Safety of secukinumab from 1 million patient-years of exposure: Experience from post-marketing setting and clinical trials

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Materials and Methods

Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject who is administered a pharmaceutical product and does not necessarily need to have a causal relationship with this treatment. If an AE is causally related to a drug, that AE is called an adverse drug reaction (ADR). Criteria for categorizing serious adverse events (SAE) were determined by one or more of the following being met: death, a life-threatening condition, hospitalization or prolongation of existing hospitalization, persistent/significant disability or incapacity, or an important medical event that may jeopardize the patient or may require medical intervention.

Coding and identification of adverse events of special interest

The safety topics of interest for secukinumab (based upon reported treatment-emergent AEs for all treatment groups) were assessed by standardized grouping with the use of customized MedDRA Query (CMQ, customized and validated for Novartis), high-level group terms (HLGTs), high-level terms (HLTs), and Standardized MedDRA Queries (SMQs).

The safety topics of interest for secukinumab (based upon reported treatment-emergent AEs for all treatment groups) were assessed by standardized grouping with the use of relevant HLTs, HLGTs, SMQs or specific groups of events belonging to a customized Novartis query for which no MedDRA group terms exist. The search group strategy is described in **Supplementary Table 1**.

Estimation of post-marketing exposure

Since the total number of patients receiving secukinumab is not controlled in the post-marketing setting, post-marketing exposure is calculated based on the worldwide sales volume in

kilograms (kg) of active substance sold during the reporting interval and the average defined daily dose (10 mg).

Safety in pooled clinical trials

The pooled safety dataset included data from 47 Phase II/III/IV secukinumab clinical trials with patients who had received subcutaneous secukinumab 150 mg and/or 300 mg (adults) for at least 16 weeks for the treatment of psoriasis (PsO; 1 phase II, 25 phase III, 4 phase IV trials), psoriatic arthritis (PsA; 8 phase III trials and 1 phase IV trial), axial spondylarthritis (axSpA including AS or non-radiographic (nr-axSpA [7 phase III trials and 1 phase IV trial]). **Supplementary Fig 1** presents the details of the studies included in the current pooled analysis.

Additional clinical details with regards to opportunistic infections and fatal infections

Infrequent but potentially clinically significant events were identified in 48 out of the 559 PMS cases with potential opportunistic infections (RR 0.004/100 PY) and additional 4 cases identified from CTs (Please refer the footnotes in Supplementary **Table 4).** A majority of the 52 cases were either insufficiently documented or were likely related to comorbidities such as post-organ transplants for underlying conditions, diabetes, recurrence of the prior same infections, other underlying autoimmune diseases, receiving only 1–3 doses of secukinumab, concomitant immunosuppressants, progressive multifocal leukoencephalopathy in a patient with multiple sclerosis concomitantly treated with dimethyl fumarate and methotrexate, concurrent cancer, chronic obstructive pulmonary disease complicated by aspergillosis, obstructive nephropathy with *Candida* pyelonephritis and sepsis greater than 5 months after secukinumab discontinuation, or post-operative infections, or information as provided was not suggestive of infection as coded in MedDRA.

Deaths (including one in CT) reported with fungal, herpes, mycobacterial, or *Staphylococcus* infections were noted with limited or confounded information:

- *Aspergillus* infection (n=1, in CTs) in the setting of underlying hepatic fibrosis, post liver transplantation, with spontaneous bacterial peritonitis and multi-organ failure
- *Pneumocystis jirovecii* pneumonia (n=1) reported approximately 6 months after secukinumab discontinuation in a patient switched to adalimumab after receiving 3 doses of secukinumab, the patient died 3 months later
- Herpes zoster and bacterial meningitis (two separate AEs) with limited information in an 82-year-old male with unknown medical history, who died 7 months after receiving secukinumab (duration unknown)
- Tuberculosis (n=2): one without any clinical details; the other with congestive heart failure, who received secukinumab for 4 months and died after an unknown duration. No prior history of tuberculosis was reported for either patient
- *Staphylococcal* sepsis/bacteremia (n=4): One with insufficient clinical information (9 months of secukinumab exposure); one with a history of unspecified adenocarcinoma who received only one dose of secukinumab; one with past exposure to cyclosporine, adalimumab, and an unknown duration of secukinumab treatment; and one who received secukinumab for 8 months, with cause of death including alcoholic liver disease-induced hepatic failure

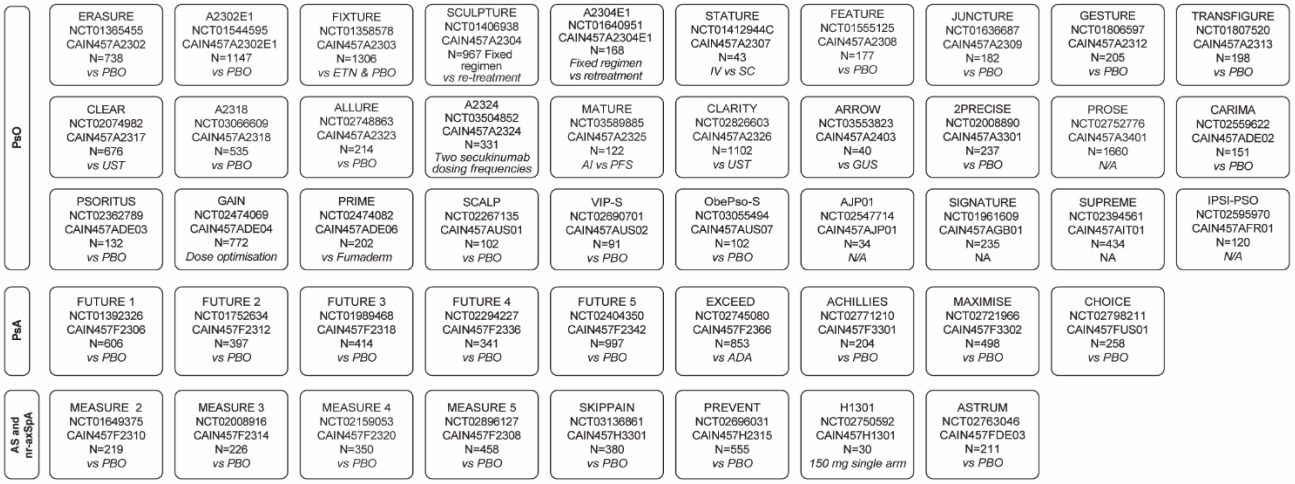
Non-IgE-mediated events

Non-IgE-mediated events were identified in 36 cases (RR 0.003/100 PY, **Supplementary Table 5**), none of which could be confirmed as related to secukinumab **(Supplementary materials)**. 25 cases without onset dates, 6 occurred within 2 weeks of the first dose, 1 with immune thrombocytopenia after 3 weeks of secukinumab initiation in the setting of cirrhosis-induced splenomegaly, and 4 occurred after 7 or more months of the first dose (Type IV hypersensitivity

reaction/N=2, immune thrombocytopenia in a setting of T-cell lymphoma/N=1, and eosinophilic granulomatosis with polyangiitis with limited information/N=1).

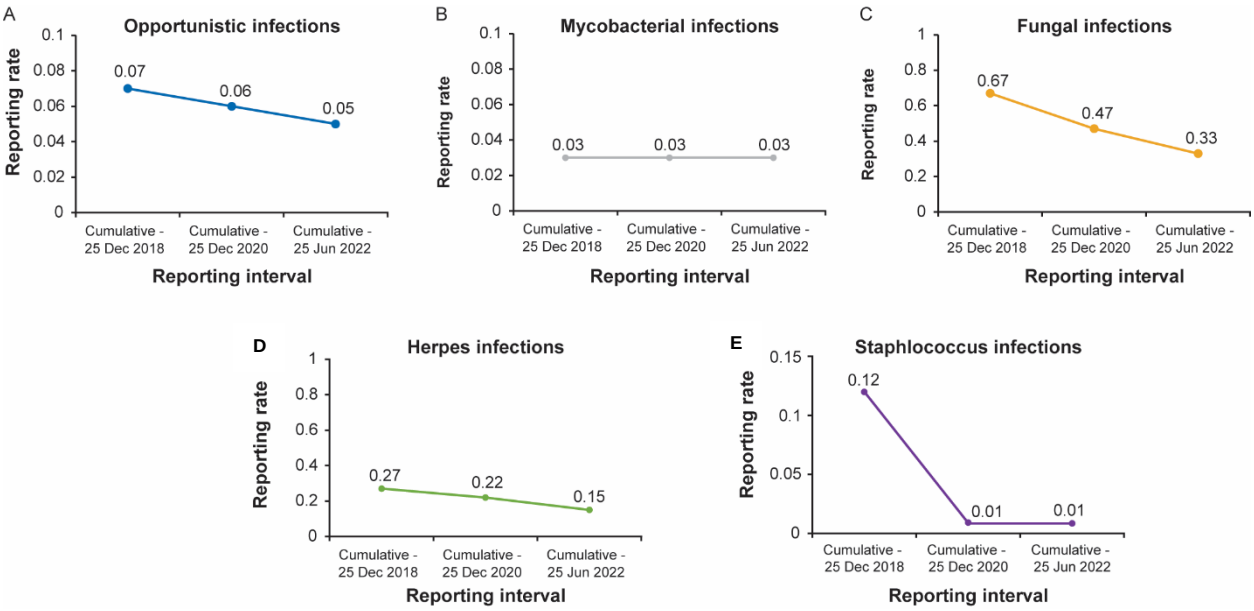
Supplementary Figures

Supplementary Fig 1. Clinical trial studies included in the pooled safety analysis



ADA, adalimumab; AI, autoinjector; AS, ankylosing spondylitis; ETN, etanercept; GUS, guselkumab; IV, intravenous; N, total number of patients per group; N/A, not applicable; nr-axSpA, non-radiographic axial spondyloarthritis; PBO, placebo; PFS, pre-filled syringe; PsA, psoriatic arthritis; PsO, psoriasis; sc, subcutaneous; UST, ustekinumab.

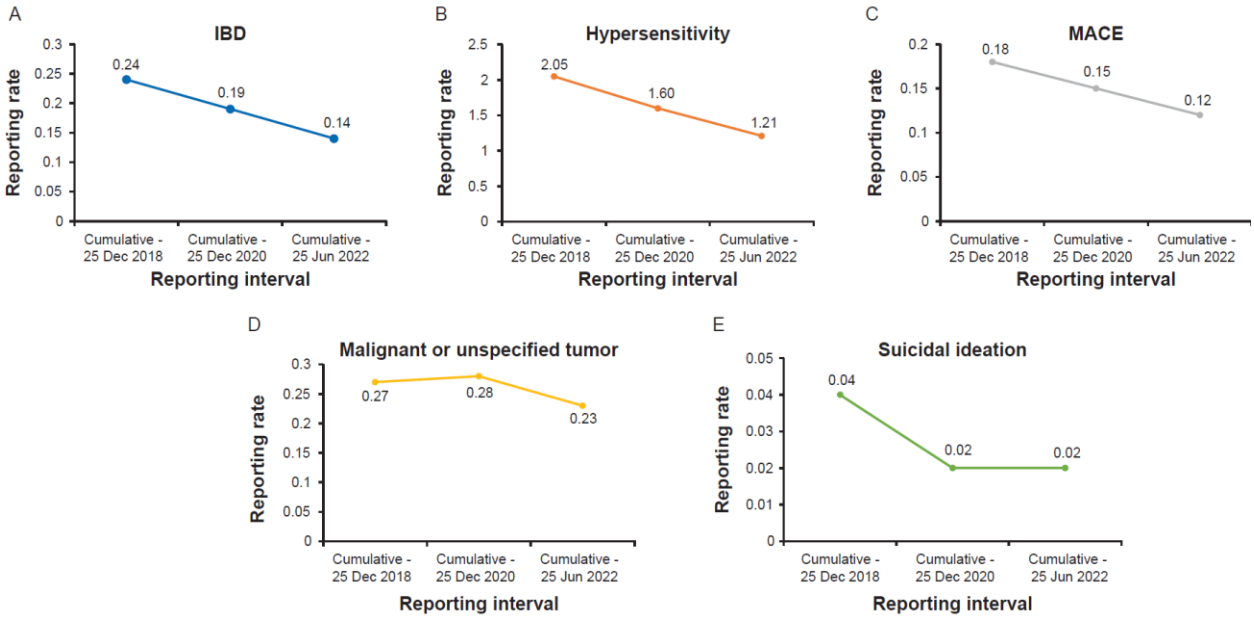
Supplementary Fig 2. Post-marketing reporting rate per 100 patient-years of adverse events related to infections with secukinumab across 3 periodic safety update reporting periods



The line graphs demonstrate the decreasing reporting rate of **(A)** opportunistic infections, **(B)** mycobacterium infections, **(C)** fungal infections (including esophageal candidiasis), **(D)** herpes infection and (**E**) Staphylococcus infections, as reported by periodic safety update reports from 25 December 2018, 25 December 2020, and 25 June 2022. Opportunistic infections included bronchopulmonary aspergillosis, cytomegalovirus gastroenteritis, gastrointestinal candidiasis, herpes zoster cutaneous disseminated, herpes zoster infection neurological, mycobacterium avium complex infection, oesophageal candidiasis, pneumocystis jirovecii pneumonia, toxoplasmosis, and tuberculosis.

CNS, central nervous system; PY, patient-years.

Supplementary Fig 3. Post-marketing reporting rate per 100 patient-years of adverse events of special interest with secukinumab across 3 periodic safety update reporting periods



Line graphs demonstrating the decreasing reporting rate of **(A)** IBD, **(B)** hypersensitivity, **(C)** MACE, **(D)** malignant or unspecified tumors and **(E)** suicidal ideation, as reported by period safety update reports from 25 December 2018, 25 December 2020 and 25 June 2022.

IBD, inflammatory bowel disease; MACE, major adverse cardiovascular events; PY, patient-years.

Supplementary Tables

Supplementary Table 1. Overview of MedDRA hierarchy levels and the terms used to code adverse events of interest

Safety event	MedDRA hierarchy level
Fungal infection	HLGT
Herpes infection	HLT
Mycobacterium infection	HLGT
Opportunistic infection	CMQ
Staphylococcus infection	HLT
COVID-19	SMQ narrow
Hypersensitivity	SMQ, narrow
Anaphylactic reaction	Algorithmic SMQ
Angioedema	SMQ, narrow
IBD[a]	NMQ
MACE[b]	NMQ
Malignant or unspecified tumor	SMQ
Suicidal ideation and behavior	SMQ

[a]NMQ included the final terms: 'colitis ulcerative', 'Crohn's disease' and 'inflammatory bowel disease'.
[b]NMQ included: fatal myocardial infarction, stroke, cardiovascular cases.

CNS, central nervous system; CMQ, customized MedDRA Query; HLGT, high-level group terms; HLT, high-level term; IBD, inflammatory bowel disease; MACE, major adverse cardiovascular event; MedDRA, Medical Dictionary for Regulatory Activities; NMQ, Novartis MedDRA Query; PT, preferred term; SMQ, standardized MedDRA Query.

Supplementary Table 2. Baseline demographics and disease characteristics from secukinumab clinical trial patient population

Characteristics	**PsO** (N=9561)	**PsA** (N=3880)	**AS and nr-axSpA** (N=2203)
Age (years), mean (SD)	45.1 (13.41)	48.6 (12.16)	40.2 (11.99)
Female, *n* (%)	3141 (32.85)	2015 (51.93)	779 (35.36)
Weight (kg), mean (SD)	87.34 (22.15)	84.36 (19.75)	77.77 (17.53)
Relevant medical history or current medical condition *n* (%)			
Hypertension	2005 (20.97)	1302 (33.56)	364 (16.52)
Hyperlipidemia	1253 (13.11)	715 (18.43)	181 (8.22)
Diabetes mellitus	669 (7.00)	321 (8.27)	46 (2.09)
IBD[a]	0	7 (0.18)	37 (1.68)
Crohn's disease	5 (0.05)	9 (0.23)	5 (0.23)
Colitis ulcerative	11 (0.12)	8 (0.21)	5 (0.23)
Smoking status	3007 (31.45)	830 (21.39)	665 (30.19)

[a]Unspecified.
AS, ankylosing spondylitis; IBD, inflammatory bowel disease; nr-axSpA, non-radiographic axial spondyloarthritis; N, number of patients in the analysis; *n*, number of patients with a response; PsA, psoriatic arthritis; PsO, psoriasis; SD, standard deviation

Supplementary Table 3. COVID infections from all sources cumulative until 25 September 2022

MedDRA PT	CT	PMS	Total
COVID-19	24	4325	4349
SARS-CoV-2 test positive	1	539	540
Coronavirus infection	2	251	253
Suspected COVID-19	1	145	146
COVID-19 pneumonia	6	82	88
Exposure to SARS-CoV-2	-	51	51
Coronavirus test positive	-	48	48
Asymptomatic COVID-19	-	33	33
SARS-CoV-1 test positive	-	6	6
SARS-CoV-2 test negative	-	6	6
Occupational exposure to SARS-CoV-2	-	1	1
SARS-CoV-1 test negative	-	1	1
SARS-CoV-2 carrier	-	1	1
SARS-CoV-2 test	-	1	1
SARS-CoV-2 test false negative	-	1	1

CT, clinical trial; COVID, Coronavirus disease; PMS, post-marketing setting; SARS-CoV, Severe acute respiratory syndrome coronavirus

Supplementary Table 4. Summary of opportunistic infections in PMS as searched by the pre-defined criteria

MedDRA HLT	Preferred Term	Number of PMS case[a]		PMS cases with ≥1 event[b]
		Non-serious	Serious	
Aspergillus infections	Aspergillus infection[c]	-	4	4
	Bronchopulmonary aspergillosis[c]	-	3	3
Atypical mycobacterial infections	Atypical mycobacterial infection	-	5	5
	Atypical mycobacterial pneumonia	-	1	1
	Mycobacterial infection	-	1	1
	Mycobacterium avium complex infection	-	2	2
	Mycobacterium ulcerans infection	-	1	1
Candida infections	*Candida* sepsis[c]		1	1
	Gastrointestinal candidiasis	3	18	21
	Mucocutaneous candidiasis	15	2	17
	Oesophageal candidiasis	21	180	201
	Peritoneal candidiasis	-	1	1
	Systemic candida[c]	-	6	6
Coccidioides infections	Coccidioidomycosis[c]	-	7	7
Cryptococcal infections	Cryptococcosis[c]	-	1	1
Cytomegaloviral infections	Cytomegalovirus colitis[c]	-	1	1
	Cytomegalovirus gastritis[c]	-	1	1
	Cytomegalovirus hepatitis[c]	-	1	1
Fungal infections NEC	Trichosporon infection	-	1	1
Herpes viral infections	Herpes simplex encephalitis	-	3	3
	Herpes simplex pharyngitis	-	1	1
	Herpes zoster cutaneous disseminated[c]	-	1	1
	Herpes zoster meningitis	-	3	3
	Herpes zoster meningoencephalitis	-	2	2
	Meningoencephalitis herpetic	-	1	1
	Varicella zoster pneumonia[c]	-	1	1
Histoplasma infections	Histoplasmosis	-	4	4
	Histoplasmosis cutaneous	-	1	1
Infections NEC	Opportunistic infection	-	7	7
Isospora infections	Isosporiasis	-	2	2
Leishmania infections	Leishmaniasis	-	1	1
Pneumocystis infections	*Pneumocystis jirovecii* pneumonia[c]	-	12	12
Polyomavirus infections	Progressive multifocal leukoencephalopathy[c]	-	1	1
Respiratory syncytial viral infections	Pneumonia respiratory syncytial viral	-	1	1
	Respiratory syncytial virus bronchitis	-	1	1
	Respiratory syncytial virus infection	9	2	11
Toxoplasma infections	Toxoplasmosis[c]	4	1	5
Tuberculous infections	Bone tuberculosis	-	1	1
	Disseminated tuberculosis[c]	-	1	1
	Intestinal tuberculosis	-	1	1
	Lupus vulgaris[c]	1	1	2
	Lymph node tuberculosis	-	3	3
	Peritoneal tuberculosis	-	1	1
	Tuberculosis	1	226	227
	Tuberculosis gastrointestinal	-	2	2
	Tuberculous pleurisy	-	1	1

[a]An AE was counted once for a given PMS case if the same AE occurred more than one time within that case.
[b]An AE was counted once for a given PMS case if the same AE was reported for both non-serious and serious within that case.
[c]The infections (MedDRA PT) are further reviewed (in Supplementary Material) due to medical significance.
AE, adverse event; HLT, high-level term; MedDRA, MedDRA, Medical Dictionary for Regulatory Activities; NEC, Necrotizing enterocolitis; PMS, post-marketing setting

Supplementary Table 5. Summary of adverse events suggesting non-IgE-mediated hypersensitivity reactions in PMS

MedDRA PT	Number of PMS cases[a]
Anti-neutrophil cytoplasmic antibody positive vasculitis	2
Eosinophilic granulomatosis with polyangiitis	2
Immune thrombocytopenia	6
Interstitial granulomatous dermatitis	2
Palisaded neutrophilic granulomatous dermatitis	1
Serum sickness	7
Serum sickness-like reaction	4
Type III immune complex mediated reaction	2
Type IV hypersensitivity reaction	10

Events selected based on medical review.
[a]Each event occurred only once within a given case, and no case contained more than one events.
MedDRA, Medical Dictionary for Regulatory Activities; PMS, post-marketing setting; PT, preferred term

Supplementary Table 6. Summary of post-marketing adverse events by groups representing diagnostic components for potential anaphylactic reaction

MedDRA search groups	Event PT	Life-threatening[a]	Hospitalization[a]	Other SAE[a]	Non-serious[a]	Total reports[b]
Group 1 (Involvement in skin or mucosal tissues)	Angioedema	2	1	2		5
	Erythema	-	1	4	21	26
	Eye oedema	-	-	-	1	1
	Eye pruritus	-	-	1	6	7
	Eye swelling	-	-	-	5	5
	Face oedema	1	1	1		3
	Flushing	-	-	1	2	3
	Injection site urticaria	-	-	-	2	2
	Lip swelling	1	-	1	7	9
	Ocular hyperemia	-	-	-	3	3
	Oedema	-	-	-	3	3
	Periorbital swelling	-	-	-	1	1
	Pruritus	-	1	4	40	45
	Rash	1	2	5	33	41
	Rash erythematous	-	-	-	5	5
	Rash pruritic	-	-	-	10	10
	Swelling	-	1	1	8	10
	Swelling face	1	2	5	10	18
	Swelling of eyelid	1	-	-	-	1
	Urticaria	-	2	6	21	29
Group 2 (Respiratory compromise)	Asthma	-	-	1	1	2
	Bronchospasm	-	-	-	1	1
	Chest discomfort	-	-	1	12	13
	Choking	-	-	2	-	2
	Choking sensation	-	-	-	1	1
	Cough	-	1	2	28	31
	Dyspnea	1	5	4	31	41
	Laryngeal edema	1	-	-	-	1
	Mouth swelling	-	-	-	1	1
	Pharyngeal swelling	-	-	2	19	21
	Sensation of foreign body	-	-	-	1	1
	Sneezing	-	-	-	4	4
	Swollen tongue	-	-	6	13	19
	Throat tightness	-	-	-	2	2
	Upper airway obstruction	-	-	1	-	1
	Wheezing	-	-	-	2	2
Group 3 (Hypotension)	Blood pressure decreased	-	-	-	3	3
	Blood pressure diastolic decreased	-	-	-	2	2
	Blood pressure systolic decreased	-	1	-	1	2
	Hypotension	-	-	-	4	4

The search groups are based on the algorithm from Introductory Guide for Standardised MedDRA Queries (SMQs) Version 25.0 (March 2022). [a]An AE was counted once for a given PMS case if the same AE occurred more than one time within that case.
[b]An AE was counted once for a given PMS case if the same AE was reported for both non-serious and serious within that case.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PMS, post-marketing setting; PT, preferred term; SAE, serious adverse event