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ORIGINAL RESEARCH

Safety of Secukinumab from 1 Million Patient-Years of Exposure: Experience from Post-Marketing Setting and Clinical Trials

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ABSTRACT

Introduction: Secukinumab is an anti-interleukin (IL)-17A monoclonal antibody indicated for multiple immunological disorders. Here, we aim to summarize secukinumab safety in clinical trials (CTs) and post-marketing setting (PMS) until 25 June 2022.

Methods: Adverse events (AEs) were summarized with crude reporting rate (RR) per 100 patient-years (PY) in PMS for all reported indications and with exposure-adjusted incident rates (EAIR) per 100 PY in pooled 47 CTs for approved indications.

Results: Secukinumab exposure totaled 1,159,260 PY in PMS and 27,765 PY in CTs. AEs were mostly (> 80%) non-serious in PMS. EAIR for serious AEs was 7.0/100 PY. Nasopharyngitis (RR 0.59/100 PY, EAIR 16.08/100 PY) and pneumonia (RR 0.14/100 PY, EAIR 0.17/100 PY) were the most common infection and serious infection, respectively. *Candida* infections (RR 0.20/100 PY, EAIR 2.16/100 PY) were the most common fungal infections. Inflammatory bowel disease (IBD) was observed in PMS (0.14/100 PY) and CTs (0.26/100 PY). Most (76%)

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patients with prior IBD did not report IBD flare during CTs. PMS monitoring identified paradoxical skin reactions including dyshidrotic eczema (RR 0.006/100 PY) and pyoderma gangrenosum (RR 0.003/100 PY).
Conclusion: Secukinumab safety profile with increased patient exposure remained favorable. Paradoxical skin reactions were identified in post-marketing monitoring.

Keywords: Clinical trials; IL-17A; Patient-year; Post-marketing setting; Safety; Secukinumab

Key Summary Points

Why carry out this study?

Greater exposure to secukinumab in real-world use adds to the safety observed in clinical trials and demonstrates favorable safety profile.

The objective of this analysis was to summarize the updated safety experience of secukinumab.

What was learned from the study?

Safety risks are described contextually with adverse events frequencies to aid in benefit–risk assessment while prescribing secukinumab.

Prescribers are informed about uncommon paradoxical skin reactions such as dyshidrotic eczema and pyoderma gangrenosum.

INTRODUCTION

Secukinumab is a fully human anti-interleukin (IL)-17A monoclonal antibody approved to treat moderate-to-severe plaque psoriasis (PsO), psoriatic arthritis (PsA), axial spondyloarthritis (axSpA) including ankylosing spondylitis (AS) and non-radiographic axSpA, pediatric PsO, juvenile psoriatic arthritis (JPsA), and enthesitis-related arthritis (ERA) in more than 100 countries [1], and was recently approved for moderate-to-severe hidradenitis suppurativa (HS) [2].

Modulation of proinflammatory cytokines, including IL-17A, with biologic therapies have potential safety implications, including infections and immune-related conditions [3, 4]. Due to multiorgan effects of IL-17 pathway activation, patients with certain underlying diseases may have comorbidities that can complicate causality analyses of the adverse events (AEs) reported for IL-17 inhibitors including secukinumab [5–8].

The safety of secukinumab has been published with respect to malignancy, latent tuberculosis, and inflammatory bowel disease (IBD) [9–11]. Long-term, 5-year, pooled safety data were reported from 28 clinical trials (CTs) involving 12,637 patients, along with post-marketing setting (PMS) exposure of 285,811 patient-years (PY) as of 25 December 2018 [12].

From 25 December 2018 through 25 June 2022, secukinumab post-marketing exposure more than quadrupled to 1,159,260 PY plus patients from CTs totaling 27,765 PY. The objective of this analysis was to summarize the updated safety experience of secukinumab [12].

METHODS

AEs reported for secukinumab in PMS and pooled CTs were reviewed cumulatively through 25 June 2022 (unless otherwise specified).

- PMS reflects safety monitoring by Novartis based on real-world evidence, is regulated by health authorities (HA), and is recorded in the Novartis safety database. PMS AEs can originate from healthcare professionals, patients, caregivers, literature, or social media. AEs received by HA and forwarded to Novartis are also included. Although details such as demographics, comorbidities, treatment indications, and dosing details may be lacking, all PMS AEs (irrespective of the reported indications) were analyzed.

- AEs in CTs were pooled from 47 phase II/III/IV studies in adults administered secukinumab 150 mg and/or 300 mg for at least 16 weeks for PsO, PsA, and axSpA. At the time of the data cutoff, the HS pivotal studies were not available for pooling but were published after the data cutoff for this report [2]. Safety of the pediatric studies were published separately [13, 14]

This analysis aimed to provide contextual descriptions of the safety experience with secukinumab primarily in PMS in conjunction with the data from pooled CTs. The AEs associated with the safety experience as described in this report are relevant for secukinumab and are called AEs of special interest (AESI). Additionally, paradoxical skin reactions identified from PMS (outside CTs) were also described in this report. All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 25.0) with individual AEs presented in MedDRA Preferred Terms (PT). The search for AESI was broader than the targeted medical concepts to include all potential events, e.g., "rash" is included in the search for hypersensitivity, although it may also be an underlying condition.

AEs and serious AEs (SAEs) definitions, AESI search criteria, estimation of post-marketing exposure, and descriptions of the CTs pool are described in Supplementary Material, Supplementary Table 1, and Supplementary Fig. 1.

Statistical Analysis

AE assessments were descriptive with reporting rate (RR) calculated as number of PMS reports divided by PMS exposure per 100 PY. Post-marketing exposure was estimated on the basis of the sold volume of drug substance and defined average daily dose (Supplementary Material). Pooled AEs in CTs were analyzed using exposure-adjusted incidence rates (EAIR) per 100 PY.

Ethical Approval

All AEs were assessed in accordance with Good Pharmacovigilance Practice Module VII and International Council for Harmonization (ICH) Guideline E2C [15]. All CTs were conducted in compliance with the Declaration of Helsinki [16], ICH Guidelines for Good Clinical Practice, and local country regulations. The protocols for the clinical trials were reviewed and approved by ethical review committees and authorities for each clinical site; all patients provided written informed consent.

RESULTS

In PMS, 169,248 case reports were received (RR 14.60/100 PY, decreased from 24.18/100 PY in December 2018, Fig. 1), and of these, 18% were serious (17% serious in December 2018).

In CTs, patients' baseline characteristics are summarized in Supplementary Table 2. AEs are summarized by indication, with secukinumab exposure up to 5.4 years (Table 1). Similarly, these AEs were mainly non-serious: the EAIR for AEs versus SAEs was 181.59 [95% confidence interval (CI) 178.46, 184.77]/100 PY versus 7.04 (95% CI 6.72, 7.37)/100 PY.

AESI are summarized for PMS and pooled CTs in Table 2. Changes in PMS RR since December 2018 are plotted in Supplementary Figs. 2 and 3, showing decreases in RR for all but 2 AESI (mycobacterial infections and malignancies, which had no change in RR).

Infections were the most frequent AESI (RR 3.19/100 PY) with 71% being non-serious. In both PMS and CTs, nasopharyngitis (RR 0.59/100 PY, EAIR 16.08/100 PY) and pneumonia (RR 0.14/100 PY, EAIR 0.17/100 PY) were the most common infection and serious infection, respectively (Table 2). Coronavirus disease 2019 (COVID-19) infections were further tracked through 25 September 2022, totaling 5816 cases in PMS and CTs (Supplementary Table 3); 81 (1.4%) of these cases were reported as COVID-related deaths.

Fungal, herpes, mycobacterial, and *Staphylococcus* infections were mainly localized or non-disseminated in nature (Table 2). *Candida*

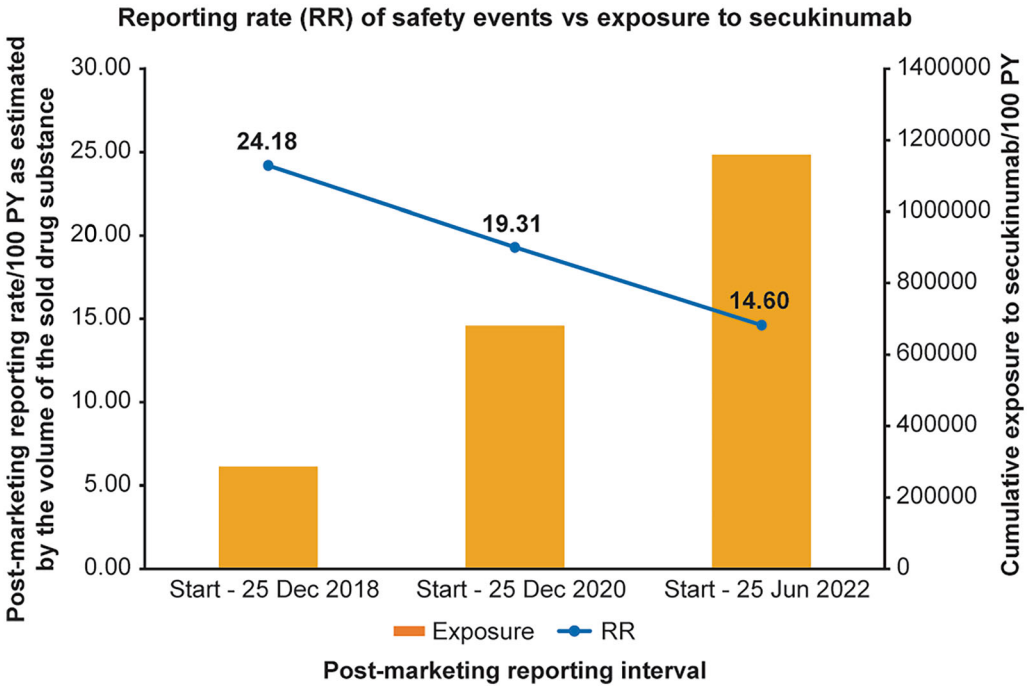

Fig. 1 Post-marketing reporting rate per 100 PY. The bar graph demonstrates the decreasing reporting rate of safety events (left *y*-axis) as the cumulative exposure of secukinumab increases (right *y*-axis), as reported by periodic safety update reports from 25 December 2018, 25 December 2020, and 25 June 2022. *PY* patient-years, *RR* reporting rate

infections (RR 0.20/100 PY, EAIR 2.16/100 PY) were the most common fungal infection, with oral candidiasis (RR 0.09/100 PY, EAIR 1.06/100 PY) as the most common *Candida* infection. Serious fungal infections were reported in 15% (576/3883, RR 0.05/100 PY) of the PMS fungal infection cases, most of which were esophageal candidiasis, oral candidiasis, and other unspecified fungal infections. History of diabetes was reported in 3.3% (76/2317, PMS) and 9% (54/582, CTs) cases with *Candida* infections that were mainly non-serious and superficial. In CTs, EAIR of *Candida* infections in patients with diabetes versus without diabetes was 2.31 (1.74, 3.02)/100 PY versus 2.14 (1.96, 2.33)/100 PY, respectively. Mycobacterial infections (RR 0.03/100 PY) included tuberculosis (RR 0.02/100 PY) and latent tuberculosis (0.008/100 PY), accounting respectively for 64% and 25% of PMS cases. In contrast, in CTs, AEs of tuberculosis were mainly latent tuberculosis (EAIR 0.04/100 PY).

Of the potential opportunistic infections (RR 0.05/100 PY, EAIR 0.17/100 PY, Supplementary Table 4), infrequent but potentially clinically significant events were identified in 48 out of the 559 PMS cases (RR 0.004/100 PY) and an additional 4 cases were identified from CTs. A majority of the 52 cases were either insufficiently documented or were likely related to comorbidities (Supplementary Material).

Deaths (eight in PMS, one in CT) reported with fungal, herpes, mycobacterial, or *Staphylococcus* infections were noted with limited or confounded information (Supplementary Material).

Hepatitis B virus (HBV) reactivation was reported in 13 cases (all in PMS, with 8 from Taiwan where HBV is endemic) as of 31 March 2023; of these, in 11 cases either there was no pertinent HBV diagnostic data or there was historical use of adalimumab, etanercept, or ustekinumab, which all share a risk of HBV reactivation as per prescribing information. In the remaining two cases, a potential association

Table 1 Summary of safety data from secukinumab clinical trials (entire treatment period)

Variables	Psoriasis (*N* = 9561)	Psoriatic arthritis (*N* = 3880)	Axial spondyloarthritis[a] (*N* = 2203)
Exposure (days), mean (SD)	605.8 (549.97)	701.4 (467.80)	739.0 (498.71)
Exposure (days), median (min–max)	370.0 (1–1982)	623.5 (8–1954)	672.0 (1–1982)
Subject years	15,857.0	7450.5	4457.0
Death, *n* (%)	19 (0.20)	14 (0.36)	5 (0.23)
Exposure-adjusted incidence rate/100 PY (95% CI)			
Any adverse event	212.36 (207.69, 217.10)	145.77 (140.68, 150.99)	150.05 (143.20, 157.13)
Any serious adverse event	7.11 (6.69, 7.56)	7.84 (7.18, 8.53)	5.49 (4.80, 6.25)
Most common adverse events, EAIR (95% CI)			
Nasopharyngitis	19.44 (18.66, 20.24)	11.36 (10.54, 12.23)	12.91 (11.76, 14.14)
Upper respiratory tract infection	6.14 (5.75, 6.56)	8.10 (7.42, 8.82)	8.28 (7.41, 9.22)
Headache	6.56 (6.15, 6.99)	3.78 (3.34, 4.26)	4.50 (3.88, 5.20)
Arthralgia	5.26 (4.90, 5.65)	4.21 (3.74, 4.72)	3.64 (3.09, 4.27)
Diarrhea	4.28 (3.96, 4.63)	4.21 (3.74, 4.72)	4.90 (4.25, 5.63)
Adverse events of special interest, EAIR (95% CI)			
Serious infections[b]	1.53 (1.35, 1.74)	1.79 (1.50, 2.13)	1.11 (0.82, 1.47)
Candida infections[c]	2.69 (2.44, 2.96)	1.72 (1.43, 2.05)	1.03 (0.75, 1.37)
Herpes viral infections[c]	2.74 (2.49, 3.02)	2.39 (2.05, 2.78)	2.01 (1.61, 2.48)
Tuberculosis-related events[d]	0.04 (0.01, 0.08)	0.04 (0.01, 0.12)	0.07 (0.01, 0.20)
Opportunistic infections[e]	0.20 (0.13, 0.28)	0.16 (0.08, 0.28)	0.11 (0.04, 0.26)
Drug hypersensitivity[f]	0.16 (0.1, 0.23)	0.2 (0.11, 0.33)	0.22 (0.11, 0.41)
Anaphylactic reaction[f]	0.04 (0.02, 0.09)	0.01 (0.00, 0.07)	–
Anaphylactic shock[f]	0.01 (0, 0.04)	0.01 (0.00, 0.07)	–
Angioedema[f]	0.08 (0.04, 0.14)	0 (0.00, 0.05)	0.04 (0.01, 0.16)
Inflammatory bowel disease[f]	0.01 (0.00, 0.05)	0.04 (0.01, 0.12)	0.02 (0.00, 0.13)
Crohn's disease[f]	0.08 (0.04, 0.13)	0.08 (0.03, 0.18)	0.27 (0.14, 0.47)
Ulcerative colitis[f]	0.13 (0.08, 0.19)	0.09 (0.04, 0.19)	0.27 (0.14, 0.47)
MACE[d]	0.40 (0.31, 0.52)	0.38 (0.25, 0.54)	0.38 (0.22, 0.61)

Table 1 continued

Variables	Psoriasis (*N* = 9561)	Psoriatic arthritis (*N* = 3880)	Axial spondyloarthritis[a] (*N* = 2203)
Malignancy[g]	0.75 (0.62, 0.90)	1.04 (0.82, 1.30)	0.45 (0.27, 0.70)

CI confidence interval, *EAIR* exposure-adjusted incidence rate per 100 patient-years, *IBD* inflammatory bowel disease, *MACE* major adverse cardiovascular events, *N* number of patients in the analysis, *n* number of patients with a response, *nr-axSpA* non-radiographic axial spondyloarthritis, *PsA* psoriatic arthritis, *PsO* psoriasis, *PT* preferred term, *PY* patient-years, *SD* standard deviation

[a]Including ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA)

[b]Rates for system organ class

[c]Rates for MedDRA high-level term

[d]Rates for Novartis MedDRA query term

[e]Rates for customized MedDRA query term

[f]Rates for MedDRA preferred term (PT; IBDs for unspecified IBD)

[g]Rates for standardized MedDRA query term (SMQ): 'malignancies and unspecified tumour'

with secukinumab may be suspected, one with concomitant risks of hepatitis C and no administered HBV prophylaxis, and the other resulting in interruption of secukinumab treatment and initiation of nucleoside analogues. Secukinumab was reintroduced 6 months later, while nucleoside analogues were continued without recurrence.

Hypersensitivity was reported with onset dates available in 31% (4332) of the 14,113 PMS cases; 70% (3024/4332) occurred ≥ 2 weeks after the first dose of secukinumab. Unspecified rash was most common, which could also be an underlying condition (Table 2). Non-immunoglobulin (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 Material).

Anaphylaxis was identified in 239 PMS cases (RR 0.02/100 PY), 27 (11%, RR 0.002/100 PY) with reported onset within 2 weeks of secukinumab initiation without alternative etiology. All 27 cases resulted in secukinumab discontinuation. An additional 115 PMS reports without an explicit anaphylaxis description were reviewed for a combination of AEs involving any two of the following: skin/mucosal tissues, respiratory compromise, and hypotension (Supplementary Table 6). However, none of the 115 cases met criteria for anaphylaxis, per standardized diagnostic criteria [17].

IBD was reported with RR 0.14/100 PY and EAIR 0.26/100 PY (Table 2). In PMS, prior history of IBD was reported in 14% (227/1578) IBD cases. In CTs, 53 patients were new-onset IBD cases while 19 had IBD flare, accounting for 24% of all 78 patients with prior history of IBD, i.e., 76% patients with prior IBD did not have IBD flare (Table 3). Gastrointestinal bleeding, perforation, or diarrhea with dehydration were reported as life-threatening in 12 PMS cases and were reported with fatal outcome in another 3 cases (all 3 had cardiovascular risks). Another patient having a history of ulcerative colitis without reported flare died of a duodenal ulcer perforation.

Malignancies (RR 0.23/100 PY, EAIR 0.78/100 PY) are summarized in Tables 2 and 4. Prior history of malignancies was found in 659 (25%) of the 2620 PMS cases with AEs of malignancy. Onset dates were reported in 1009/2620 (39%) PMS cases; one-fourth of these (245, or 9% of the 2620 cases) reported malignancies (mostly carcinomas and non-melanoma skin cancers) within 6 months after the first dose of secukinumab. Additionally, there were malignancies reported ≥ 6 months after being treated with secukinumab for ≤ 6 months.

Major adverse cardiovascular events (MACE, RR 0.12/100 PY, EAIR 0.39/100 PY, Table 2) were

Table 2 Summary of AEs of special interest in post-marketing setting and pooled clinical trials

AEs of special interest		AE reports in post-marketing setting							EAIR per 100 PY (95% CI) in pooled clinical trials (N = 15,644; total exposure = 27,765 PY)
		No. of reports	RR/100 PY[c]	RR[c] change from 2018	Common AE[f,k]	Non-serious[a]	Serious[a]	Any[b]	
Infection	All infections	36,983	3.19	Decrease from 5.15	Pneumonia	21	1595	1616	Most common: nasopharyngitis[f]: 16.08
	Serious infections	10,720	0.92	(Dec 2018)	Lower RTI[f]	101	1054	1155	(15.56, 16.62)
				Decrease from 1.39	COVID-19[f]	2685	849	3524	Serious infections: 1.54 (1.39, 1.69)
				(Dec 2018)	Cellulitis[f]	7	733	740	Most common: pneumonia[f]: 0.17 (0.12, 0.23); cellulitis[f]: 0.11 (0.07, 0.15)
					Infection[f]	1973	421	2392	
					Nasopharyngitis[f]	6485	318	6798	
					Influenza[f]	3405	238	3636	
					Sinusitis[f]	2123	149	2272	
	Fungal infection[d]	3883	0.33	Decreased (Supp Fig. 2C)	Esophageal candidiasis	21	180	201	*Candida* infections[e]: 2.16 (1.99, 2.34)
					Oral candidiasis	1010	83	1091	Most common: oral candidiasis[f]: 1.06 (0.94, 1.19)
					Candida infection	751	68	819	
					Fungal infection	647	59	706	
	Herpes viral infection[d]	1808	0.15	Decreased (Supp. Fig. 2E)	Herpes zoster	806	90	896	2.53 (2.34, 2.73); most common: oral herpes[f]: 1.40 (1.27, 1.55)
					Oral herpes	581	38	619	
	Mycobacterial infection[d]	354	0.03	No change (Supp. Fig. 2B)	Tuberculosis	1	226	227	Tuberculosis-related events[g]: 0.07 (0.03, 0.13); most common: latent tuberculosis[f]: 0.04 (0.02, 0.11)
					Latent tuberculosis	54	34	88	
	Opportunistic infections[d]	559	0.05	Decreased (Supp. Fig. 2A)	All retrieved events are in Supplementary Table 4				0.17 (0.13, 0.23); most common: esophageal candidiasis[f]: 0.13 (0.09, 0.18)
	Staphylococcal infections[d]	750	0.06	Decreased (Supp. Fig. 2F)	*Staphylococcal* infection[l]	24	337	361	*Staphylococcal* skin infection[f]: 0.07 (0.04, 0.11); *Staphylococcal* infection[f]: 0.07 (0.04, 0.11)
					Furuncle	242	40	282	

Table 2 continued

AEs of special interest	AE reports in post-marketing setting							EAIR per 100 PY (95% CI) in pooled clinical trials (N = 15,644; total exposure = 27,765 PY)
	No. of reports	RR/100 PY[c]	RR[c] change from 2018	Common AE[f,k]	Non-serious[a]	Serious[a]	Any[b]	
Hypersensitivity[d]	14,113	1.21	Decreased	Rash	5272	407	5673	Drug hypersensitivity[f]: 0.18 (0.13, 0.24); hypersensitivity[f]: 0.15 (0.11, 0.20); anaphylactic reaction[f]: 0.03 (0.01, 0.06); anaphylactic shock[f]: 0.01 (0, 0.03); angioedema[f]: 0.05 (0.03,0.09)
Anaphylactic reactions[h]	239[h]	0.02	(Supp. Fig. 3B), also the lowest RR since first approval	Hypersensitivity	1995	264	2255	
Angioedema[i]	3160[i]	0.27		Urticaria	1470	175	1643	
				Reported clinical signs suggesting angioedema[i]:				
				Urticaria	1470	175	1643	
				Swelling face	382	101	482	
IBD[d]	1578	0.14	Decreased (Supp. Fig. 3A)	Ulcerative colitis, Crohn's disease, IBD				Any event term: 0.26 (0.20, 0.33); colitis ulcerative[f]: 0.14 (0.1, 0.19); Crohn's disease[f]: 0.11 (0.07, 0.15)
								IBD[f]: 0.02 (0.01, 0.05)
Malignancy[d]	2620	0.23	Stable (Supp. Fig. 3D)	Neoplasms malignant site unspecified NEC[e,m]			413	0.78 (0.68, 0.89)
				Skin neoplasms malignant and unspecified (excl melanoma)[e,n]			350	
				Breast and nipple neoplasms malignant[e,o]			342	
MACE (composite)[d,j]	1435	0.12	Decreased (Supp. Fig. 3C)	Including myocardial, stroke, and cardiovascular death				0.39 (0.32, 0.47)

Table 2 continued

AEs of special interest	AE reports in post-marketing setting							EAIR per 100 PY (95% CI) in pooled clinical trials (*N* = 15,644; total exposure = 27,765 PY)
	No. of reports	RR/100 PY[c]	RR[c] change from 2018	Common AE[f,k]	Non-serious[a]	Serious[a]	Any[b]	
Suicidal ideation and behavior[d]	234	0.02	Decreased (Supp Fig. 3E)	Suicidal ideation[f]			158	SIB[d] 0.08 (0.05, 0.12); suicidal ideation[f]: 0.04 (0.02, 0.07); suicide attempt[f]: 0.03 (0.01, 0.05); completed suicide[f] 0.01 (0.00, 0.03)
				Suicide attempt[f]			27	
				Completed suicide[f]			15	
				Intentional overdose[f]			13	

AE adverse event, *CI* confidence interval, *IBD* inflammatory bowel disease, *MACE* major cardiovascular event, *PMS* post-marketing setting, *PY* patient-year, *EAIR* exposure-adjusted incidence rate per 100 patient-years, *RR* reporting rate, *SIB* suicidal ideation and behavior

[a]An AE was counted once for a given PMS case if the same AE occurred ≥ 1 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 the same case

[c]Cumulative post-marketing RR

[d]Search criteria defined in Supplementary Table I

[e]MedDRA high-level term (HLT)

[f]MedDRA preferred term (PT)

[g]Searched for any of the following MedDRA PTs: joint tuberculosis, latent tuberculosis, *Mycobacterium* tuberculosis complex test positive, pulmonary tuberculosis, tuberculin test positive, *Mycobacterium* test positive, tuberculosis

[h]Using the standardized MedDRA queries (SMQ) for anaphylactic reactions (narrow search), the following were identified: anaphylactic reaction (*N* = 123), anaphylactic shock (*N* = 37), anaphylactoid reaction (*N* = 6), circulatory collapse (*N* = 36), Shock (*N* = 19), shock symptom (*N* = 2), type I hypersensitivity (*N* = 19). Of the 239 cases, 27 were suspected

[i]SMQ for angioedema. Of the 3160 cases, 58 were already included in the SMQ search for anaphylactic reactions

[j]Major adverse cardiovascular events, defined as myocardial infarction, stroke, or cardiovascular death

[k]AE reported in ≥ 10% of the PMS cases received for the same safety topic

[l]Infection sites were not specified except for seven reports with systemic infections including *Staphylococcal* septic shock, *Staphylococcal* bacteremia (due to intravenous line infection), *Staphylococcal* endocarditis, and *Staphylococcal* osteomyelitis

[m]Most common MedDRA PTs: neoplasm malignant (*N* = 304), squamous cell carcinoma (*N* = 84), adenocarcinoma (*N* = 16)

[n]Most common MedDRA PTs: basal cell carcinoma (*N* = 167), skin cancer (*N* = 112), squamous cell carcinoma of skin (*N* = 53)

[o]Most common MedDRA PTs: breast cancer (*N* = 262), invasive ductal breast carcinoma (*N* = 30), breast cancer metastatic (*N* = 13)

Table 3 Summary of pooled clinical trial data describing reports of IBD history

History of IBD	Reported IBD as TEAE in pooled clinical trials		Total patients in pooled clinical trials
	Yes	No	
Yes	19 (24.4%)	59 (75.6%)	78[a]
No	53 (0.3%)	15,513 (99.7%)	15,566
Total	72 (0.5%)	15,572 (99.5%)	15,644

% values are based on row totals

IBD inflammatory bowel disease, *axSpA* axial spondyloarthritis, *PsA* psoriatic arthritis, *PsO* psoriasis, *TEAE* treatment-emergent adverse events

[a]*n* = 16 (0.17%) in PsO, *n* = 21 (0.54%) in PsA, *n* = 41 (1.86%) in axSpA, overall, 0.5% patients had a history of IBD

commonly reported with preexisting risk factors. In PMS, preexisting cardiovascular risks were observed in 613 of 1435 (43%) cases reporting MACE. In CTs, relevant medical histories included hypertension (33.6%), hyperlipidemia (18.4%) and diabetes mellitus (8.3%).

Suicidal ideation and behavior (SIB) were reported in PMS (RR 0.02/100 PY) and CTs (EAIR 0.08/100 PY) with death by suicide in 17 cases [15 in PMS (RR 0.001/100 PY), 2 in CTs (EAIR 0.01/100 PY)] (Table 2). Relevant medical history was identified in 75 of 234 PMS cases including depression, bipolar disorder, post-traumatic stress disorder (*n* = 45), suicidal ideation or behavior (*n* = 14), concomitant anti-depressive agents (*n* = 8), concurrent alcoholism (*n* = 2), and unspecified mental disorders (*n* = 6).

Dyshidrotic eczema (DE) and pyoderma gangrenosum (PG) were identified by Novartis as paradoxical skin reactions based on the well-documented post-marketing case reports. At data cutoff for this report, there were 74 PMS cases with DE (RR 0.006/100 PY) and 39 PMS cases with PG (RR 0.003/100 PY). In CTs, the EAIR for DE was 0.28 (95% CI 0.22, 0.34)/100 PY. By contrast, PG was reported in only one secukinumab-treated patient in CTs [EAIR 0 (95% CI 0.0, 0.02)/100 PY].

DISCUSSION

As secukinumab exposure has surpassed more than 1 million PY through PMS and CTs, it is important to understand whether the previously reported safety profile remains applicable. The presented AEs were retrieved from more extensive post-marketing exposure and a larger CT pool. A majority of these AEs were non-serious in both PMS and CTs. Additionally, although the HS pivotal studies were not available for pooling in this report, the separately published HS safety data did not reveal any new safety findings [2].

Infections were reported consistently in PMS and CTs with nasopharyngitis, pneumonia, and oral candidiasis as the most common infection, serious infection, and fungal infection, respectively. EAIR of *Candida* infections was similar between patients with and without diabetes. COVID-19-related mortality rate was 1.4%, comparable to the background COVID mortality rate (1.1%) in the USA [18]. No increased risk for COVID-19 infection was found. Infrequent but clinically significant fungal, herpes, mycobacterial or *Staphylococcus* infections remained rare and were reported with either limited or confounded information precluding valid inference. In a meta-analysis, the incidence of opportunistic infections was similar between secukinumab and ixekizumab but was lower than bimekizumab [19].

Hypersensitivity events after 2 weeks of exposure to secukinumab could not be induced by secukinumab unless they were non-IgE-mediated. In PMS, 70% of the cases with available onset dates occurred ≥ 2 weeks after initiating secukinumab. Non-IgE-mediated events (based on the reported event terms) were rare without evidence of association with secukinumab. Anaphylaxis remained rare.

Table 4 Summary of post-marketing data describing reports of malignancy

Malignancy types	All-cause mortality as reported			Total reports
	Non-fatal	Fatal		
		Cancer death	Non-cancer death	
Cases with NMSC	348	–	2	350
NMSC	337	–	2	339
NMSC + hematological	3	–	–	3
NMSC + skin melanoma	8	–	–	8
Skin melanoma	120	2	–	122
Skin melanoma + hematological	1	1	–	2
Hematological	233	10	3	246
Hematological + non-hematological	38	8	–	46
Non-hematological	1737	87	30	1854
Total	2477	108	35	2620

Treatment duration	< 6 months	≥ 6 to < 12 months	≥ 1 to < 2 years	≥ 2 to < 3 years	≥ 3 years	Unknown	Total reports
Time from the first dose to the reported onset of malignancies							
< 6 months	62	10	10[b]	13[b]	10[b]	28	133
≥ 6 to < 12 months	5	35	12	11	6	26	95
1–3 years	6	11	54	30	34	20	155
> 3 years	–	–	1	–	11	1	13
Unknown	172	110	179	127	100	1536	2224
Total	245[a]	166	256	181	161	1611	2620

PM post-marketing, *TTO* time elapsed since first secukinumab dose and onset of malignancy, *NMSC* nonmelanoma skin cancer, *PMS* post-marketing setting
[a]Malignancies in MedDRA high-level term reported in ≥ 5% of all 2620 PMS cases: skin neoplasms malignant and unspecified (excl melanoma) [*N* = 41, including basal cell carcinoma (*N* = 24)], breast and nipple neoplasms malignant (*N* = 25), neoplasms malignant site unspecified NEC [*N* = 24, including squamous cell carcinoma (*N* = 14)], respiratory tract and pleural neoplasms malignant cell type unspecified NEC (*N* = 18), prostatic neoplasms malignant (*N* = 12)
[b]Malignancies reported ≥ 6 months after being treated with secukinumab for ≤ 6 months

IBD was previously analyzed on the basis of 21 pooled CTs across 3 indications (PsO, PsA, and axSpA) through 25 June 2017, showing ulcerative colitis (EAIR up to 0.2/100 PY), Crohn's disease (EAIR up to 0.4/100 PY), and unspecified IBD (EAIR up to 0.1/100 PY). Of these patients with IBD, 30 were new-onset cases; 11 had IBD flares accounting for 23% of the total 48 patients with a history of IBD, i.e., 37 (77%) of the patients with a history of IBD did not experience IBD flare [11]. In the current analysis, as presented in Table 1, the EAIR for IBD were either similar to or lower than previously reported. Cumulative CT data continued to affirm that 76% of the patients with a history of IBD did not report IBD flares. Additionally, the EAIR of IBD for secukinumab is comparable to the IBD rates reported in the general PsO, PsA, and axSpA populations [20–22], although differences in data collection and analysis methodologies are noted between CTs and observational studies, which may preclude a direct comparison.

Other targeted safety monitoring included malignancy, HBV reactivation, MACE, and SIB. In PMS reporting, one-fourth of malignancy cases with reported onset dates (9% of all PMS malignancy cases) occurred within 6 months after initiating secukinumab, which could suggest that secukinumab was not a causative factor [23]. The malignancy EAIR in pooled CTs for secukinumab is comparable to the rates reported in other CTs of IL-17A inhibitors (ixekizumab and brodalumab) [24, 25]. Relevant risk factors were commonly present when reporting HBV reactivation, MACE, and SIB in PMS. Underlying cardiovascular or metabolic conditions were also common in CTs. HBV reactivation in one patient did not reoccur after resuming secukinumab treatment along with anti-viral prophylaxis, which is reflective of the importance of mitigating the risk of adverse outcomes.

Paradoxical skin reactions were proactively detected during PMS monitoring. As a paradoxical skin reaction, PG was only reported in one CT patient. Due to its rarity, incidence of PG may not be determined. Psoriasis is predominantly driven by T helper 17 (Th17) cells, while atopic dermatitis is largely driven by Th2 cells. When Th17 cells are inhibited, the balance may shift toward Th2 cells, resulting in an eczematous paradoxical reaction. Paradoxical psoriasiform and eczematous eruptions have been identified as the most common type of paradoxical reactions and have been previously associated with exposure to tumor necrosis factor-α inhibitors (91.2% of all cases), IL-17A/17R inhibitors (3.5%), IL-4R-α inhibitors (2.7%), IL-12/23 inhibitors (2.4%), and IL-23 inhibitors (0.01%) [26].

Limitations to PMS data include insufficient information, lack of adjustment for confounders, medically unconfirmed data sources, and duplicate reports. Lower PMS RR may result from the recent COVID-19 pandemic causing limited access to healthcare professionals and reduced AE reporting [27]. Additionally, PMS RR are not equivalent to EAIR in CTs, given differences in the reliability of reported cases (numerator) and the overall at-risk population (denominator). Despite these limitations, monitoring RR over years provides insights into safety profiles over time. PMS data also serve as an effective mechanism for ongoing safety monitoring and identification of new safety findings not observed in CTs, due to limited sample sizes, compared with post-marketing use.

CONCLUSION

PMS analyses with more than 1 million PY of exposure were consistent with the safety profile of secukinumab observed in an increasing number of pooled CTs in different dermatologic and rheumatologic populations. Additionally, routine PMS of cumulative patients treated with secukinumab have identified paradoxical skin reactions, which due to their nature and very low frequency do not alter the previously established benefit–risk balance of secukinumab.

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Data Availability. The datasets generated during and/or analyzed for the current analysis are not publicly available as the data were pooled from multiple clinical trials. Each of the clinical trials are listed in Supplementary Fig. 1. All the study results were disclosed in ClinicalTrials.gov. The post-marketing data were for regulatory reporting purposes and are not publicly available. The post-marketing AE reports were generated from the Novartis safety database, which are required for safety reporting to health authorities. These post-marketing data are not from a clinical trial or specific study setup. Rather, they are based on post-marketing spontaneous reports made to Novartis in the context of routine pharmacovigilance. This reporting comes from various regions/countries with their respective data privacy laws; therefore, these post-marketing data cannot be shared in a repository. In this manuscript, these post-marketing data were de-identified.

Declarations

Conflict of Interest. Mark Lebwohl is an employee of Mount Sinai and receives research funds from Abbvie, Amgen, Arcutis, Avotres, Boehringer Ingelheim, Cara therapeutics, Dermavant Sciences, Eli Lilly, Incyte, Inozyme, Janssen Research & Development, LLC, Ortho Dermatologics, Pfizer, Sanofi-Regeneron, and UCB, Inc., and is a consultant for Almirall, AltruBio Inc., Anaptys Bio, Apogee, Arcutis, Inc., AstraZeneca, Atomwise, Avotres Therapeutics, Brickell Biotech, Boehringer Ingelheim, Bristol Myers Squibb, Castle Biosciences, Celltrion, Corevitas, Dermavant Sciences, EPI, Evommune, Inc., Facilitation of International Dermatology Education, Forte biosciences, Foundation for Research and Education in Dermatology, Galderma, Genentech, Incyte, LEO Pharma, Meiji Seika Pharma, Mindera, Pfizer, Sanofi-Regeneron, Seanergy, Strata, Takeda, Trevi, and Verrica. Alice B Gottlieb has received research/educational grants from Anaptyps Bio, Highlights Therapeutics, Moonlake Immunotherapeutics AG, Janssen, Novartis, Bristol Myers Squibb, and UCB Pharma, (all paid to Mount Sinai School of Medicine); has received honoraria as an advisory board member and consultant for Amgen, Anaptyps Bio, Avotres Therapeutics, Boehringer Ingelheim, Bristol Myers Squibb, Dice Therapeutics, Eli Lilly, Highlights Therapeutics, Janssen, Novartis, Sanofi, UCB, and Xbiotech. Philip J Mease has received grant/research support from AbbVie,

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Ethical Approval. All AEs were assessed in accordance with Good Pharmacovigilance Practice Module VII and International Council for Harmonization (ICH) Guideline E2C. All CTs were conducted in compliance with the Declaration of Helsinki, ICH Guidelines for Good Clinical Practice, and local country regulations. The protocols for the clinical trials were reviewed and approved by ethical review committees and authorities for each clinical site; all patients provided written informed consent.

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