ORIGINAL ARTICLE

Long-term Safety of Secukinumab Over Five Years in Patients with Moderate-to-severe Plaque Psoriasis, Psoriatic Arthritis and Ankylosing Spondylitis: Update on Integrated Pooled Clinical Trial and Post-marketing Surveillance Data

Alice B. GOTTLIEB[1], Atul DEODHAR[2], Iain B. MCINNES[3], Xenofon BARALIAKOS[4], Kristian REICH[5], Stefan SCHREIBER[6], Weibin BAO[7], Kwaku MARFO[8], Hanno B. RICHARDS[8], Luminita PRICOP[7], Abhijit SHETE[8], Vivek TRIVEDI[7], Deborah KEEFE[7], Charis C. PAPAVASSILIS[8], Piotr JAGIELLO[8], Philemon PAPANASTASIOU[8], Philip J. MEASE[9] and Mark LEBWOHL[10]

[1]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, USA, [2]Division of Arthritis & Rheumatic Diseases, Oregon Health & Science University, Portland, Oregon, USA, [3]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK, [4]Rheumazentrum Ruhrgebiet Herne, Ruhr-University Bochum, Bochum, Germany, [5]Translational Research in Inflammatory Skin Disease, Institute for Health Services Research in Dermatology and Nursing, University Medical Center Hamburg-Eppendorf, Hamburg, Germany, [6]Department of Medicine I, University Hospital Schleswig-Holstein, Kiel, Germany, [7]Novartis Pharmaceuticals Corporation, East Hanover, New Jersey, USA, [8]Novartis Pharma AG, Basel, Switzerland, [9]Swedish Medical Center and University of Washington, Seattle, Washington, USA, and [10]Mount Sinai Hospital, New York, USA

Secukinumab, a selective interleukin (IL)-17A inhibitor, is approved for use in adult and paediatric psoriasis, psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis. The aim of this study was to report the long-term safety of secukinumab in pooled data from 28 clinical trials and a post-marketing safety surveillance in psoriasis, psoriatic arthritis and ankylosing spondylitis patients. Analyses included 12,637 secukinumab-treated patients, corresponding to 15,063, 5,985 and 3,527 patient-years of exposure in psoriasis, psoriatic arthritis and ankylosing spondylitis patients, respectively. Incidences of serious adverse events were low, with no identifiable patterns across indications. Active tuberculosis or latent tuberculosis infections were rare. The incidence of opportunistic infections was <0.2/100 patient-years, the incidence of malignancy was ≤1/100 patient-years, and the incidence of major adverse cardiovascular events was <0.7/100 patient-years, with no apparent increases over time. Secukinumab demonstrated a favourable safety profile for up to 5 years of treatment across the 3 indications, and no new safety signals were identified.

Key words: ankylosing spondylitis; biologics; interleukin; psoriasis; psoriatic arthritis; safety.

Accepted Feb 11, 2022; Epub ahead of print Feb 11, 2022

Acta Derm Venereol 2022; 102: adv00698.

DOI: 10.2340/actadv.v102.563

Corr: Alice B. Gottlieb, Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, NY, USA. E-mail: alicegottliebderm@gmail.com

SIGNIFICANCE

Secukinumab is approved for use in chronic systemic inflammatory conditions, such as psoriasis, psoriatic arthritis and ankylosing spondylitis. A long-term safety analysis using data from multiple clinical trials and post-marketing experience across indications is required to identify risks that may become evident in a larger dataset and over a long duration. This long-term (5 years) safety analysis enhances the previously published pooled safety report of secukinumab with a larger dataset (12,637 patients) pooled from 28 clinical trials and post-marketing surveillance data (total exposure 285,811 patient-years), which provides a broader understanding of the safety of secukinumab and supports its long-term use in these chronic conditions.

Psoriasis (PsO), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) result from a complex interplay among environmental, genetic and immune triggers. Treatment is typically intended for a long duration; therefore, understanding the long-term safety profile of therapeutic agents is essential for clinical decision-making.

Interleukin (IL)-17-mediated inflammation plays a pivotal role in the pathogenesis of chronic immune-mediated inflammatory diseases (IMIDs) (1–3). Therapeutic blockade of the IL-17 pathway results in the inhibition of both pathological and physiological mechanisms. The IL-17 family members IL-17A and IL-17F have pleiotropic effects on multiple immune cell types and play an important role in host defence against infections (specifically fungal infections) (1, 4). Therefore, it is important to address the effect of IL-17 blockade on opportunistic infections.

The pathogenesis of PsO, PsA and AS share common systemic inflammatory pathways and cytokines. Because of the inflammatory disease burden and genetic overlap, patients with IMIDs are more susceptible to cardiovascular disease (CVD), metabolic comorbidities and inflammatory bowel diseases (IBDs) vs the general population (5–13). These comorbidities, along with the concomitant medications used to treat these conditions, may affect the safety profile of treatments for PsO, PsA and AS.

Assessing the safety profile of a drug using data from multiple clinical trials and post-marketing experience across indications is best suited to identify risks that may

become evident in a larger dataset. Secukinumab, a direct IL-17A inhibitor, has shown long-lasting efficacy and safety in treating the complete spectrum of psoriatic and spondyloarthritis (SpA) disease manifestations, including the nails, scalp, palms and soles, as well as PsA and axial SpA (axSpA) (14–21).

Secukinumab is currently approved in more than 100 countries for use in PsO, PsA and axSpA. Over 20,000 patients have been treated with secukinumab in a clinical trial setting, and approximately 500,000 patients have been treated worldwide since launch (22). A longer-term report (17) of pooled safety and tolerability data for secukinumab across the 3 indications (up to 5 years of treatment in PsO and PsA; up to 4 years in AS) was consistent with the safety profile observed in individual clinical trials (14–16, 18–21).

This integrated safety assessment (ISA) in PsO, PsA and AS patients who received secukinumab treatment for up to 5 years included pooled clinical trial data and post-marketing safety surveillance data. The current report enhances the previously published pooled safety report (17) with a larger dataset and longer exposure to secukinumab.

MATERIALS AND METHODS

Analysis design

The ISA included data from 28 clinical trials (19 PsO trials (11 Phase III, 8 Phase IV); 5 PsA trials (Phase III); 4 AS trials (Phase III)) and post-marketing safety surveillance data of secukinumab in the PsO, PsA and AS indications, along with the periodic safety update report (PSUR) from the time of initial secukinumab treatment to a cut-off date of 25 December 2018 (**Fig. 1**). Patients who received at least 1 dose of secukinumab, including those who were initially randomised to placebo and re-randomised to secukinumab per study protocol, were included in this analysis. Dosing regimens included intravenous (up to 10 mg/kg) and subcutaneous (75, 150 or 300 mg) secukinumab. All cumulative data for up to 5 years of secukinumab treatment in PsO, PsA and AS patients are reported.

Clinical trial analyses

Patients aged ≥18 years with moderate-to-severe plaque PsO, active PsA or AS were included in individual clinical trials per specific study protocols. The inclusion and exclusion criteria of the patients, along with the individual study designs, have been reported previously (14–16, 19, 20, 23–27). All analyses were performed at descriptive level using SAS version 9.4.

At the time of enrolment, patients may have had active/ongoing CVD (unless severe or uncontrolled); a previous history of IBD, including Crohn's disease (CD) or uveitis (but not if active or ongoing); a history of basal cell carcinoma or actinic keratosis (successfully treated with no evidence of recurrence in the past 3 months); carcinoma *in situ* of the cervix or non-invasive malignant colon polyps (successfully removed); or latent tuberculosis (provided prophylactic treatment had started before enrolment). Per specific study protocols, patients may also have continued taking sulfasalazine, methotrexate, corticosteroids and/or non-steroidal anti-inflammatory drugs (NSAIDs) at stable doses in the respective studies.

Patients with an inadequate response (therapy ≥3 months) or intolerance to tumour necrosis factor-α inhibitors (TNFi: not more than 1 in AS studies and not more than 3 in PsO and PsA studies) were included in these trials. Two PsO clinical trials (19) included patients with a prior history of biologics other than TNFi (alefacept, briakinumab, efalizumab and ustekinumab) after an appropriate washout period.

Safety assessments

Adverse events (AEs) and serious adverse events (SAEs) were retrieved using the clinical trial database. The AE preferred terms (PTs) and adverse events of special interest (AESIs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 21.1). In the clinical trial database, AEs, SAEs and AESIs were analysed using exposure-adjusted incidence rates (EAIRs; patient incidence rate/100 patient-years (PY)) calculated as the number of events/total exposure time. Data are summarized overall and by indication.

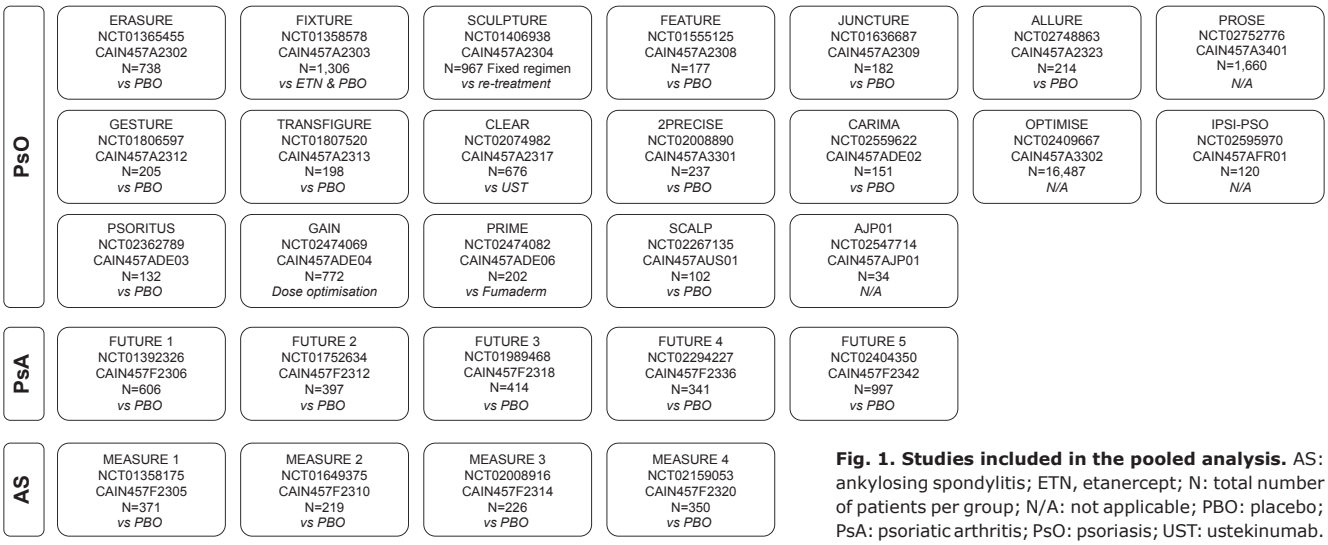

Fig. 1. Studies included in the pooled analysis. AS: ankylosing spondylitis; ETN, etanercept; N: total number of patients per group; N/A: not applicable; PBO: placebo; PsA: psoriatic arthritis; PsO: psoriasis; UST: ustekinumab.

Post-marketing safety surveillance data

Post-marketing safety surveillance includes all non-clinical trial exposure to secukinumab and is based on worldwide sales. The AEs, SAEs and AESIs from post-marketing data were retrieved using the Novartis Safety Database and reported as crude incidence/PY.

Ethics

All clinical studies were conducted in compliance with the Declaration of Helsinki (28), International Council for Harmonisation Guidelines for Good Clinical Practice, and local country regulations.

RESULTS

Study population

Safety analyses of the pooled clinical trials included 12,637 patients treated with secukinumab (8,819, 2,678 and 1,140 patients with PsO, PsA and AS, respectively). Cumulative secukinumab exposure in PsO, PsA and AS patients was 15,063, 5,985 and 3,527 per 100 PY, respectively.

At baseline, the rates of hypertension (37.6%), hyperlipidaemia (21.5%) and diabetes mellitus (10.2%) were numerically higher in patients with PsA vs patients with PsO (21.4%, 13.5% and 6.8%) and AS (23.2%, 9.6% and 3.2%). The rate of uveitis at baseline was higher in the AS dataset (18.0%), which was expected given the predisposition of these patients to uveitis (29). In the pooled PsO, PsA and AS datasets, a baseline medical history of IBD was reported by 1 (0.01%), 6 (0.22%) and 22 (1.9%) patients, respectively. A medical history of CD or ulcerative colitis (UC) at baseline was reported in 5 (0.06%) and 13 (0.15%) patients in the PsO cohort, 6 (0.22%) and 4 (0.15%) patients in the PsA cohort and 5 (0.4%) and 4 (0.4%) patients in the AS cohort (**Table I**).

Table I. Baseline demographics and relevant or current medical conditions

Characteristic	Psoriasis Any secukinumab N = 8,819	PsA Any secukinumab N = 2,678	AS Any secukinumab N = 1,140
Age (years), mean (SD)	44.9 (13.5)	48.8 (12.1)	42.5 (12.1)
Female, *n* (%)	2,889 (32.8)	1,410 (52.7)	373 (32.7)
Weight (kg), mean (SD)	86.6 (21.3)	84.3 (19.7)	79.7 (17.7)
Relevant medical history or current medical condition, *n* (%)			
Hypertension	1,888 (21.4)	1,007 (37.6)	265 (23.2)
Hyperlipidaemia	1,188 (13.5)	577 (21.5)	109 (9.6)
Diabetes mellitus	598 (6.8)	274 (10.2)	37 (3.2)
IBD	1 (0.01)	6 (0.22)	22 (1.9)
Crohn's disease	5 (0.06)	6 (0.22)	5 (0.4)
Ulcerative colitis	13 (0.15)	4 (0.15)	4 (0.4)
Uveitis	3 (0.03)	14 (0.52)	205 (18.0)
Smoking (yes)	2,978 (33.8)	536 (20.0)	349 (30.6)

AS: ankylosing spondylitis; IBD: inflammatory bowel disease; N: number of patients in the analysis; *n*: number of patients with a response; PsA: psoriatic arthritis; SD: standard deviation.

Safety summary

Over the entire observation period, the EAIR of any AE with secukinumab treatment was 224.9, 159.2 and 125.5 per 100 PY in PsO, PsA and AS patients, respectively. The EAIR/100 PY of any SAE was 7.0, 8.2 and 5.8 in PsO, PsA and AS patients, respectively, showing no

Table II. Summary of pooled safety data from secukinumab clinical trials

Characteristic	Psoriasis Any secukinumab N = 8,819	Psoriatic arthritis Any secukinumab N = 2,678	Ankylosing spondylitis Any secukinumab N = 1,140
Exposure (days), mean (SD)	623.9 (567.7)	816.2 (580.7)	1,130.1 (583.0)
Exposure (days), median (min–max)	366.0 (1.0–1,982.0)	671.0 (8.0–1,984.0)	1,037.0 (1.0–1,991.0)
Death, *n* (%)	14 (0.2)	11 (0.4)	9 (0.8)
Discontinuations due to adverse events, *n* (%)	466 (5.3)	162 (6.0)	88 (7.7)
Exposure-adjusted incidence rate/100 PY (95% CI)			
Any adverse event	224.9 (219.8, 230.1)	159.2 (152.7, 166.0)	125.5 (117.8, 133.5)
Any serious adverse event	7.0 (6.6, 7.5)	8.2 (7.4, 9.0)	5.8 (5.0, 6.7)
Most common adverse events, IR (95% CI)			
Nasopharyngitis	22.6 (21.8, 23.5)	11.6 (10.7, 12.6)	10.7 (9.48, 12.0)
Headache	7.3 (6.8, 7.8)	3.8 (3.3, 4.4)	3.8 (3.2, 4.6)
Diarrhoea	4.2 (3.9, 4.6)	3.9 (3.4, 4.5)	4.0 (3.3, 4.7)
Upper respiratory tract infection	5.3 (4.9, 5.7)	8.8 (8.0, 9.6)	4.5 (3.8, 5.3)
Adverse events of special interest, IR (95% CI)			
Serious infections[a]	1.4 (1.2, 1.6)	1.8 (1.5, 2.2)	1.2 (0.9, 1.6)
Candida infections[b]	2.9 (2.7, 3.2)	1.5 (1.2, 1.9)	0.7 (0.5, 1.1)
Opportunistic infections[c]	0.19 (0.1, 0.3)	0.18 (0.1, 0.3)	0.14 (0.1, 0.3)
Inflammatory bowel disease[d]	0.01 (0.0, 0.1)	0.03 (0.0, 0.1)	0.03 (0.0, 0.2)
Crohn's disease[d]	0.1 (0.05, 0.2)	0.1 (0.04, 0.2)	0.4 (0.2, 0.7)
Ulcerative colitis[d]	0.1 (0.08, 0.2)	0.1 (0.04, 0.2)	0.2 (0.1, 0.5)
Major adverse cardiovascular event[e]	0.4 (0.3, 0.5)	0.4 (0.3, 0.6)	0.7 (0.4, 1.0)
Uveitis[d]	0.01 (0.0, 0.05)	0.1 (0.04, 0.2)	1.2 (0.9, 1.7)
Malignancy[f]	0.9 (0.7, 1.0)	1.0 (0.77, 1.3)	0.5 (0.3, 0.8)

[a]Rates for system organ class. [b]Rates for high-level terms. [c]Opportunistic infections were bronchopulmonary aspergillosis, cytomegalovirus gastroenteritis, gastrointestinal candidiasis, herpes zoster cutaneous disseminated, herpes zoster infection neurological, mycobacterium avium complex infection, oesophageal candidiasis, pneumocystis jirovecii pneumonia, toxoplasmosis, tuberculosis. [d]Rates for preferred terms. [e]Rates for Novartis Medical Dictionary for Regulatory Activities (MedDRA) query terms. [f]Rates for standardized MedDRA query terms – "malignancies and unspecified tumour".
CI: confidence interval; IR: incidence rate; N: total number of patients per group; *n*: number of patients with an event; PY: patient-years; SD: standard deviation.

noticeable patterns across indications (**Table II**). Overall, 14 (0.2%), 11 (0.4%) and 9 (0.8%) deaths were reported among PsO, PsA and AS patients, respectively. Discontinuation from the clinical trial due to AEs was reported in 466 (5.3%), 162 (6.0%) and 88 (7.7%) PsO, PsA and AS patients, respectively (Table II).

Most common adverse events

The EAIRs of AE PTs in secukinumab-treated patients were comparable across PsO, PsA and AS studies (Table II), with no new safety signals identified from those previously reported. The most common AEs during the entire safety period in PsO, PsA and AS patients were nasopharyngitis (EAIR/100 PY: 22.6, 11.6 and 10.7, respectively), headache (EAIR/100 PY: 7.3, 3.8 and 3.8, respectively), diarrhoea (EAIR/100 PY: 4.2, 3.9 and 4.0, respectively) and upper respiratory tract infection (URTI; EAIR/100 PY: 5.3, 8.8 and 4.5, respectively) (Table II).

Adverse events of special interest

Infections. Over the entire observation period, the EAIRs/100 PY for serious infections were 1.4, 1.8 and 1.2 in PsO, PsA and AS patients, respectively (Table II). The incidence of opportunistic infections was less than 0.2/100 PY across the 3 indications (PsO 0.19/100 PY; PsA 0.18/100 PY; AS 0.14/100 PY) (Table II).

Candida infections. Over the entire observation period, AEs related to *Candida* infection were reported in 426 (4.8%), 90 (3.4%) and 25 (2.2%) PsO, PsA and AS patients, respectively. This corresponded to an incidence of 2.9, 1.5 and 0.7 per 100 PY in PsO, PsA and AS patients, respectively (Table II). The most common type of *Candida* infection was oral candidiasis (EAIR/100 PY: PsO 1.54; PsA 0.83; AS 0.31). Across indications, *Candida* infections were responsive to standard treatment and did not necessitate study drug discontinuation.

Viral infections. No increased risk of viral infections was observed in patients treated with secukinumab vs placebo in the short term, and EAIRs were generally comparable over the long term. No dose-response relationship was observed for safety events with secukinumab treatment within each indication (**Table III**). Across indications and doses (300 and 150 mg), the most common viral infection was viral influenza (MedDRA term) (Table III). The EAIR/100 PY for any viral infection in PsO, PsA and AS patients was 3.5, 2.7 and 3.3, respectively.

Inflammatory bowel disease. The incidence of IBD (standardized MedDRA query (SMQ); includes preferred terms (PTs) of IBD, CD or UC) ranged from 0.01–0.1/100 PY in PsO, 0.03–0.1/100 PY in PsA and 0.03–0.4/100 PY in AS patients (Table II). Among PsO patients, 20 (16 new onset), 14 (12 new onset) and 2 (both new onset) patients reported UC, CD and IBD, respectively. Among PsA patients, 6 (5 new onset), 6 (4 new onset) and 2 (both new onset) patients reported UC, CD and IBD, respectively. Among AS patients, 8 (5 new onset), 15 (11 new onset), and 1 (new onset) patients reported UC, CD and IBD, respectively.

Uveitis. In PsO patients, the EAIR of uveitis was 0.01/100 PY (2 patients) over the entire treatment period; both cases were mild-to-moderate and new onset. In PsA patients, the EAIR of uveitis was 0.1/100 PY (6 patients); all cases reported were mild-to-moderate in patients with no previous history of uveitis. In AS patients, the EAIR of uveitis was 1.2/100 PY (42 cases) (Table II).

Major adverse cardiovascular events. Over the entire treatment period, the incidence of major adverse cardio-

Table III. Exposure-adjusted incidence rates of viral infections with secukinumab

MedDRA Term	Any secukinumab 300 mg 95% CI	Any secukinumab 150 mg 95% CI	Any secukinumab 95% CI	Placebo[a] 95% CI
Psoriasis	N = 7,481	N = 1,866	N = 8,819	N = 1,076
Any viral infection	3.8 (3.4, 4.2)	2.9 (2.4, 3.5)	3.5 (3.2, 3.9)	7.1 (4.4, 10.8)
Viral influenza	3.3 (2.9, 3.6)	2.7 (2.2, 3.3)	3.1 (2.8, 3.4)	5.4 (3.1, 8.7)
Viral lower respiratory tract infection	0.01 (0.0, 0.05)	0.05 (0.01, 0.2)	0.02 (0.0, 0.06)	0.0 (0.0, 1.2)
Viral upper respiratory tract infection	0.5 (0.4, 0.6)	0.2 (0.09, 0.4)	0.4 (0.3, 0.5)	1.7 (0.5, 3.9)
Herpes viral infections	3.29 (2.95, 3.65)	2.39 (1.92, 2.93)	3.02 (2.74, 3.32)	–
Psoriatic arthritis	N = 1,198	N = 1,795	N = 2,678	N = 883
Any viral infection	3.5 (2.7, 4.5)	2.6 (2.0, 3.2)	2.7 (2.3, 3.2)	4.1 (2.2, 7.0)
Viral influenza	2.6 (1.9, 3.5)	2.2 (1.7, 2.7)	2.2 (1.8, 2.6)	3.2 (1.5, 5.8)
Viral lower respiratory tract infection	0.1 (0.01, 0.4)	0.03 (0.0, 0.2)	0.05 (0.01, 0.2)	0.0 (0.0, 1.2)
Viral upper respiratory tract infection	0.8 (0.4, 1.3)	0.4 (0.2, 0.7)	0.5 (0.4, 0.7)	0.9 (0.2, 2.8)
Herpes viral infections	2.60 (1.90, 3.48)	2.37 (1.85, 2.98)	2.30 (1.93, 2.73)	–
Ankylosing spondylitis	N = 113	N = 864	N = 1,140	N = 388
Any viral infection	3.5 (1.7, 6.4)	3.0 (2.3, 3.8)	3.3 (2.7, 4.0)	5.7 (2.3, 11.8)
Viral influenza	3.1 (1.4, 5.9)	2.9 (2.2, 3.7)	3.1 (2.5, 3.7)	5.7 (2.3, 11.8)
Viral lower respiratory tract infection	NR	NR	NR	NR
Viral upper respiratory tract infection	0.3 (0.01, 1.8)	0.09 (0.01, 0.3)	0.2 (0.08, 0.4)	0.0 (0.0, 3.0)
Herpes viral infections	1.70 (0.55, 3.96)	2.00 (1.44, 2.69)	1.77 (1.35, 2.28)	–
Viral meningitis	0.00 (0.00, 1.22)	0.00 (0.00, 0.16)	0.03 (0.00, 0.16)	–

[a]Placebo-controlled period in the studies included in the pooled analysis was up to week 16/24. Novartis Data on File May 2020.
Safety analyses included all patients who received ≥1 dose of SEC (including placebo switchers).
CI: confidence interval: MedDRA: Medical Dictionary for Regulatory Activities; N: total number of patients per group; NR: not reported.

vascular events (MACE) was 0.4/100 PY in both PsO and PsA patients and 0.7/100 PY in AS patients (Table II).

Malignancy. Among PsO patients, malignant or unspecified tumours (SMQ) were reported in 127 patients (EAIR 0.9/100 PY) over the entire observation period (Table II). The most common type of malignancy reported was basal cell carcinoma (41 patients: EAIR 0.3/100 PY). Two PsO patients reported PTs related to haematological malignancy, namely, acute leukaemia, B cell lymphoma, lymphoproliferative disorder and plasma cell myeloma.

Overall, 60 PsA patients reported a malignant or unspecified tumour (EAIR 1.0/100 PY) (Table II). Basal cell carcinoma was the most common malignancy reported (19 patients: EAIR 0.32/100 PY). PTs related to haematological malignancies in PsA patients were chronic lymphocytic leukaemia (2 patients) and B cell lymphoma (1 patient). Malignant or unspecified tumours were reported in 19 AS patients (EAIR 0.5/100 PY) (Table II). One AS patient reported B cell lymphoma.

Year-by-year incidence of adverse events of special interest

Serious infections, *Candida* infection, IBD, UC and CD showed no increase on a year-by-year basis with secukinumab treatment across PsO, PsA and AS studies (**Fig. 2**).

Incidence of adverse events of special interest by secukinumab dose

Overall, the reported EAIRs for any AE, any SAE, serious infections, IBD and MACE for the approved 300 mg and 150 mg secukinumab doses were comparable and no noticeable trends were observed in the dose-response relationship with secukinumab treatment in terms of safety events within each indication. However, *Candida* infections were more common in PsO patients treated with the 300 mg dose compared with the 150 mg dose. The imbalance between doses was limited to non-serious, localised mucosal or cutaneous candidiasis, with no reports of chronic or systemic disease in any treatment group.

Suicidality

Over the entire observation period, among PsO patients, 6 patients attempted suicide, 2 committed suicide, 5 reported suicidal ideation, and 1 reported suicidal depression (EAIR 0.09/100 PY). A total of 4 PsA patients reported suicidal ideation (EAIR 0.07/100 PY). Among AS patients, 1 patient reported suicidal depression (EAIR 0.03/100 PY). No new safety signals in relation to suicidality were identified.

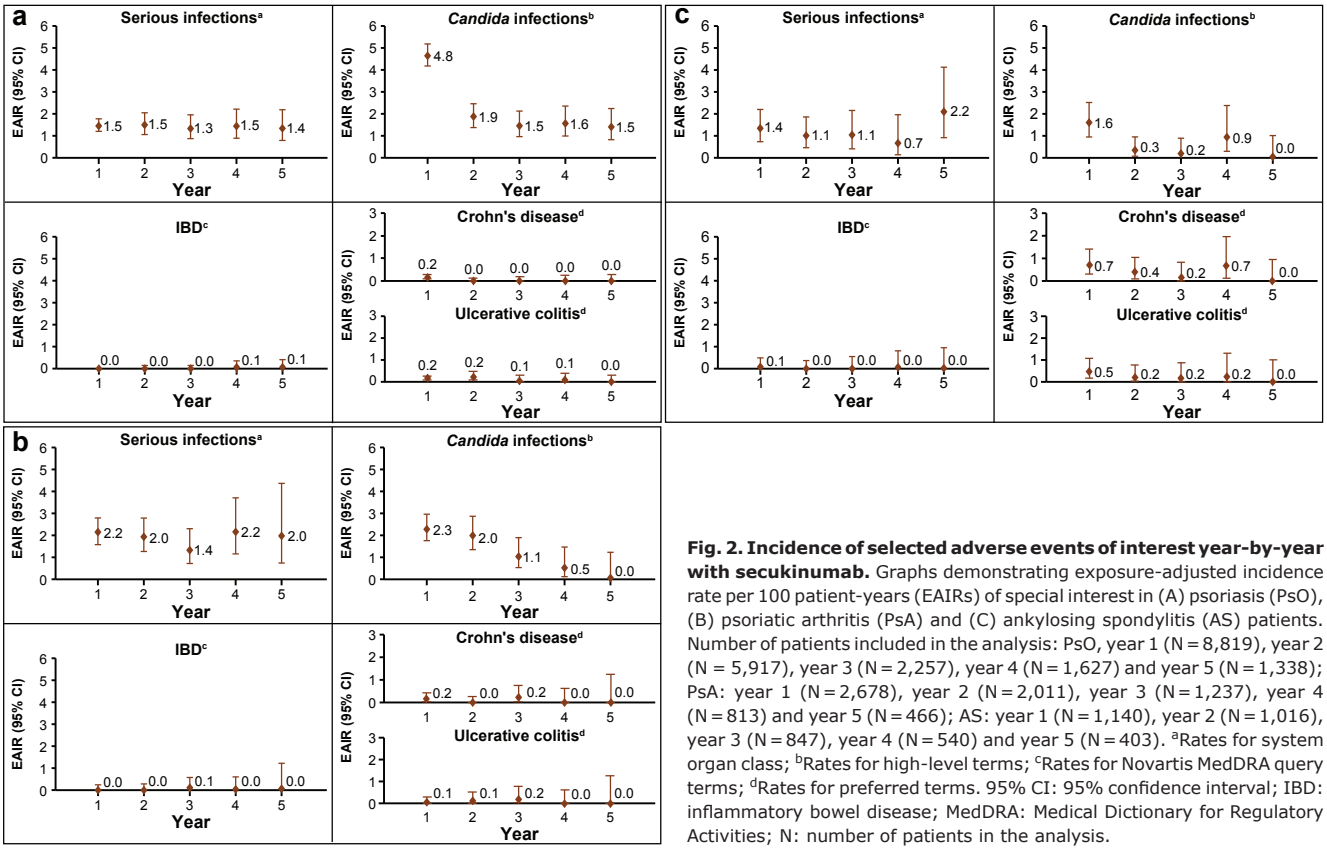

Fig. 2. Incidence of selected adverse events of interest year-by-year with secukinumab. Graphs demonstrating exposure-adjusted incidence rate per 100 patient-years (EAIRs) of special interest in (A) psoriasis (PsO), (B) psoriatic arthritis (PsA) and (C) ankylosing spondylitis (AS) patients. Number of patients included in the analysis: PsO, year 1 (N = 8,819), year 2 (N = 5,917), year 3 (N = 2,257), year 4 (N = 1,627) and year 5 (N = 1,338); PsA: year 1 (N = 2,678), year 2 (N = 2,011), year 3 (N = 1,237), year 4 (N = 813) and year 5 (N = 466); AS: year 1 (N = 1,140), year 2 (N = 1,016), year 3 (N = 847), year 4 (N = 540) and year 5 (N = 403). [a]Rates for system organ class; [b]Rates for high-level terms; [c]Rates for Novartis MedDRA query terms; [d]Rates for preferred terms. 95% CI: 95% confidence interval; IBD: inflammatory bowel disease; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients in the analysis.

Injection-site reactions

The incidence of injection-site reactions (high-level term) in PsO, PsA and AS patients was 1.6, 1.3 and 0.6 per 100 PY, respectively.

Post-marketing safety surveillance data

As of 25 December 2018, across the approved indications, the cumulative post-marketing exposure to secukinumab was estimated to be 285,811 PY.

The cumulative crude exposure-adjusted reporting rates (EARRs) for infections and infestations and for serious infections were 5.2 and 1.4 per 100 PY, respectively. The cumulative EARRs of malignancy and MACE were 0.3 and 0.2 per 100 PY, respectively. Most assessable cases were confounded by multiple risk factors or alternative explanations for events related to malignancies or MACE. The cumulative EARR reported for IBD was 0.2/100 PY. The reporting rate for suicidal ideation and behaviour was 0.04/100 PY.

The risk of IBD, serious infections, malignancy and MACE determined in the 6 PSUR periods was consistent with the previously reported safety profile of secukinumab (**Fig. 3**).

DISCUSSION

This large safety analysis included 12,637 patients (cumulative secukinumab exposure in PsO, PsA and AS patients: 15,063, 5,985 and 3,527 per 100 PY, respectively) pooled from 28 clinical trials with up to 5 years of data, in addition to post-marketing surveillance data (total exposure 285,811 PY). This analysis demonstrated that secukinumab was associated with generally low frequencies of AEs with no discernible patterns regarding SAEs across indications. The most frequently reported AE across indications was URTI.

Pooled analyses typically have a large dataset and are a reliable source for assessing less-frequent treatment-emergent AEs. Furthermore, long-term follow-up may indicate an increase in the frequency of safety events over time. The present analysis was conducted to answer 2 primary questions: (1) whether the overall safety profile of secukinumab was consistent with that reported in previous clinical trials (14–16, 18–21) and pooled safety findings (17), and (2) whether there were any new safety findings in a larger dataset with long-term exposure to secukinumab.

We analysed a larger dataset (12,637 vs 7,355 patients (17)) with a longer exposure to secukinumab across the PsO (15,063 PY vs 10,417 PY (17)), PsA (5,985 PY vs 3,867 PY (17)) and AS (3,527 PY vs 1,943 PY (17)) indications compared with a previous safety publication. In the present analysis, the cumulative post-marketing exposure to secukinumab was approximately 285,811 PY (cut-off date 25 December 2018) compared with 96,054 PY in the previous report (17).

Secukinumab was associated with a low frequency of AEs, with no identifiable pattern among SAEs across the

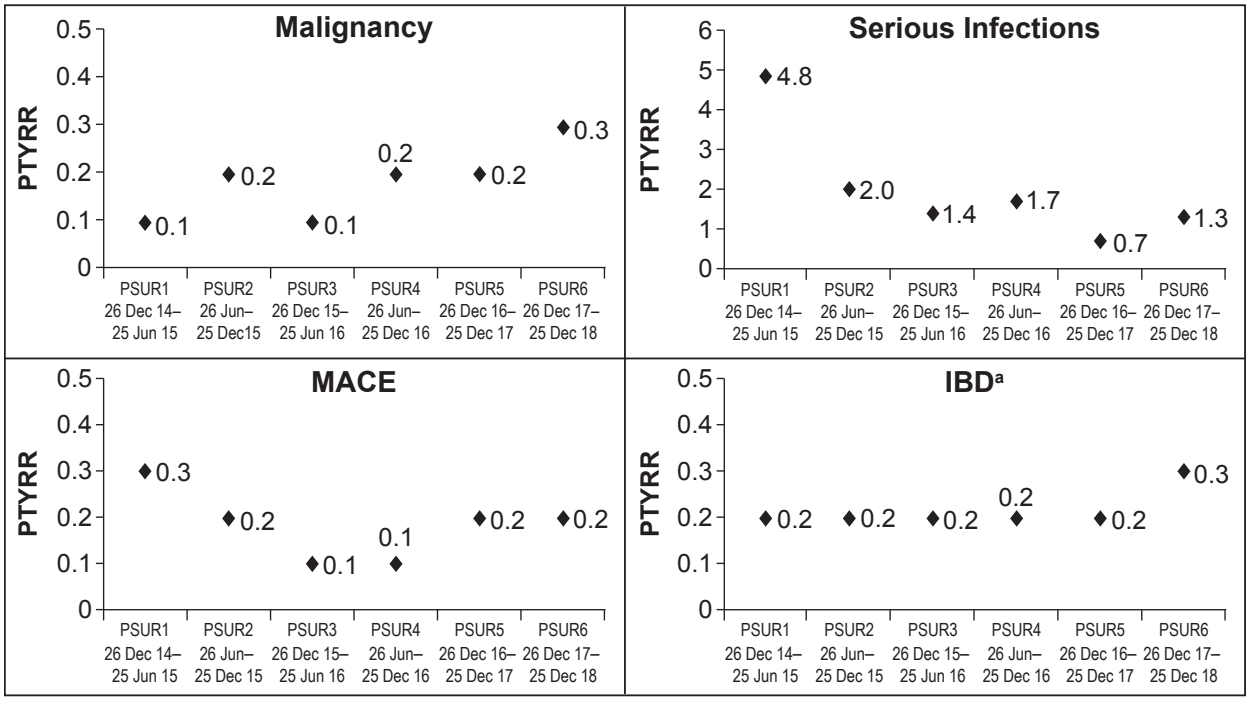

Fig. 3. Crude incidence (reporting rate) of adverse events with secukinumab across 6 periodic safety update reporting periods. Graphs demonstrating crude incidence reporting rate/100 patient-years (PY) for malignancy, serious infections, major adverse cardiovascular event (MACE) and inflammatory bowel disease (IBD) across the 3 indications, based on periodic safety update report (PSUR) data from 2014 to 2018. [a]Rates for total IBD (unspecified IBD, Crohn's disease and/or ulcerative colitis). AS: ankylosing spondylitis; EARR: exposure-adjusted reporting rate; N: number of patients in the analysis; PsA: psoriatic arthritis; PsO: psoriasis; PTYRR: patient-treatment years reporting rate.

treatment groups in PsO, PsA and AS. The incidence rates of AESIs, such as serious infections, IBD, malignancy and MACE and suicidality-related AEs were consistent with findings from previous reports (14–21, 30), with no new safety signals across any indication. Consistent with previous data (17), in this pool, Candida infections were more common in PsO patients receiving secukinumab 300 mg vs secukinumab 150 mg. Overall, the rates of occurrence of injection-site reactions reported in this analysis were low and consistent with event rates reported previously (17–20).

Any modulation of the host immune response in chronic inflammatory conditions using a biologic agent may increase the risk for infections, including fungal infections (31). Furthermore, immune dysregulation in conditions such as PsO and spondyloarthritis have the potential to predispose patients to severe infections (32). It is noteworthy that secukinumab selectively targets IL-17A and does not affect the T helper type 1 (Th1) pathway. The host immunity regulated via the Th1 pathway is expected to remain largely intact in patients receiving secukinumab treatment. In this large pooled dataset comprising patients who received secukinumab for a period of up to 5 years, the incidence of serious infections ranged from 1.2/100 to 1.8/100 PY, with no clinically meaningful differences in EAIRs across the 3 indications. The reported EAIRs for any viral respiratory infections with secukinumab treatment in the PsO, PsA and AS datasets were 3.5/100 PY, 2.7/100 PY and 3.3/100 PY, respectively. Overall, the risk of viral respiratory infections did not appear to increase with secukinumab treatment. These results are consistent with those from an independent review, which concluded that IL-17A inhibition was not associated with an increased risk of viral infections (33). The incidence of infections during secukinumab treatment indicated a favourable benefit-risk profile, which is essential in clinical decision-making to manage patients with IMIDs, such as PsO, PsA and AS.

Compared with the general population, patients with PsO, PsA and AS have an up to 4-fold increased risk of IBD (13). Smoking, infections and high doses of NSAIDs (used in PsA/AS) are risk factors associated with manifestation or relapse of existing IBD (12, 13, 34–36). Furthermore, previous failure of a TNFi in patients with PsO, PsA or AS has been reported to be related to IBD-associated exacerbations and lesser disease control (13, 37). An estimated one-third of patients with IBD experience exacerbation of symptoms within 12 months of withdrawal of the TNFi (38).

This analysis included patients with PsO, PsA and AS who were previously treated (with inadequate response) with a TNFi. The pooled datasets also included a considerable population of patients who were smokers at baseline (33.8% PsO, 20.0% PsA and 30.6% AS). However, the effects of current smoking and prior TNFi in contributing to IBD in secukinumab-treated patients are currently indeterminate. In this large pooled dataset, the incidence of CD, UC or unspecified IBD was low and ranged from 0.01/100 PY to 0.4/100 PY in patients with PsO, PsA or AS. Overall, these reported IBD event rates with secukinumab treatment are consistent with previously reported uncommon (EAIR <1%) event rates (13). The analysis confirmed no relevant interaction between the use of secukinumab and relapse/worsening of known or new-onset IBD.

Anterior uveitis is the most common extra-articular manifestation of AS occurring in approximately 20–30% of patients with AS (39). In our analysis, 18% of patients in the pooled AS safety clinical trial dataset had uveitis at baseline; over the course of 5 years, the incidence of uveitis was 1.2/100 PY in the AS population (compared with 0.01/100 PY in PsO and 0.1/100 PY in PsA patients).

A population-based longitudinal cohort study from 1994 to 2010 in 188,882 patients reported an increased incidence of MACE in PsA, AS and PsO patients (8), indicating immune-mediated conditions are probably independent risk factors for MACE. Furthermore, hypertension, dyslipidaemia, diabetes and smoking are regarded as traditional cardiovascular risk factors (6), and the elevated risk of CVD in patients with PsO, PsA and AS is partially attributable to the presence of these traditional risk factors (5, 6). In our pooled dataset, at baseline, 21.4–37.6% of patients had hypertension, 9.6–21.5% had hyperlipidaemia, 3.3–10.2% had diabetes mellitus and 20.0–33.8% were smokers. Despite the presence of baseline risk factors for MACE in this analysis, the incidence of MACE did not appear to increase over time in patients with PsO, PsA or AS.

The risk of malignancy was consistent with the rates across indications in the previous report (17). The use of a larger dataset and the longer exposure to secukinumab did not appear to increase the risk of malignancy over time. An in-depth analysis of malignancy risk in secukinumab-treated PsO, PsA and AS patients compared with patients from the Surveillance, Epidemiology and End Results (SEER) Program in the US has been published recently (40).

Similar to previous findings (17), we did not observe an increased rate of reported AESIs over time with secukinumab treatment on a year-by-year interval basis.

Post-marketing safety data are considered complementary to data from randomised controlled trials. Secukinumab was associated with a consistent safety profile in a post-marketing setting across 6 successive PSUR periods (26 December 2014 to 25 December 2018), with 285,811 cumulative post-marketing PY in the approved indications of PsO, PsA and AS.

Limitations and strengths

Despite reassuring findings, there are certain limitations to this safety analysis. Individual study protocols have

defined inclusion and exclusion criteria of clinical trials, which may not fully reflect routine clinical practice. Studies included in the analysis may differ in terms of baseline selection criteria, patient characteristics and treatment regimens. The lack of a long-term placebo comparison, due to ethical considerations, limits comparisons. Post-marketing safety surveillance results have not been separated by individual dose regimen or by indication. The mean exposure to study treatment should be considered when interpreting results of the current analysis. Furthermore, it should be noted that the mean exposure to study treatment reduced over time in the year-by-year analysis.

The strength of this report is that these analyses integrate safety data from a large patient population pooled (>12,000 patients) from over 28 clinical trials across multiple indications and are complemented with a large post-marketing surveillance safety dataset. Furthermore, the use of EAIRs that adjust for potential differences in the duration of drug exposure enhances the robustness of this analysis. This long-term (up to 5 years) safety assessment also provides a broader understanding of the safety of secukinumab and supports its long-term use in chronic systemic inflammatory conditions. The data cut-off timing of post-marketing surveillance did not include the COVID-19 pandemic.

Conclusion

In this updated safety analysis, secukinumab demonstrated a favourable safety profile over long-term treatment in patients with PsO, PsA and AS. The safety profile of secukinumab in these pooled populations was consistent with that reported previously in the individual studies of secukinumab (13–20). No new safety signals were identified.

ACKNOWLEDGEMENTS

The authors thank the patients who participated in these studies and the study investigators. The authors thank Sandeep Subramaniam, Avinash Thakur and Vivek Sanker (Novartis Healthcare Private limited, Hyderabad, India), and Trudy Mcgarry (Novartis Ireland Limited, Dublin, Ireland) for editorial and medical writing support, which was funded by Novartis Pharma AG, Switzerland, in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

This analysis was funded by Novartis Pharma AG. Novartis is committed to sharing with qualified external researchers, access to patient-level data and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel on the basis of scientific merit. All data provided is anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations.

Conflicts of interest. ABG has received honoraria as an advisory board member and consultant for AnaptsysBio, Avotres Therapeutics, Boehringer Ingelheim, Bristol-Myers Squibb Co., Incyte, GSK, Janssen, Pharma, Eli Lilly, Novartis, Pfizer, Sun Pharmaceutical Industries, Inc., UCB, Dermavant, and Xbiotech, and has received research/educational grants from Boehringer Ingelheim, Incyte, Janssen, Novartis, UCB, Xbiotech, and Sun Pharma. AD has been a consultant & Advisory Board member for AbbVie, Amgen, Aurinia, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Glaxo Smith Kline, Janssen, MonnLake, Novartis, Pfizer, and UCB, and has received research grants from AbbVie, Eli Lilly, Glaxo Smith Kline, Novartis, Pfizer, UCB. IBM has received grant/research support from AbbVie, Janssen, Novartis, Lilly, Celgene, UCB Pharma, BMS, Boehringer Ingelheim, AstraZeneca, Pfizer and has acted as a consultant for AbbVie, Janssen, Novartis, Lilly, Celgene, Compugen, UCB Pharma, BMS, Boehringer Ingelheim, AstraZeneca and Pfizer. XB has received grant/research support and/or consultancy fees from AbbVie, Amgen, Bristol-Myers Squibb, Celltrion, Celgene, Chugai, Gilead, Janssen, Lilly, MSD, Novartis, Pfizer, Sandoz, UCB. KR has served as advisor and/or paid speaker for and/or participated in clinical trials sponsored by Abbvie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Forward Pharma, Gilead, Galderma, Janssen-Cilag, Kyowa Kirin, Leo, Lilly, Medac, Novartis, Ocean Pharma, Pfizer, Sanofi, UCB; and is a co-founder of Moonlake Immunotherapeutics. SS received fees for Advisory Boards/Consulting Fees from Abbvie, Allergan, Amgen, AMT, Arena, Biogen, Bristol-Myers Squibb, Boehringer, Celgene, Celltrion, Falk, Janssen, Gilead, Lilly, Merck, Pfizer, Roche, Takeda; Tillotts. Funding (Grants): none. Research/Clinical Trials: all of the above. Speaker Fees: Abbvie, Amgen, Arena, Biogen, Bristol-Myers Squibb, Celgene, Celltrion, Falk, Ferring, Janssen, Gilead, Lilly, Merck, Pfizer, Roche, Takeda, Tillotts. WB, KM, HBR, LP, AS, VT, DK, CCP, PJ, and PP are employed by Novartis. PJM reports research grants, consulting, and/or speaker for Abbvie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galapagos, GlaxoSmithKline, Janssen, Novartis, Pfizer, SUN Pharma, and UCB. ML is an employee of Mount Sinai and receives research funds from: Abbvie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Dermavant Sciences, Eli Lilly, Incyte, Janssen Research & Development, LLC, Ortho Dermatologics, Regeneron, and UCB, Inc., and is a consultant for Aditum Bio, Almirall, AltruBio Inc., AnaptysBio, Arcutis, Inc., Aristea Therapeutics, Arrive Technologies, Avotres Therapeutics, BiomX, Boehringer-Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Dr Reddy's Laboratories, Evelo Biosciences, Evommune, Inc., Facilitatation of International Dermatology Education, Forte Biosciences, Foundation for Research and Education in Dermatology, Helsinn Therapeutics, Hexima Ltd, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Seanergy, and Verrica.

REFERENCES

1. Beringer A, Noack M, Miossec P. IL-17 in chronic inflammation: from discovery to targeting. Trends Mol Med 2016; 22: 230–241.
2. Blauvelt A, Chiricozzi A. The immunologic role of IL-17 in psoriasis and psoriatic arthritis pathogenesis. Clin Rev Allergy Immunol 2018; 55: 379–390.
3. Patel DD, Lee DM, Kolbinger F, Antoni C. Effect of IL-17A blockade with secukinumab in autoimmune diseases. Ann Rheum Dis 2013; 72: ii116–ii123.
4. McGeachy MJ, Cua DJ, Gaffen SL. The IL-17 family of cytokines in health and disease. Immunity 2019; 50: 892–906.
5. Elmets CA, Leonardi CL, Davis DMR, Gelfand JM, Lichten J, Mehta NN, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J Am Acad Dermatol 2019; 80: 1073–1113.
6. Liew JW, Ramiro S, Gensler LS. Cardiovascular morbidity and mortality in ankylosing spondylitis and psoriatic arthritis. Best Pract Res Clin Rheumatol 2018; 32: 369–389.

7. Molto A, Dougados M. Comorbidities in spondyloarthritis including psoriatic arthritis. Best Pract Res Clin Rheumatol 2018; 32: 390–400.
8. Ogdie A, Yu Y, Haynes K, Love TJ, Maliha S, Jiang Y, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. Ann Rheum Dis 2015; 74: 326–332.
9. Perez-Chada LM, Merola JF. Comorbidities associated with psoriatic arthritis: review and update. Clin Immunol 2020; 214: 108397.
10. Puig L. Cardiometabolic comorbidities in psoriasis and psoriatic arthritis. Int J Mol Sci 2017; 19: 58.
11. Zhao SS, Ermann J, Xu C, Lyu H, Tedeschi SK, Liao KP, et al. Comparison of comorbidities and treatment between ankylosing spondylitis and non-radiographic axial spondyloarthritis in the United States. Rheumatology (Oxford) 2019; 58: 2025–2030.
12. Ananthakrishnan AN, Bernstein CN, Iliopoulos D, Macpherson A, Neurath MF, Ali RAR, et al. Environmental triggers in IBD: a review of progress and evidence. Nat Rev Gastroenterol Hepatol 2018; 15: 39–49.
13. Schreiber S, Colombel JF, Feagan BG, Reich K, Deodhar AA, McInnes IB, et al. Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials. Ann Rheum Dis 2019; 78: 473–479.
14. Armstrong AW, Vender R, Kircik L. Secukinumab in the treatment of palmoplantar, nail, scalp, and pustular psoriasis. J Clin Aesthet Dermatol 2016; 9: S12–S16.
15. Baeten D, Sieper J, Braun J, Baraliakos X, Dougados M, Emery P, et al. Secukinumab, an interleukin-17A inhibitor, in ankylosing spondylitis. N Engl J Med 2015; 373: 2534–2548.
16. Blauvelt A, Prinz JC, Gottlieb AB, Kingo K, Sofen H, Ruer-Mulard M, et al. Secukinumab administration by pre-filled syringe: efficacy, safety and usability results from a randomized controlled trial in psoriasis (FEATURE). Br J Dermatol 2015; 172: 484–493.
17. Deodhar A, Mease PJ, McInnes IB, Baraliakos X, Reich K, Blauvelt A, et al. Long-term safety of secukinumab in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis: integrated pooled clinical trial and post-marketing surveillance data. Arthritis Res Ther 2019; 21: 111.
18. Gottlieb AB, Blauvelt A, Prinz JC, Papanastasiou P, Pathan R, Nyirady J, et al. Secukinumab self-administration by prefilled syringe maintains reduction of plaque psoriasis severity over 52 weeks: results of the FEATURE trial. J Drugs Dermatol 2016; 15: 1226–1234.
19. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al. Secukinumab in plaque psoriasis – results of two phase 3 trials. N Engl J Med 2014; 371: 326–338.
20. Paul C, Lacour JP, Tedremets L, Kreutzer K, Jazayeri S, Adams S, et al. Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE). J Eur Acad Dermatol Venereol 2015; 29: 1082–1090.
21. Reich K, Warren RB, Coates LC, Di Comite G. Long-term efficacy and safety of secukinumab in the treatment of the multiple manifestations of psoriatic disease. J Eur Acad Dermatol Venereol 2020; 34: 1161–1173.
22. Data on file. COSENTYX Access. Novartis Pharmaceuticals Corp; June 2021.
23. Blauvelt A, Reich K, Tsai TF, Tyring S, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate-to-severe plaque psoriasis up to 1 year: Results from the CLEAR study. J Am Acad Dermatol 2017; 76: 60–69.e9.
24. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015; 386: 1137–1146.
25. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, van der Heijde D, et al. Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. N Engl J Med 2015; 373: 1329–1339.
26. Mrowietz U, Leonardi CL, Girolomoni G, Toth D, Morita A, Balki SA, et al. Secukinumab retreatment-as-needed versus fixed-interval maintenance regimen for moderate to severe plaque psoriasis: a randomized, double-blind, noninferiority trial (SCULPTURE). J Am Acad Dermatol 2015; 73: 27–36.e21.
27. Thaci D, Blauvelt A, Reich K, Tsai TF, Vanaclocha F, Kingo K, et al. Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial. J Am Acad Dermatol 2015; 73: 400–409.
28. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310: 2191–2194.
29. Stolwijk C, van Tubergen A, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Rheum Dis 2015; 74: 65–73.
30. Strober BE, Langley RGB, Menter A, Magid M, Porter B, Fox T, et al. No elevated risk for depression, anxiety or suicidality with secukinumab in a pooled analysis of data from 10 clinical studies in moderate-to-severe plaque psoriasis. Br J Dermatol 2018; 178: e105–e107.
31. Vallabhaneni S, Chiller TM. Fungal infections and new biologic therapies. Curr Rheumatol Rep 2016; 18: 29.
32. Wakkee M, de Vries E, van den Haak P, Nijsten T. Increased risk of infectious disease requiring hospitalization among patients with psoriasis: a population-based cohort. J Am Acad Dermatol 2011; 65: 1135–1144.
33. Schett G, Sticherling M, Neurath MF. COVID-19: risk for cytokine targeting in chronic inflammatory diseases? Nat Rev Immunol 2020; 20: 271–272.
34. Felder JB, Korelitz BI, Rajapakse R, Schwarz S, Horatagis AP, Gleim G. Effects of nonsteroidal antiinflammatory drugs on inflammatory bowel disease: a case-control study. Am J Gastroenterol 2000; 95: 1949–1954.
35. Molodecky NA, Kaplan GG. Environmental risk factors for inflammatory bowel disease. Gastroenterol Hepatol (NY) 2010; 6: 339–346.
36. Timmer A. Environmental influences on inflammatory bowel disease manifestations. Lessons from epidemiology. Dig Dis 2003; 21: 91–104.
37. Molnar T, Lakatos PL, Farkas K, Nagy F, Szepes Z, Miheller P, et al. Predictors of relapse in patients with Crohn's disease in remission after 1 year of biological therapy. Aliment Pharmacol Ther 2013; 37: 225–233.
38. Kennedy NA, Warner B, Johnston EL, Flanders L, Hendy P, Ding NS, et al. Relapse after withdrawal from anti-TNF therapy for inflammatory bowel disease: an observational study, plus systematic review and meta-analysis. Aliment Pharmacol Ther 2016; 43: 910–923.
39. Gouveia EB, Elmann D, Morales MS. Ankylosing spondylitis and uveitis: overview. Rev Bras Reumatol 2012; 52: 742–756.
40. Lebwohl M, Deodhar A, Griffiths CEM, Menter MA, Poddubnyy D, Bao W, et al. The risk of malignancy in patients with secukinumab-treated psoriasis, psoriatic arthritis and ankylosing spondylitis: analysis of clinical trial and postmarketing surveillance data with up to five years of follow-up. Br J Dermatol 2021; 185: 935–944.