 (PsO and PsA only), IL-23 inhibitor (IL-23i) (PsO and PsA

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Submitted 8 January 2020; accepted 24 March 2020

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only) and IL-17 inhibitors (IL-17i) [1, 4]. IL-17 and related cytokines play a key role in the pathogenesis of inflammatory diseases such as PsO, PsA and axSpA.

Ixekizumab is an IgG4 mAb that selectively targets IL-17A with high affinity [2, 5]. The Food and Drug Administration and European Medicines Agency approved ixekizumab for the treatment of moderate-to-severe plaque PsO in adults, and PsA. Recently, the Food and Drug Administration approved ixekizumab for the treatment of radiographic axSpA. As long-term use of systemic treatments is usually required to maintain adequate disease control, there is a need to monitor the long-term safety of these drugs. For each indication, updated safety reports and profiles with higher patient-years (PY) exposure of ixekizumab have been regularly published [6–10]. A previous integrated analysis from 13 clinical trials with 17 003.4 PY exposure in 5898 adult patients with moderate-to-severe plaque PsO treated with ixekizumab has shown safety signals consistent with the known safety profile and approved labels [6–8]. In addition, a previous integrated safety study with 1822.2 PY exposure in 1118 patients has not reported unexpected new safety outcome of ixekizumab in the long-term treatment of PsA [9, 10].

Beyond the differences in the risk of certain adverse events (AEs) that can be affected by the background disease, we recognize the importance of reporting the safety profile for ixekizumab overall, and across different diseases. Moreover, safety data have been used as the basis for determining which drug to prescribe for which patient [11, 12]. In this report, we present the results of an integrated analysis that evaluated the safety and tolerability of ixekizumab with up to 5 years of exposure across three different populations: PsO (March 2019 cutoff), PsA (March 2019 cutoff) and axSpA (April 2019 cutoff; includes both radiographic and non-radiographic axSpA), comprising 21 clinical trials.

Methods

Patients and study design

Data were pooled from 21 randomized, controlled clinical trials of ixekizumab in PsO ($n = 13$), PsA ($n = 4$) and axSpA ($n = 4$). Of 13 PsO studies, three randomized, double-blind, controlled Phase 3 studies (UNCOVER-1, -2 and -3) were the largest and contributed the most patients for this analysis. The designs of these studies are described in detail elsewhere [5, 13]. Briefly, patients aged ≥18 years with moderate-to-severe plaque PsO (≥10% body surface area involvement, Static Physician's Global Assessment of ≥3, Psoriasis Area and Severity Index ≥12 at baseline) who were candidates for systemic therapy and/or phototherapy were included in the analyses. UNCOVER-1, -2 and -3 studies had 12-week, randomized, placebo-controlled periods. UNCOVER-2 and -3 studies had an additional etanercept group up to week 12 (supplementary Table S1, available at *Rheumatology* online).

In the case of PsA, the present analysis was performed on data from SPIRIT-P1 [14], SPIRIT-P2 [15], SPIRIT-P3 (NCT02584855) and SPIRIT H2H (NCT03151551). SPIRIT-P1 and SPIRIT-P2 were Phase 3 randomized, double-blind, placebo-controlled trials involving patients with active PsA. SPIRIT-P1 patients were biologic-naïve and SPIRIT-P2 patients were TNF inhibitor-experienced. The detailed designs of these studies (SPIRIT-P1 and SPIRIT-P2) are described elsewhere [14, 15]. SPIRIT-P3 (NCT02584855) was a Phase 3 study with a 36- to 64-week open-label treatment period examining the effect of ixekizumab every two weeks followed by a randomized withdrawal period in patients with active PsA who were csDMARD-inadequate responders and biologic DMARD-naïve. SPIRIT-H2H (NCT03151551) was a Phase 4, randomized, open-label, 52-week study in biologic DMARD-naïve patients with PsA.

Safety data for axSpA patients treated with ixekizumab was integrated from COAST-V (biologic-naïve) [16], COAST-W (TNF inhibitor-experienced) [17], COAST-X (NCT02757352) and COAST-Y (NCT03129100). Patients with radiographic axSpA (COAST-V, -W) fulfilled both Assessment of Spondyloarthritis International Society and modified NY criteria based on the presence of sacroiliitis on X-rays, whereas patients in COAST-X were classified as non-radiographic axSpA. Study designs of COAST-V and COAST-W are described elsewhere [16, 17]. In these studies, patients were randomized to placebo, adalimumab (active reference arm, COAST-V only) or ixekizumab.

The protocol for all of the studies included in this analysis was approved by the Institutional Review Board or Ethics Committee at each participating site. All studies were conducted in accordance with the ethical principles of the Declaration of Helsinki. All eligible patients provided written informed consent before undergoing study-related procedures.

Safety evaluation

AEs were classified based on the Medical Dictionary for Regulatory Activities (MedDRA) version 21.1. A treatment-emergent adverse event (TEAE) was an event that first occurred or worsened in severity after baseline, on or before the last day, within the treatment period. The narrow terms have been used for the TEAE computation and preferred terms are presented. Safety topics of special interest included infections, serious infections and infestations, candidiasis, opportunistic infections, injection-site reactions (ISRs), allergic reaction/hypersensitivity, cytopenia, depression, major adverse cardiovascular events (MACE), non-melanoma skin cancer (NMSC), malignancies (excluding NMSC), iritis, iridocyclitis, and IBD including Crohn's disease and ulcerative colitis. According to Registre Epidemiologique des Maladies de l'Appareil Digestif (EPIMAD) criteria, IBD events classified as 'definite' and 'probable' per external adjudication are included when determining the incidence rate (IR) and were considered positively adjudicated. For PsO and PsA trials, MACE and IBD events

analysis were done internally followed by *post hoc* externally adjudicated analysis. For PsA trials, MACE was prospective adjudication. For axSpA trials, prespecified specific and non-specific terms were sent for external prospective adjudication. Depression was measured using Quick Inventory of Depressive Symptomatology – Self Report 16 items (QIDS-SR16), and/or Colombia Suicide Scale Rating Scale (C-SSRS). QIDS-SR16 was used for all the pivotal Phase 3 PsO, PsA and axSpA trials, and C-SSRS was used for all of the axSpA trials. Opportunistic infections were reported according to the consensus recommendations for infections reported published by Winthrop *et al.* [18]. Latent tuberculosis (TB) infection was based by either latent tuberculosis or a positive result on any of the following annual tests: tuberculin skin test, interferon-gamma release assay, or mycobacterium tuberculosis complex test. Patients who tested positive for latent TB at screening were allowed to be rescreened and enrolled after receiving at least 4 weeks of appropriate latent TB infection therapy, and having no evidence of hepatotoxicity (alanine aminotransferase/aspartate aminotransferase remained $\leq$2 times the upper limit of normal).

Statistical analysis

All randomized patients who received at least one dose of the study drug were included in the safety analysis population. Overall exposure was summarized in total PY, calculated as PY is the sum of duration of ixekizumab exposure (days) for all patients in the treatment group divided by 365.25. TEAEs are summarized by frequencies and exposure-adjusted IRs. IRs were calculated by dividing the total number of patients experiencing the TEAE for each patient time by the sum of all patients' time (in 100 years) of exposure during the treatment period. The entire time on study during the treatment period was used. This analysis includes data from the beginning of the study to the 21 March 2019 cutoff for integrated safety data for all PsO and PsA, and to 1 April 2019 cutoff for integrated safety data for all axSpA studies. No major events occurred in PsO and PsA trials between the March and April cutoffs.

Results

Patient demographic and baseline characteristics

Baseline demographics are provided in Table 1. The mean (S.D.) age was 45.8 (13.14) years for patients with PsO, 49.1 (11.9) for patients with PsA and 42.8 (12.6) for axSpA participants. The proportion of males included in this analysis ranged from 48.5 to 69.9%, and 74.1–91.3% of the participants were white. The BMI mean was 30.6 (7.3) kg/m^2 (PsO), 30.0 (6.9) kg/m^2 (PsA) and 27.5 (5.6) kg/m^2 (axSpA). At baseline, 14.8, 38.4 and 29.7% of patients with PsO, PsA and axSpA, respectively, were smokers, which is within the prevalence of smoking in the PsO, PsA and axSpA populations [19–24]. The duration of symptoms was numerically lower in the population with PsA compared with patients with axSpA and PsO [9.4 (8.6) years *vs* 15.2 (10.9), and 18.7 (12.2), respectively]. Patients who were naïve or experienced previous/current use of csDMARD, and also patients with or without previous biologic experience, were included in this analysis. The concomitant use of NSAIDs was numerically higher in patients with axSpA (90.7%) compared with patients with PsO (44.9%) and PsA (65.3%). More patients with PsA had concomitant use of csDMARDs (70.7%) compared with PsO (10.8%) and axSpA (38.8%). Patients with PsO had numerically lower concomitant use of oral CSs (6.8%) in comparison with patients with PsA (25.2%) and axSpA (19.4%).

Exposure

A total of 8228 patients with a cumulative ixekizumab exposure of 20 895.9 PY, up to 5 years of exposure in patients with PsO, up to 3 years in patients with PsA and 2 years in patients with axSpA, were included in this analysis (Table 2 and supplementary Fig. S1, available at *Rheumatology* online). This included 5898 patients with PsO (17 331.1 PY), 1401 patients with PsA (2228.6 PY) and 929 patients with axSpA (1336.2 PY) pooled from 21 clinical trials. The mean exposure was 1073.3 days in the population with PsO, 581.4 days in the PsA population and 525.3 days in the axSpA population.

General safety

Overall, the IR of patients with at least one TEAE across the entire safety period was 29.5 per 100 PY in patients with PsO, 50.6 per 100 PY in patients with PsA and 55.9 per 100 PY in patients with axSpA (Table 2). This represented 86.6% (n = 5108) of patients with PsO, 80.5% (n = 1128) with PsA and 80.4% (n = 747) with axSpA. The TEAEs reported in all studies generally decreased over the observational period of up to 5 years (Fig. 1). Severe TEAEs were reported by 16.7% (n = 987), 8.1% (n = 114) and 8.9% (n = 83) of patients with PsO, PsA and axSpA, respectively. The most frequently reported TEAEs ($\geq$10%) for PsO, PsA and axSpA populations were nasopharyngitis (25.7, 14.4 and 15.8%, respectively), upper respiratory tract infection (15.6, 13.2 and 10.5%, respectively) and ISR (9.7, 11.1 and 9.8%, respectively) (Table 2). The IRs of nasopharyngitis ranged from 8.8 to 11.0 per 100 PY, 5.3 to 8.3 per 100 PY for upper respiratory tract infection and 3.3 to 7.0 per 100 PY for ISR. Over the entire treatment period, serious adverse events (SAEs) were reported by 933 patients with PsO (IR 5.4 per 100 PY), 133 patients with PsA (IR 6.0 per 100 PY) and 74 patients with axSpA (IR 5.5 per 100 PY). IR of SAEs were stable over the time in patients with PsO (5.8–6.9 per 100 PY), PsA (5.5–7.7 per 100 PY) and axSpA (5.0–6.3 per 100 PY) (Fig. 1). Discontinuation from the study due to AEs was reported by 8.3% (n = 488, IR 2.8 per 100 PY) of patients with PsO, 8.1% (n = 114, IR 5.1 per 100 PY) with PsA and 5.6% (n = 52, IR 3.9 per 100 PY) with axSpA (Table 2). In the PsO

Table 1 Demographic and baseline characteristics[a]

Characteristics	Pooled PsO IXE (*N* = 5898)	Pooled PsA IXE (*N* = 1401)	Pooled axSpA IXE (*N* = 929)
Age, years, mean (S.D.)	45.8 (13.14)	49.1 (11.9)	42.8 (12.6)
Male, *n* (%)	4000 (67.8)	679 (48.5)	649 (69.9)
White, *n* (%)	5174 (87.8)	1278 (91.3)	687 (74.1)
BMI, kg/m^2, mean (S.D.)	30.6 (7.3)	30.0 (6.9)	27.5 (5.6)
Tobacco use (current), *n* (%)	874 (14.8)	538 (38.4)	276 (29.7)
Duration of symptoms in years, mean (S.D.)	18.7 (12.2)	9.4 (8.6)	15.2 (10.9)
Previous systemic therapy[b], *n* (%)			
Never used	2104 (35.7)	290 (20.7)	–
Non-biologic	1986 (33.7)	773 (55.2)	922 (99.2)
Biologic	729 (12.4)	71 (5.1)	305 (32.8)
Biologic and non-biologic	1079 (18.3)	267 (19.1)	–
Concomitant therapy, *n* (%)			
NSAIDs	2646 (44.9)	915 (65.3)	843 (90.7)
csDMARDs	638 (10.8)	991 (70.7)	360 (38.8)
Oral CSs	400 (6.8)	353 (25.2)	180 (19.4)

[a]All PsO ixekizumab exposure safety population, all PsA ixekizumab exposure safety population, and axSpA safety population. [b]Patients with PsO and PsA; previous systemic therapies are either non-biologic only, biologic only, or biologic and non-biologic. Patients with axSpA could have both previous therapies. axSpA: axial SpA; csDMARDs: conventional synthetic DMARDS; IXE: ixekizumab; *N*: number of patients in analysis population; *n*: number of patients in each category; PsO: psoriasis.

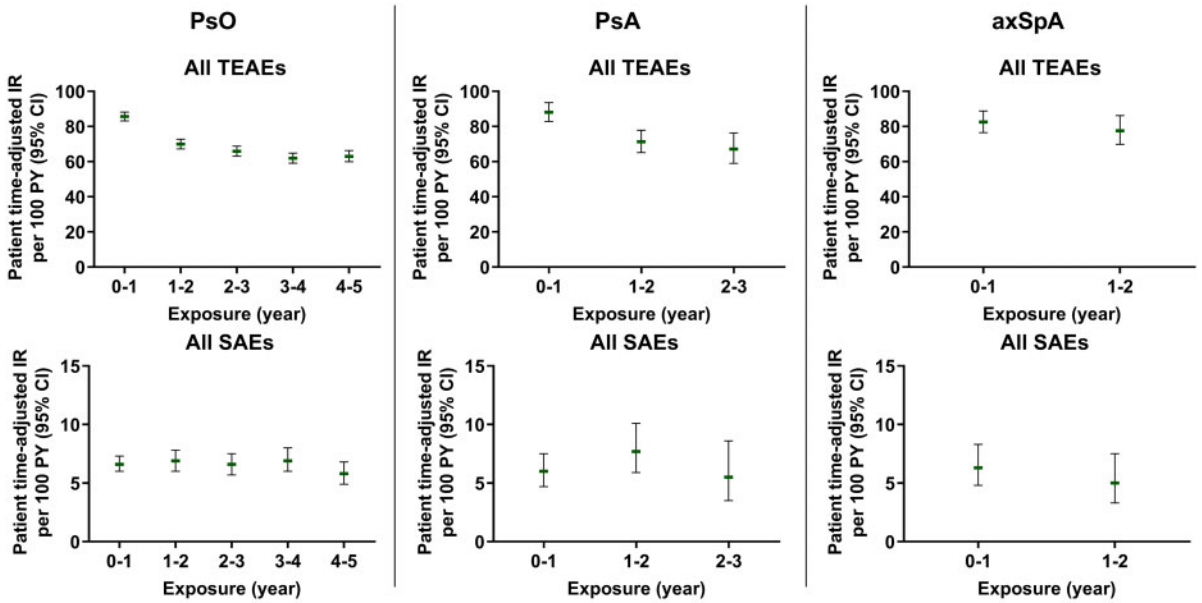
Table 2 Summary of reported adverse events (incidence rates per 100 PY)

	Pooled PsO IXE (*N* = 5898)			Pooled PsA IXE (*N* = 1401)			Pooled axSpA IXE (*N* = 929)		
Total PY	17331.1			2228.6			1336.2		
Patient days of exposure (minimum–maximum)	1–2236			8–1219			15–990		
Mean exposure (patient-days)	1073.3			581.4			525.3		
Median exposure (patient-days)	1177.0			504.5			533.0		
	n (%)	IR	95% CI	*n* (%)	IR	95% CI	*n* (%)	IR	95% CI
Death	35 (0.6)	0.2	0.1, 0.3	6 (0.4)	0.3	0.1, 0.6	2 (0.2)	0.1	0.0, 0.6
AE leading to D/C (including death)	488 (8.3)	2.8	2.6, 3.1	114 (8.1)	5.1	4.3, 6.1	52 (5.6)	3.9	3.0, 5.1
SAE[a]	933 (15.8)	5.4	5.0, 5.7	133 (9.5)	6.0	5.0, 7.1	74 (8.0)	5.5	4.4, 7.0
Patients with ≥1 TEAE[b]	5108 (86.6)	29.5	28.7, 30.3	1128 (80.5)	50.6	47.7, 53.7	747 (80.4)	55.9	52.0, 60.1
Mild	1342 (22.8)	7.7	7.3, 8.2	461 (32.9)	20.7	18.9, 22.7	306 (32.9)	22.9	20.5, 25.6
Moderate	2778 (47.1)	16.0	15.4, 16.6	553 (39.5)	24.8	22.8, 27.0	358 (38.5)	26.8	24.2, 29.7
Severe	987 (16.7)	5.7	5.4, 6.1	114 (8.1)	5.1	4.3, 6.1	83 (8.9)	6.2	5.0, 7.7
Most common TEAEs[c]									
Nasopharyngitis	1518 (25.7)	8.8	8.3, 9.2	202 (14.4)	9.1	7.9, 10.4	147 (15.8)	11.0	9.4, 12.9
Upper respiratory tract infection	923 (15.6)	5.3	5.0, 5.7	185 (13.2)	8.3	7.2, 9.6	98 (10.5)	7.3	6.0, 8.9
Injection-site reaction	573 (9.7)	3.3	3.0, 3.6	156 (11.1)	7.0	6.0, 8.2	91 (9.8)	6.8	5.5, 8.4
Headache	509 (8.6)	2.9	2.7, 3.2	56 (4.0)	2.5	1.9, 3.3	31 (3.3)	2.3	1.6, 3.3

[a]The data collection for the clinical trial database does not contain specification on when events become serious, the numbers may represent more events considered serious than what was actually serious during the treatment period. [b]Patients with multiple occurrences of the same event are counted under the highest severity. AE: adverse event; axSpA: axial SpA; D/C: discontinuation; IR: incidence rate; IXE: ixekizumab; *N*: number of patients in analysis population; *n*: number of patients in each category; PsO: psoriasis; PY: patient-years; SAE: serious adverse event; TEAE: treatment-emergent adverse event. [c]The most common TEAEs are defined as IR>2.0.

population, the main causes of discontinuation were positive TB tests and TB ($n = 67$, IR 0.4 per 100 PY, including one case of pulmonary TB and one case of TB), maternal exposure during pregnancy ($n = 18$, I of 0.3 per 100 PY; calculation adjusted to women only; more details are provided in supplementary Table S2,

Fig. 1 Exposure-adjusted IR of TEAEs and SAEs (all ixekizumab exposure safety populations)



The data points on the graph are the IR (95% CI)/100 PY at successive year intervals from year 0 to year 5 for PsO, years 0–3 for PsA and years 0–2 for axSpA. Overall TEAEs and SAEs. The CIs for the IRs are from likelihood ratio test of treatment effect from the Poisson regression model. AEs: adverse events; axSpA: axial SpA; IR: exposure-adjusted incidence rate; PsO: psoriasis; PY: patient-years; SAEs: serious adverse events; TEAEs: treatment-emergent adverse events.

available at *Rheumatology* online), prostate cancer ($n = 11$, IR 0.1 per 100 PY; calculation adjusted to men only), psoriatic arthropathy ($n = 11$, IR 0.1 per 100 PY) and ulcerative colitis ($n = 10$, IR 0.1 per 100 PY). The main causes of discontinuation in the PsA population were Latent TB (either latent tuberculosis or a positive result on any of the following annual tests: tuberculin skin test, interferon-gamma release assay, or mycobacterium tuberculosis complex test; n = 20, IR = 0.8 per 100 PY), ISR ($n = 5$, IR 0.2 per 100 PY) and pneumonia ($n = 3$, IR 0.1 per 100 PY). The main causes of discontinuation reported by the axSpA population were ISR ($n = 5$, IR 0.4 per 100 PY), ulcerative colitis ($n = 3$, IR 0.2 per 100 PY), Crohn's disease ($n = 2$, IR 0.1 per 100 PY) and benign neoplasms, malignant and unspecified (including cysts and polyps; $n = 4$, IR 0.3 per 100 PY).

A total of 43 deaths were reported among all ixekizumab-treated patients with 20 895.9 PY of exposure (35 PsO, 6 PsA and 2 axSpA) reported with an IR of 0.2 (Table 2). The predominant causes of death in the PsO population included major cardiovascular event ($n = 14$), unknown ($n = 5$; more details are provided in supplementary Table S3, available at *Rheumatology* online), neoplasm ($n = 5$) and respiratory ($n = 3$). The six reported deaths in the PsA population were due to cardiovascular event ($n = 2$), metastatic renal cell carcinoma ($n = 1$), cerebrovascular accident ($n = 1$), pneumonia ($n = 1$) and drowning ($n = 1$). In the axSpA population, the causes of deaths were suicide ($n = 1$) and murder ($n = 1$). Ixekizumab does not appear to be associated with individual causes of death across indications.

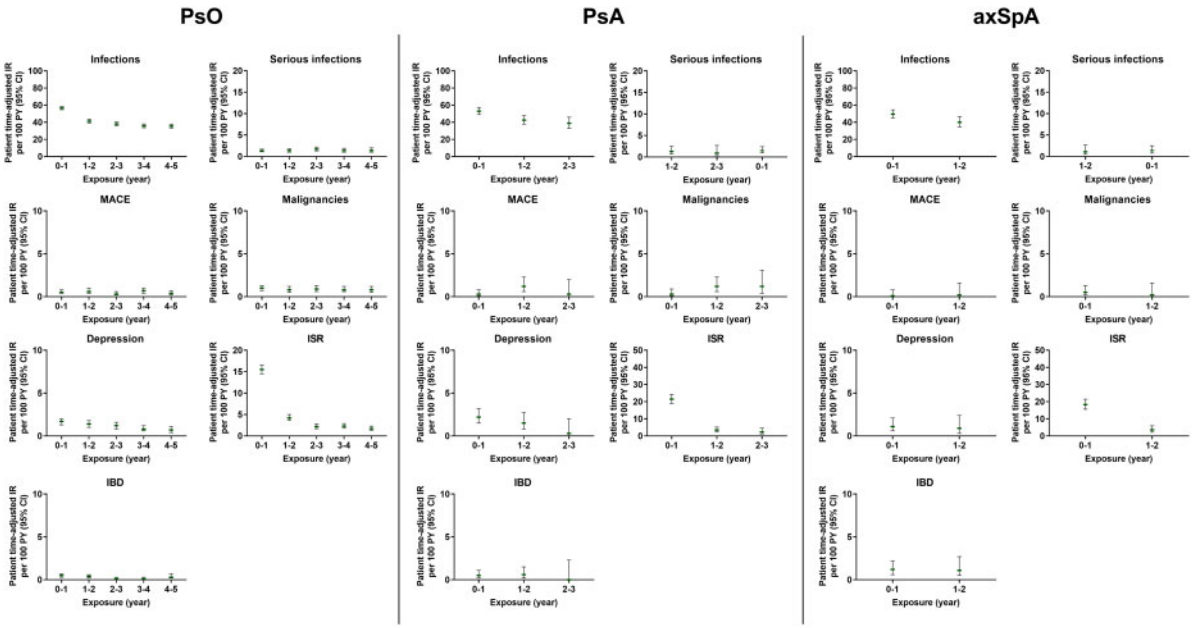
Adverse events of special interest

As assessed based on year of exposure, IRs across indications decreased for infections, ISRs and depression, and were relatively constant for serious infections, MACE, malignancies and IBD (Fig. 2).

Infections

Over the entire treatment period, infections were the most commonly reported TEAEs across indications (Table 3). Infections were reported by 3865 patients with PsO (IR 22.3 per 100 PY), 759 patients with PsA (IR 34.1 per 100 PY) and 478 patients with axSpA (IR 35.8 per 100 PY). Across all indications, the most common types of infections reported were nasopharyngitis, upper respiratory tract infection and bronchitis. Infections were more common during the first year of ixekizumab exposure, the IRs were 56.6, 53.0 and 49.5 per 100 PY in patients with PsO, PsA and axSpA, respectively, and decreased over time to 35.5, 38.9 and 40.1 per 100 PY, respectively (Fig. 2). Overall, the IRs for SAEs infections and infestations were reported by 225 patients with PsO (IR 1.3 per 100 PY), 28 patients with PsA (IR 1.3 per 100 PY) and 17 patients with axSpA (IR 1.3 per 100 PY)

Fig. 2 Exposure-adjusted IR of adverse events of special interest in PsO, PsA and axSpA safety population



The data points on the graph are the IR (95% CI)/100 PY at successive year intervals from year 0 to year 5 for PsO, years 0–3 for PsA and years 0–2 for axSpA. Overall infections, serious infections, MACE, malignancies, depression, ISR and IBD. The CIs for the IRs are from likelihood ratio test of treatment effect from the Poisson regression model. axSpA: axial SpA; IR: incidence rates; ISR: injection-site reactions; IXE: ixekizumab; MACE: major adverse cardiovascular events; PsO: psoriasis; PY: patient-years.

Table 3 Summary of reported infections (IR per 100 PY)

	Pooled PsO IXE (*N* = 5898)			Pooled PsA IXE (*N* = 1401)			Pooled axSpA IXE (*N* = 929)		
	n (%)	IR	95% CI	*n* (%)	IR	95% CI	*n* (%)	IR	95% CI
Infections	3865 (65.5)	22.3	21.6, 23.0	759 (54.2)	34.1	31.7, 36.6	478 (51.5)	35.8	32.7, 39.1
Nasopharyngitis	1518 (25.7)	8.8	8.3, 9.2	202 (14.4)	9.1	7.9, 10.4	147 (15.8)	11.0	9.4, 12.9
Upper respiratory tract infection	923 (15.6)	5.3	5.0, 5.7	185 (13.2)	8.3	7.2, 9.6	98 (10.5)	7.3	6.0, 8.9
Bronchitis	399 (6.8)	2.3	2.1, 2.5	91 (6.5)	4.1	3.3, 5.0	55 (5.9)	4.1	3.2, 5.4
SAEs infections and infestations	225 (3.8)	1.3	1.1, 1.5	28 (2.0)	1.3	0.9, 1.8	17 (1.8)	1.3	0.8, 2.0
Candida infections	327 (5.5)	1.9	1.7, 2.1	45 (3.2)	2.0	1.5, 2.7	22 (2.4)	1.6	1.1, 2.5
Opportunistic infections	512 (8.7)	3.0	2.7, 3.2	86 (6.1)	3.9	3.1, 4.8	23 (2.5)	1.7	1.1, 2.6
Oral candidiasis	140 (2.4)	0.8	0.7, 1.0	16 (1.1)	0.7	0.4, 1.2	1 (0.1)	0.1	0.0, 0.5
Oesophagus candidiasis	13 (0.2)	0.1	0.0, 0.1	2 (0.1)	0.1	0.0, 0.4	3 (0.3)	0.2	0.1,0.7
Herpes zoster	110 (1.9)	0.6	0.5, 0.8	16 (1.1)	0.7	0.4, 1.2	11 (1.2)	0.8	0.5, 1.5
Latent tuberculosis infections[a]	105 (1.8)	0.6	0.5, 0.7	35 (2.5)	1.6	1.1, 2.2	1 (0.1)	0.1	0.0, 0.5

[a]includes either latent tuberculosis or a positive result on any of the following annual tests: tuberculin skin test, interferon-gamma release assay, or mycobacterium tuberculosis complex test. axSpA: axial SpA; IR: incidence rate; IXE: ixekizumab; *N*: number of patients in analysis population; *n*: number of patients in each category; PsO: psoriasis; PY: patient-years; SAE: serious adverse event; TB: tuberculosis.

(Table 3). Infection was reported in 87% of patients with PsO and who had concomitant use of oral CSs, and 74.0% of patients with PsO who had concomitant csDMARDs use. The concomitant use of csDMARDs or oral CSs did not impact the proportion of patients with PsA (53.6% for csDMARDs and 60.1% for oral CSs) and axSpA (47.8% for csDMARDs and 58.3% for oral CSs) who reported infection. However, no relationship between concomitant therapy and infection has been established.

Opportunistic infections according to MedDRA-preferred terms were reported by 512 patients with PsO (IR 3.0 per 100 PY), 86 patients with PsA (IR 3.9 per 100 PY) and 23 patients with axSpA (IR 1.7 per 100 PY; Table 3). Opportunistic infections were mainly oral and oesophagus candidiasis, and localized herpes zoster. Oral candidiasis occurred in 140 patients with PsO (IR 0.8 per 100 PY), 16 patients with PsA (IR 0.7 per 100 PY) and 1 patient with axSpA (IR 0.1 per 100 PY). Overall, a total of 18 oesophagus candidiasis cases were reported in PsO ($n = 13$, IR 0.1 per 100 PY), PsA ($n = 2$, IR 0.1 per 100 PY) and axSpA ($n = 3$, IR 0.2 per 100 PY) populations. Herpes zoster was reported by 110 patients with PsO [IR 0.6 per 100 PY; including 99 patients who were White, 7 Asian (5 in Japan, 1 in Canada and 1 in the USA), 2 Black or African American, and 2 American Indian or Alaska Native; supplementary Table S4, available at *Rheumatology* online], 16 patients with PsA (IR 0.7 per 100 PY; including 15 patients who were White, and 1 American Indian or Alaska native) and 11 patients with axSpA [IR 0.8 per 100 PY; including 6 who were White, 4 Asian (2 in Taiwan and 2 in Korea), and 1 American Indian or Alaska native]. Most herpes zoster were mild to moderate and infrequent ophthalmic or disseminated involvement. Across all indications, there were no cases of deep organ or bloodstream candidiasis reported in the safety population. Yearly TB testing was performed in most of the PsO and PsA studies. Latent TB infection was reported by 105 patients with PsO (IR 0.6 per 100 PY), 35 patients with PsA (IR 1.6 per 100 PY) and 1 patient with axSpA (IR 0.1 per 100 PY). There were no confirmed cases of reactivation of TB across the indications.

Injection site reactions, hypersensitivity/allergic and anti-drug antibodies

Overall, ISRs were the second most common TEAE of special interest across indications (Table 4). Over the entire safety period, ISRs were reported by 892 patients with PsO (IR 5.1 per 100 PY), 259 patients with PsA (IR 11.6 per 100 PY) and 154 patients with axSpA (IR 11.5 per 100 PY). Severe ISR were reported by 35 patients with PsO (IR 0.2 per 100 PY), 5 patients with PsA (IR 0.2 per 100 PY) and 6 patients with axSpA (IR 0.4 per 100 PY). ISRs were the cause of discontinuation for nine patients with PsO (IR 0.1 per 100 PY), five patients with PsA (IR 0.2 per 100 PY) and five patients with axSpA (IR 0.4 per 100 PY). The most common specific terms reported were ISR (non-specific), followed by injection-site erythema and injection site pain. Over the first year of exposure to ixekizumab (year 0–1), ISRs were reported by 15.5 per 100 PY, 21.5 per 100 PY and 18.3 per 100 PY of patients with PsO, PsA and axSpA, respectively. During the exposure period from years 1–2, ISRs were reported as 4.2 per 100 PY in patients with PsO, 3.5 per 100 PY in patients with PsA and 3.6 per 100 PY in patients with axSpA (Fig. 2). At year 5, patients with PsO reported an IR of 1.7 per 100 PY. Overall, allergic reaction/hypersensitivity occurred with IRs of 5.1 per 100 PY ($n = 876$) in the population with PsO, 4.5 per 100 PY ($n = 100$) in population with PsA and 5.5 per 100 PY ($n = 74$) in the population with axSpA (Table 4). There were no confirmed cases of anaphylaxis in the clinical trial program. Over the different populations, ~5–22% of ixekizumab-treated patients developed anti-drug antibody; the majority of these were low titers. Of the patients treated with ixekizumab, ~1–8% had confirmed neutralizing antibodies, measured as previously published [25]. An association between immunogenicity and TEAEs has not been established.

Major adverse cardiovascular events

Over the entire treatment period, MACE occurred in 85 patients with PsO (IR 0.5 per 100 PY; including 38 smokers and 47 non-smokers), in 12 patients with PsA (IR 0.5 per 100 PY; including 6 smokers and 6 non-smokers) and in 2 patients with axSpA (IR 0.1 per 100 PY; including 1 smoker and 1 non-smoker) (Table 4 and supplementary Table S5, available at *Rheumatology* online). The most common category of events was non-fatal myocardial infarction (PsO: $n = 45$, IR 0.3 per 100 PY; PsA: $n = 6$, IR 0.3 per 100 PY; axSpA: $n = 2$, IR 0.1 per 100 PY), followed by nonfatal stroke (PsO: $n = 21$, IR 0.1 per 100 PY; PsA: $n = 4$, IR 0.2 per 100 PY) and vascular death (PsO: $n = 20$, IR 0.1 per 100 PY; PsA: $n = 2$, IR 0.1 per 100 PY). Vascular death and nonfatal stroke were infrequent with frequency and IR in patients with PsO and PsA. There were no cases of vascular death and nonfatal stroke reported in the axSpA population. Over the years, the IR of MACE remained consistent across indications, and the IRs of reported cases per year ranged from 0.1 to 1.2 per 100 PY (Fig. 2).

Malignancies

Malignancies (excluding NMSC) occurred in 89 patients with PsO (IR 0.5 per 100 PY; including 28 smokers and 61 non-smokers), 7 patients with PsA (IR 0.3 per 100 PY; including 1 smoker and 6 non-smokers) and 6 patients with axSpA (IR 0.4 per 100 PY; including 3 smokers and 3 non-smokers) (Table 4 and supplementary Table S6, available at *Rheumatology* online). In the PsO population, the most common malignancy (excluding NMSC) was prostate cancer ($n = 12$). NMSC was reported by 51 patients with PsO (IR 0.3 per 100 PY; including 14 smokers and 37 non-smokers) and 9 patients with PsA (IR 0.4 per 100 PY; including 3 smokers and 6 non-smokers). No cases of NMSC were reported in the axSpA population. The most common NMSC in the PsO population was basal cell carcinoma ($n = 42$), followed by squamous cell carcinoma ($n = 12$). In the PsA population, basal cell carcinoma ($n = 6$) and Bowen's disease ($n = 3$) were the most reported NMSC. As assessed based on yearly exposure periods, IRs for malignancies were <1.2 per 100 PY and were constant across the ixekizumab treatment period (Fig. 2).

Depression and suicide

At baseline, 17 patients with PsO, 6 patients with PsA and 12 patients with axSpA reported a very severe QIDS-SR16 score (21–27). Overall, depression, based on Standardized MedDRA queries, during ixekizumab

Table 4 Summary of selected TEAEs

	Pooled PsO IXE (*N* = 5898)			Pooled PsA IXE (*N* = 1401)			Pooled axSpA IXE (*N* = 929)		
	n (%)	IR	95% CI	*n* (%)	IR	95% CI	*n* (%)	IR	95% CI
Injection-site reactions	892 (15.1)	5.1	4.8, 5.5	259 (18.5)	11.6	10.3, 13.1	154 (16.6)	11.5	9.8, 13.5
Mild	591 (10.0)	3.4	3.1, 3.7	207 (14.8)	9.3	8.1, 10.6	113 (12.2)	8.5	7.0, 10.2
Moderate	266 (4.5)	1.5	1.4, 1.7	47 (3.4)	2.1	1.6, 2.8	35 (3.8)	2.6	1.9, 3.6
Severe	35 (0.6)	0.2	0.1, 0.3	5 (0.4)	0.2	0.1, 0.5	6 (0.6)	0.4	0.2, 1.0
Hypersensitivity/allergic reactions	876 (14.9)	5.1	4.7, 5.4	100 (7.1)	4.5	3.7, 5.5	74 (8.0)	5.5	4.4, 7.0
Malignancies	134 (2.3)	0.8	0.7, 0.9	15 (1.1)	0.7	0.4, 1.1	6 (0.6)	0.4	0.2, 1.0
NMSC	51 (0.9)	0.3	0.2, 0.4	9 (0.6)	0.4	0.2, 0.8	0 (0.0)	0.0	0.0, 0.6
Other malignancies (excluding NMSC)	89 (1.5)	0.5	0.4, 0.6	7 (0.5)	0.3	0.1, 0.7	6 (0.6)	0.4	0.2, 1.0
IBD[abg]	29 (0.5)	0.2	0.1, 0.2	3 (0.2)	0.1	0.0, 0.4	13 (1.4)	1.0	0.6, 1.7
Crohn's disease	12 (0.2)	0.1	0.0, 0.1	2(0.1)	0.1	0.0, 0.4	7 (0.8)	0.5	0.2, 1.1
Ulcerative colitis	17 (0.3)	0.1	0.1, 0.2	1 (0.1)	0.0	0.0, 0.3	6 (0.6)	0.4	0.2, 1.0
Depression[c]	203 (3.4)	1.2	1.0, 1.3	37 (2.6)	1.7	1.2, 2.3	13 (1.4)	1.0	0.6, 1.7
Suicidal behaviour/self-injury	17 (0.3)	0.1	0.1, 0.2	1 (0.1)	0.0	0.0, 0.3	2 (0.2)	0.1	0.0, 0.6
Cytopenia[d]	124 (2.1)	0.7	0.6, 0.9	56 (4.0)	2.5	1.9, 3.3	23 (2.5)	1.7	1.1, 2.6
MACE	85 (1.5)	0.5	0.4, 0.6	12 (0.9)	0.5	0.3, 0.9	2 (0.2)	0.1	0.0, 0.6
Vascular death[e]	20 (0.4)	0.1	0.1, 0.2	2 (0.1)	0.1	0.0, 0.4	0 (0.0)	0.0	0.0, 0.6
Myocardial infarction, nonfatal	45 (0.8)	0.3	0.2, 0.4	6 (0.4)	0.3	0.1, 0.6	2 (0.2)	0.1	0.0, 0.6
Stroke, nonfatal[f]	21 (0.4)	0.1	0.1, 0.2	4 (0.3)	0.2	0.1, 0.5	0 (0.0)	0.0	0.0, 0.6
Iritis	3 (<0.1)	<0.1	0.0, 0.1	1 (0.1)	<0.1	0.0, 0.3	6 (0.6)	0.4	0.2, 1.0
Iridocyclitis	2 (<0.1)	<0.1	0.0, <0.1	0 (0.0)	0.0	NA	42 (4.5)	3.1	2.3, 4.3

[a]The data represents adjudicated cases. Events classified as 'definite' and 'probable' per external adjudication are included when determining IR and were considered positively adjudicated. IR was calculated as the total of 'definite' and 'probable' cases/total patient-years, then multiplied by 100. [b]In the axSpA program, one patient event of UC was reported in placebo group and later adjudicated as CD; and another placebo patient with history of UC had reported event of UC but was later adjudicated as insufficient information. [c]Broad, according to SMQ or sub-SMQ classification. [d]Broad, according to SMQ classification. [e]Including cardiovascular and cerebrovascular causes excluding haemorrhagic deaths outside of the CNS. [f]Nonfatal stroke includes ischaemic, haemorrhagic and undetermined stroke type. axSpA: axial SpA; IR: incidence rate per 100 patient-years; gIn PsA program, one patient had reported event of anal abscess and anal fistula, this event was considered consistent with IBD but was not adjudicaded as CD or UC due to insufficient information. IXE: ixekizumab; MACE: major adverse cardiovascular event; *N*: number of patients in analysis population; *n*: number of patients in each category; NMSC: nonmelanoma skin cancer; PsO: psoriasis; SMQ: Standardized Medical Dictionary for Regulatory Activities queries; TEAE: treatment-emergent adverse event.

treatment occurred in 203 patients with PsO (IR 1.2 per 100 PY), 37 patients with PsA (IR 1.7 per 100 PY) and 13 patients with axSpA (IR 1.0 per 100 PY) (Table 4). Over the total exposure period, the IRs of reported depression were low (≤2.2 per 100 PY across indications) and decreased across the treatment periods (Fig. 2). Suicidal behavior/self-injury was reported by 17 patients with PsO (IR 0.1), 1 patient with PsA (IR 0.0) and 2 patients with axSpA (IR 0.1).

Inflammatory bowel disease

As described in Table 4, per external adjudication, 29 patients with PsO had reported IBD confirmed as ulcerative colitis ($n = 17$, IR 0.1 per 100 PY; which included 14 patients with *de novo* cases and 3 patients with IBD history) and Crohn's disease ($n = 12$, IR <0.1 per 100 PY; which were all *de novo* cases). Similarly, three patients with PsA had reported *de novo* cases of IBD confirmed as ulcerative colitis ($n = 1$, IR <0.05 per 100 PY) and Crohn's disease ($n = 2$, IR 0.1 per 100 PY). In the axSpA population, 13 patients had reported IBD confirmed as ulcerative colitis ($n = 6$, IR 0.4 per 100 PY; which included 3 patients with *de novo* cases and 3 patients with IBD history) and Crohn's disease ($n = 7$, IR of 0.5 per 100 PY which included 6 patients with de novo cases and 1 patient with history of IBD).

Other TEAEs of special interest

The IRs of cytopenia (broad term) were less frequent in the PsO population compared with PsA and axSpA, with IR reported at 0.7, 2.5 and 1.7 per 100 PY, respectively. Severe cytopenia, based on MedDRA preferred terms, were reported by five patients with PsO (including one case of grade 3 neutropenia by Common Terminology Criteria for Adverse Events criteria) and one patient with PsA (including one case of neutropenia; upon review, neutrophil count was determined to be above the lower limit of normal and considered within normal range). No

cases of severe cytopenia were reported in patients with axSpA. Overall, there were no confirmed cases of ixekizumab-related anaphylaxis events. Iritis occurred in three patients with PsO, one patient with PsA and six patients with axSpA. Overall, iridocyclitis was reported by 44 patients across populations, 2 of which were reported by PsO patients and 42 of which were reported by patients with axSpA (IR 3.1 per 100 PY).

Discussion

Chronic diseases such as PsO, PsA and axSpA require long-term treatment management. Therefore, long-term assessment of safety is needed to evaluate the benefit–risk of treatment. In this large long-term safety analysis, 8228 patients with PsO, PsA or axSpA were pooled from 21 clinical trials with up to 5 years of exposure to ixekizumab. The IR of TEAEs and SAEs did not increase with long-term exposure to ixekizumab. The most common TEAEs, infections, ISRs and allergic reactions/hypersensitivity, were reported most frequently in the first year of ixekizumab exposure, with the IR decreasing over time and exposure. These results are consistent with previous safety reports for ixekizumab [6, 8, 9]. Our data did not suggest a clear relationship between hypersensitivity reactions and immunogenicity in patients who received ixekizumab [6, 8, 9]. However, this finding does not preclude that there may be individual cases of hypersensitivity related to immunogenicity. Although ISRs were common, the frequencies of patients with ISRs decreased substantially with longer ixekizumab exposure. ISRs did not typically lead to discontinuation. The use of immunomodulating therapies may be associated with increased infection risk [26, 27]. During ixekizumab treatment, the rate of patients with infections did not increase with longer ixekizumab exposure and the serious infection rate was low. Most TEAEs of infections were upper respiratory tract and other common infection types. As expected, opportunistic infections were mainly oral and oesophagus *Candida* species infections, probably owing to the known role of IL-17A in host defence against these infections; however, there were no reports of deep organ or bloodstream candidiasis noted in the safety analysis [28]. Overall, annual TB testing revealed 141 patients across populations (PsO $n = 105$, PsA $n = 35$, axSpA $n = 1$) with latent TB infections. Positive TB tests led to discontinuation (which was protocol-specified for a portion of the studies) for 67 patients with PsO and 20 patients with PsA. However, no confirmed cases of TB reactivation occurred in the ixekizumab clinical trials, including patients with latent or previously treated *Mycobacterium tuberculosis* infection.

Patients with PsO, PsA and axSpA have a 1- to 4-fold increased risk relative to the general population for the development of IBD, with the role of IL-17 inhibition remaining unclear [29–34]. In the present analysis, the IR of reported IBD (including ulcerative colitis and Crohn's disease) overall ranged from 0.2 to 0.8 per 100 PY, which is in the range of background rates of the respective disease indications [29–34].

The strengths of this report include a robust safety dataset of 21 clinical trials with a total of 8228 patients with a cumulative ixekizumab exposure of 20 895.9 PY, up to 5 years, that allows the opportunity to better understand the long latency of AEs. Our analysis results in a consistent safety profile regarding the long-term safety of ixekizumab in patients with PsO, PsA or axSpA. Limitations of this analysis include a limited sample size for PsA and axSpA populations with respectively 1401 and 929 patients, and consequently a limited ixekizumab exposure of 2228.6 PY (PsA) and 1336.2 PY (axSpA). Additionally, despite the extended population included in this analysis, in real world practice, patient populations are heterogeneous and have more diverse comorbidities than those entering clinical trials. The most significant limitation of this study is the survival bias occurring in the long-term extension, as only the patients who continue to do well stay in the study. Therefore, AEs of patients who discontinued the study were not recorded, and therefore we are unable to further the understanding of short latency events. Long-term safety studies, including post-marketing studies, are ongoing in order to continue to evaluate the safety of ixekizumab for patients with PsA and axSpA.

In conclusion, the safety profile of ixekizumab in this long-term study is consistent with the known safety profile for ixekizumab and is similar across PsO, PsA and axSpA indications. No additional safety concerns were found in this analysis.

Acknowledgements

The authors would like to thank the patients, their families and the study personnel who participated in these clinical trials. The authors also would like to thank Elsa Mevel, an employee of Eli Lilly and Company, and Ananya Biswas and Manju Janardhanan, employees of Eli Lilly Services India Pvt. Ltd, for medical writing support and assistance with preparation and submission of this paper.

Funding: These studies were funded by Eli Lilly and Company, which contributed to study design, data collection, data analysis, data interpretation, manuscript preparation and publication decisions.

Disclosure statement: M.C.G. has received grant/research support and is a consultant for Eli Lilly and Company, AbbVie, Galapagos, Gilead, Pfizer and Novartis; E.M. has served as a consultant, received grant/research support from, and has participated in speakers bureaus for: AbbVie, Bristol-Myers Squibb, Eli Lilly and Company, GlaxoSmithKline, Pfizer and Roche; T.T. has served as a consultant and participated in speakers bureaus for: AbbVie, Astellas, Eisai, Eli Lilly and Company, Janssen, Mitsubishi Tanabe, Novartis, Takeda and Pfizer; K.A.P. has been a consultant, and/or scientific adviser, and/or investigator, and/or scientific

officer, and/or speaker for Amgen, Anacor, AbbVie, Akros, Allergan, Astellas, Astra-Zenica, Baxalta, Baxter, BMS, Boehringer-Ingelheim, Can-Fite, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly and Company, Forward Pharma, Galderma, Genentech, GSK, Janssen, Kyowa Hakko Kirin, Leo Pharma, Medimmune, Meiji Seika Pharma, Merck (MSD), Merck-Serono, Mitsubishi Pharma, Novartis, Pfizer, Regeneron, Roche, Sanofi/Genzyme, Takeda, UCB and Valeant; C.S. has served as a consultant for: AbbVie, Eli Lilly and Company and Roche, and has received grant/research support from Roche; S.S. has served as a consultant for: AbbVie, Crescendo, DermTech, Eli Lilly and Company, Gilead, Janssen, Myriad, Novartis, Regeneron, Samsung, Sanofi and UCB, has participated in speakers bureaus for: AbbVie, Genentech, Eli Lilly and Company, Janssen, Novartis, Pfizer, Regeneron, Sanofi and UCB, owns stock in: Amgen, Boston Scientific, Gilead, Medtronic and Pfizer, and is a board member of: Myriad and the National Psoriasis Foundation; G.G., H.P., J.R.L., A.K., S.L.L., D.H.A. and W.X. are current employees and shareholders of Eli Lilly and Company; H.M.-O. has received grant/research support from: Janssen and Pfizer, honoraria/speakers fees from: AbbVie, Celgene, Eli Lilly and Company, Janssen and UCB; M.G.L. is an employee of Mount Sinai, which receives research funds from: AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly and Company, Incyte, Janssen/Johnson & Johnson, Leo Pharma, MedImmune/AstraZeneca, Novartis, Pfizer, Sciderm, UCB, Valeant and ViDac, and is a consultant for: Allergan, Aqua, Arcutis, Boehringer Ingelheim, Leo Pharma, Menlo, Promius and Verrica.

Supplementary data

Supplementary data are available at *Rheumatology* online.

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