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ORIGINAL RESEARCH ARTICLE

Secukinumab in Pediatric Patients with Plaque Psoriasis: Pooled Safety Analysis from Two Phase 3 Randomized Clinical Trials

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Abstract

Background Plaque psoriasis affects ~ 1% of the pediatric population, negatively impacting quality of life. The efficacy and safety of secukinumab in pediatric patients with moderate to severe or severe chronic plaque psoriasis have been established in two pivotal phase 3 trials (open-label, NCT03668613; double-blind, NCT02471144).

Objectives The aims were to report the pooled safety of secukinumab up to 52 weeks from two studies in subgroups of pediatric patients stratified by age and bodyweight, and to present, alongside the pediatric data, the pooled safety data from four pivotal adult secukinumab trials.

Methods The safety of secukinumab was evaluated in subgroups of pediatric patients defined by age (6 to < 12 and 12 to < 18 years) and bodyweight (< 25 kg, 25 to < 50 kg, and ≥ 50 kg) in the pooled population. Patients received secukinumab low dose (LD; 75/75/150 mg), secukinumab high dose (HD; 75/150/300 mg), placebo, or etanercept (0.8 mg/kg). For safety analyses, data were pooled from the pediatric studies NCT03668613 and NCT02471144, and presented alongside the pooled data from four adult pivotal studies (NCT01365455, NCT01636687, NCT01358578, NCT01555125).

Results A total of 198 pediatric patients (overall exposure: 184.6 patient-years [PY]) and 1989 adult patients (1749.5 PY) receiving secukinumab up to week 52 were included in this analysis. At week 52, the incidence of adverse events (AEs) was lower in the lower age and bodyweight subgroups. The AEs reported within these subgroups were consistent with the overall AEs reported in this analysis. Overall, exposure-adjusted incidence rates for treatment-emergent AEs were lower in the secukinumab-treated pediatric pool (198.8/100 PY) compared with the etanercept (266.3/100 PY) and adult pools (256.1/100 PY). Up to 52 weeks, the incidence rates of the AEs in the secukinumab-treated patients in the 6 to < 12 years subgroup and 12 to < 18 years subgroup were 167.7/100 PY and 214.7/100 PY, respectively. Similarly, incidence rates of the AEs in the secukinumab-treated patients in the < 25 kg, 25 kg to < 50 kg, and ≥ 50 kg subgroups were 177.3/100 PY, 192.5/100 PY, and 206.8/100 PY, respectively. Nasopharyngitis was the most frequently reported AE in secukinumab-treated pediatric patients across age (< 12 years: 11.8/100 PY; ≥ 12 years: 42.4/100 PY) and bodyweight (< 25 kg: 22.8/100 PY; 25 kg to < 50 kg: 19.0/100 PY; ≥ 50 kg: 43.0/100 PY). Of the 198 secukinumab-treated pediatric patients, one reported nail *Candida*, one reported skin *Candida*, and two reported vulvovaginal *Candida*. Transient and mostly mild events of neutropenia were observed with secukinumab, none leading to study treatment discontinuation. No incidence of treatment-emergent anti-drug antibodies was reported in pediatric patients treated with secukinumab.

Conclusions Secukinumab was well tolerated in pediatric patients with moderate to severe and severe plaque psoriasis across age and bodyweight subgroups. The overall safety profile of secukinumab in pediatric patients was consistent with that of adult patients.

ClinicalTrials.gov Identifier NCT03668613 (Novartis Study Code CAIN457A2311, referred to as A2311), actual study start date: August 29, 2018; actual primary completion date: September 19, 2019; estimated study completion date: September 14, 2023. NCT02471144 (Novartis Study Code CAIN457A2310, referred to as A2310), study start date: September 29, 2015; primary completion date: December 13, 2018; estimated study completion date: March 31, 2023.

Extended author information available on the last page of the article

Key Points

Secukinumab showed a favorable safety profile across age and bodyweight subgroups of pediatric patients with moderate to severe or severe chronic plaque psoriasis up to week 52.

The safety of secukinumab was comparable with that of placebo, with no major differences in the adverse event profile between the low-dose and high-dose secukinumab groups.

No new or unexpected safety signals were reported in the pediatric population treated with secukinumab, and the proportion of patients with infections was similar between age and bodyweight subgroups. The overall safety profile of secukinumab-treated pediatric patients was consistent with its known profile in the adult population.

1 Introduction

Plaque psoriasis, a chronic, systemic inflammatory condition marked by red, scaly patches of the skin, affects approximately 1% of the pediatric population (children and adolescents) [1]. The prevalence of pediatric psoriasis varies depending on the demography investigated, ranging from 0.13% in the United States (US) to 2.1% in Europe [1–5]. Psoriasis in the pediatric population is likely to have been underestimated owing to misdiagnosis or failure to seek medical attention for mild disease, racial disparities in prevalence, and lack of access to health care facilities [1].

Psoriasis impairs quality of life (QoL) and puts an additional psychological burden on pediatric patients during their formative years, affecting their mental health for the rest of their lives [6]. Early diagnosis and treatment is, therefore, essential in improving their QoL and psychological well-being [7]. Pediatric psoriasis also has a significant unmet need owing to delays in diagnosis and therapy initiation and the availability of a limited number of approved systemic therapies [8]. A retrospective study reported the effectiveness and safety of anti-tumor necrosis factor alpha and anti-interleukin-12/23 (anti-IL-12/23) agents in pediatric patients under 12 years of age [9]. Despite this, there are limited data available on the safety of approved pediatric treatments. Moreover, there is a lack of consistent worldwide treatment recommendations for pediatric patients with moderate to severe psoriasis [7, 10, 11].

Secukinumab, a fully human monoclonal antibody that neutralizes IL-17A, demonstrated sustained long-term efficacy and a favorable safety profile in the adult population and has been approved for the treatment of adults with moderate to severe plaque psoriasis [12, 13]. Recently, secukinumab has also been approved as a first-line treatment of children and adolescents aged ≥ 6 years with moderate to severe plaque psoriasis [14, 15]. In two studies, secukinumab was found to be efficacious and well tolerated in pediatric patients with moderate to severe [16, 17] and severe [18] chronic plaque psoriasis. However, an assessment of safety data from the larger pool of pediatric patients with plaque psoriasis across the two studies and across different age and bodyweight subgroups has not yet been reported.

In the current analysis, we report the pooled safety data from the aforementioned phase 3 trials to assess the safety profile of secukinumab in pediatric patients with moderate to severe (ClinicalTrials.gov: NCT03668613; Novartis Study Code CAIN457A2311, hereafter referred to as A2311 [16, 17]) and severe (ClinicalTrials.gov: NCT02471144; Novartis Study Code CAIN457A2310, hereafter referred to as A2310 [18]) chronic plaque psoriasis. Data from four pivotal adult trials (ClinicalTrials.gov: NCT01365455 [19], NCT01636687 [20], NCT01358578 [21], NCT01555125 [22]) were also collated and compared with the findings of the pooled pediatric safety dataset to assess the similarities and differences between pediatric and adult patients.

2 Methods

2.1 Study Design and Patients

A2311 is a phase 3, multicenter, randomized, open-label study with historical placebo control. It included patients aged 6 to < 18 years with moderate to severe chronic plaque psoriasis randomized 1:1 to receive either secukinumab low dose (LD) or secukinumab high dose (HD). Patients were stratified by bodyweight and disease severity (moderate or severe) at randomization. Patients received the appropriate secukinumab dose according to their bodyweight category. The details of the methodology of study A2311 are published elsewhere [16, 17].

A2310 is a phase 3, multicenter, randomized, double-blind, placebo- and active-controlled (etanercept) study. Patients with severe chronic plaque psoriasis, aged 6 to < 18 years were randomized 1:1:1:1 to receive secukinumab LD, secukinumab HD, placebo, or etanercept (0.8 mg/kg). Patients were stratified by age and bodyweight at randomization. The details of the methodology of study A2310 are published elsewhere [18].

Moderate to severe plaque psoriasis was defined as a Psoriasis Area and Severity Index (PASI) score of ≥ 12, an Investigator's Global Assessment modified 2011 (IGA mod

2011) score of ≥ 3, and body surface area (BSA) involvement of ≥ 10% at randomization; severe plaque psoriasis was defined as a PASI score of ≥ 20, an IGA mod 2011 score of 4, and BSA involvement of ≥ 10% at randomization.

Patients in both studies weighing < 25 kg received 75 mg secukinumab in both LD and HD groups, those weighing 25–50 kg received 75 mg (LD group) or 150 mg (HD group), and patients weighing ≥ 50 kg received 150 mg (LD group) or 300 mg (HD group). The inclusion and exclusion criteria for both studies have been described previously [16–18].

2.2 Objectives and Outcomes

In the current analysis, the safety of secukinumab was assessed in subgroups of pediatric patients stratified by age (6 to < 12 and 12 to < 18 years) and bodyweight (< 25 kg, 25 to < 50 kg, and ≥ 50 kg) after pooling the data from the two pivotal phase 3 trials to evaluate secukinumab in pediatric patients with plaque psoriasis (NCT03668613 and NCT02471144, Table 1) [16–18]. The safety findings from the pooled pediatric dataset were compared with the findings from an adult safety dataset of four pivotal studies of secukinumab in chronic plaque psoriasis, which included 150 mg and 300 mg treatment arms [19–22].

Safety outcomes assessed were adverse events (AEs), serious AEs (SAEs), most frequent AEs by system organ class (SOC), most frequent AEs by preferred term (PT), AEs leading to treatment discontinuation, and AEs of special interest. Safety assessments also included absolute neutrophil count and injection-site reactions (ISRs). Absolute neutrophil count was defined by Common Terminology Criteria for Adverse Events (CTCAE) grades. ISRs corresponded to AEs coded with the High-Level Term (HLT) "Injection-site reaction" and some with the HLT "Administration-site reaction" or "Application- and instillation-site reactions."

Upper respiratory tract infections (URTIs) constituted a common PT AE and the most common HLT under the "Infections and infestations" SOC in the current analysis. This warranted a more thorough investigation into URTIs, which were therefore analyzed in addition by a broader Customized Medical Dictionary for Regulatory Activities (MedDRA) Query (CMQ). This included all PTs corresponding to the HLT "URTI," PT "viral URTI," PT "pharyngitis bacterial," PT "tonsillitis bacterial," PT "viral pharyngitis," PT "pharyngitis streptococcal," and PT "sinusitis bacterial."

Table 1 Total number of patients in each subgroup

Variable	Subgroups	A2311 study		A2310 study	
		LD	HD	LD	HD
Age	< 12 years	17	16	8	9
	≥ 12 years	25	26	32	31
Bodyweight	< 25 kg	8		5	
	25 to < 50 kg	13	12	17	15
	≥ 50 kg	25	26	22	21

Patients < 25 kg received 75 mg in both secukinumab dose groups

HD high dose, *LD* low dose

2.3 Statistical Analyses

All safety assessments were analyzed using the safety set, which included patients who took at least one dose of study drug during the treatment period. The pooled pediatric safety data were analyzed by age and bodyweight subgroups at weeks 12 and 52. For safety assessments up to week 12 (placebo-controlled period), data from all patients until their week 12 or early discontinuation visit were included. For safety assessments up to week 52, data from all patients until their week 52 or early discontinuation visit were included (placebo was not included beyond week 12). Patients who switched to secukinumab from placebo in the A2310 study were included in the week 52 analysis. AEs were grouped by primary SOC and PT according to MedDRA version 23.0. AEs are presented as absolute and relative frequencies (i.e., absolute incidence) for the induction period. For safety analysis up to 52 weeks, exposure-adjusted incidence rates (EAIRs) for AEs were expressed as incidence rate (IR) per 100 patient-years (PY) of exposure.

3 Results

3.1 Demographic and Baseline Disease Characteristics

In the pediatric pool, the demographic and baseline characteristics were comparable in the two secukinumab treatment groups (Table 2). The average age of secukinumab-treated patients in the pediatric and adult pools was 13 and 45 years, respectively. The details of overall demographic and baseline disease characteristics are presented in Table S1 (see the electronic supplementary material). Both pediatric and adult populations were predominantly Caucasians. Approximately 60% and 30% of patients were female in the pediatric and adult pools, respectively. The average bodyweight of patients in the pediatric group was 54 kg, while adults weighed an average of 87 kg. In the pediatric pool, patients in the etanercept and placebo groups had severe plaque psoriasis because they participated in the A2310 study, which enrolled patients with only severe plaque psoriasis [18] (Table 2).

At baseline, the mean PASI scores and the mean total BSA in the "Any secukinumab," placebo, and etanercept groups were 23.2 and 34.3, 28.0 and 39.0, and 28.4 and 43.1, respectively. Among the secukinumab-treated patients, a

Table 2 Demographic and baseline disease characteristics in the pediatric pool (randomized set)

Characteristics	SEC LD *N* = 82	SEC HD *N* = 82	Any SEC *N* = 164	PBO *N* = 41	ETN *N* = 41
Age, years, mean ± SD	13.1 ± 3.22	13.0 ± 3.31	13.0 ± 3.25	13.7 ± 3.27	13.5 ± 2.94
6–12 years, *n* (%)	25 (30.5)	25 (30.5)	50 (30.5)	10 (24.4)	10 (24.4)
12–18 years, *n* (%)	57 (69.5)	57 (69.5)	114 (69.5)	31 (75.6)	31 (75.6)
Female, *n* (%)	47 (57.3)	48 (58.5)	95 (57.9)	22 (53.7)	25 (61.0)
Bodyweight, kg, mean ± SD	53.5 ± 17.59	54.7 ± 19.62	54.1 ± 18.58	55.7 ± 22.28	52.0 ± 19.43
< 25 kg, *n* (%)	6 (7.3)	7 (8.5)	13 (7.9)	3 (7.3)	4 (9.8)
25 to < 50 kg, *n* (%)	30 (36.6)	27 (32.9)	57 (34.8)	17 (41.5)	16 (39.0)
≥ 50 kg, *n* (%)	46 (56.1)	48 (58.5)	94 (57.3)	21 (51.2)	21 (51.2)
Caucasian, *n* (%)	73 (89.0)	72 (87.8)	145 (88.4)	36 (87.8)	30 (73.2)
BMI (kg/m^2), mean ± SD	21.0 ± 4.50	21.7 ± 4.42	21.3 ± 4.46	22.2 ± 6.20	21.0 ± 4.80
Baseline PASI score, mean ± SD	22.9 ± 7.60	23.5 ± 8.85	23.2 ± 8.22	28.0 ± 8.09	28.4 ± 9.06
PASI score ≤ 20, *n* (%)	27 (32.9)	25 (30.5)	52 (31.7)	0 (0.0)	0 (0.0)
PASI score > 20, *n* (%)	55 (67.1)	57 (69.5)	112 (68.3)	41 (100.0)	41 (100.0)
Baseline total BSA, mean ± SD	33.4 ± 13.18	35.2 ± 17.77	34.3 ± 15.62	39.0 ± 17.6	43.1 ± 19.56
Baseline IGA mod 2011 score, *n* (%)					
3 (moderate disease)	29 (35.4)	30 (36.6)	59 (36.0)	0 (0.0)	0 (0.0)
4 (severe disease)	53 (64.6)	52 (63.4)	105 (64.0)	41 (100.0)	41 (100.0)
Severity of psoriasis[a], *n* (%)					
Moderate	30 (36.6)	34 (41.5)	64 (39.0)	0 (0.0)	0 (0.0)
Severe	52 (63.4)	48 (58.5)	100 (61.0)	41 (100.0)	41 (100.0)
Time since first diagnosis of plaque-type psoriasis, years, mean ± SD	4.4 ± 3.98	4.7 ± 4.27	4.5 ± 4.12	6.0 ± 5.09	4.6 ± 3.73
Previous biologic psoriasis therapy, *n* (%)	9 (11.0)	6 (7.3)	15 (9.1)	0 (0.0)	1 (2.4)
Previous systemic psoriasis therapy, *n* (%)	43 (52.4)	39 (47.6)	82 (50.0)	20 (48.8)	19 (46.3)
Psoriatic arthritis history, *n* (%)	6 (7.3)	3 (3.7)	9 (5.5)	3 (7.3)	3 (7.3)
Obesity history, *n* (%)	3 (3.7)	3 (3.7)	6 (3.7)	1 (2.4)	1 (2.4)

BMI body mass index, *BSA* body surface area, *ETN* etanercept, *HD* high dose, *IGA mod 2011* Investigator's Global Assessment modified 2011, *LD* low dose, *N* total number of patients, *n* number of patients, *PASI* Psoriasis Area and Severity Index, *PBO* placebo, *SD* standard deviation, *SEC* secukinumab

[a]Disease severity strata: moderate = PASI score 12–20 and IGA mod 2011 score 3/4 or PASI score ≥ 20 and IGA mod 2011 score 3 and BSA involvement of ≥ 10 %; severe = PASI score ≥ 20 and IGA mod 2011 score 4 and BSA involvement of ≥ 10 %

majority (61%) had severe plaque psoriasis at baseline. Psoriatic arthritis and obesity were the most common comorbidities in the pediatric pool, accounting for 5.5% and 3.7% in the "Any secukinumab" group, respectively (Table 2).

3.2 Overall Safety Findings

A total of 164 pediatric patients (overall exposure of 37.8 PY) and 1382 adult patients (314.4 PY) in the secukinumab group, 41 pediatric patients (9.7 PY) and 323 adult patients (73.0 PY) in the etanercept group, and 41 pediatric patients (9.5 PY) in the placebo group up to week 12 were included (Table S2; see the electronic supplementary material). Analyses up to week 52 included 198 pediatric patients (overall exposure of 184.6 PY) and 1989 adult patients (1749.5 PY) in the secukinumab group, and 41 pediatric patients (38.0 PY) and 323 adult patients (296.5 PY) in the etanercept group (Table S3). The median (min–max) duration of exposure to "Any secukinumab" dose was 84 (9–126) days in the pediatric pool and 84 (1–141) days in the adult pool up to week 12. The corresponding values up to week 52 were 364 (9–421) days in the pediatric pool and 363 (1–421) days in the adult pool. More detailed data on age and bodyweight at week 12 can be found in the electronic supplementary material (Tables S4, i and ii).

The EAIRs for treatment-emergent AEs (TEAEs) were lower in the secukinumab-treated pediatric pool compared with all other groups ("Any secukinumab" group in the pediatric pool: 198.8/100 PY; etanercept group in the pediatric pool: 266.3/100 PY; "Any secukinumab" group in the adult pool: 256.1/100 PY; etanercept group in the adult pool: 248.0/100 PY). The EAIR for TEAEs leading to study treatment discontinuation was 2.7/100 PY

for the "Any secukinumab" group in the pediatric pool compared with 3.5/100 PY in the adult pool. The corresponding values were 2.7/100 PY and 4.1/100 PY for the etanercept groups in the pediatric and adult pools, respectively (Table 3). "Infections and infestations" was the most commonly affected SOC in all groups, and was lower in the "Any secukinumab" group (108.8/100 PY; LD: 107.2/100 PY; HD: 110.6/100 PY) than the etanercept group (125.8/100 PY) in the pediatric pool, but higher in the "Any secukinumab" dose group (101.3/100 PY; LD: 98.1/100 PY; HD: 104.5/100 PY) than the etanercept group (92.0/100 PY) in the adult pool (Table 3). The EAIR of SAEs in "Any secukinumab"-treated pediatric patients was 7.3/100 PY, which was lower than for pediatric patients treated with etanercept (14.5/100 PY), which is similar to that for the "Any secukinumab"-treated adult pool (7.5/100 PY) and higher than that for etanercept-treated adults (6.9/100 PY, Table 3).

The most frequently reported PT was nasopharyngitis followed by headache in all groups. The EAIRs of URTIs (CMQ) were higher in pediatric patients versus adults (65.5 vs 52.8/100 PY) in the "Any secukinumab" group, and in pediatric patients versus adults in the etanercept group (72.0 vs 52.0/100 PY). The EAIRs for hypersensitivity (Standardized MedDRA Query [SMQ]) were 11.0/100 PY in the "Any secukinumab" group (8.0/100 PY in the LD group and 14.2/100 PY in the HD group) and 14.5/100 PY in the etanercept group in the pediatric pool, and 11.5/100 PY and 11.2/100 PY in the "Any secukinumab" and etanercept groups in the adult pool, respectively (Table 3). Details regarding EAIRs for treatment-emergent SAEs are further described in Table S6.

Grade 4 neutropenia was not reported in any pediatric patient. One secukinumab-treated pediatric patient presented with a case of CTCAE grade 3 neutropenia (< 1.0–0.5 × 10^9/L), which resolved spontaneously without intervention. The EAIRs for neutropenia (Novartis customized MedDRA Query [NMQ]) in the pediatric pool were 4.5/100 PY in the "Any secukinumab" group (5.6/100 PY in the LD group, 3.3/100 PY in the HD group) and 2.7/100 PY in the etanercept group. No serious infections were associated with cases of neutropenia. The neutropenia events observed with secukinumab were generally mild and transient, and did not lead to study treatment discontinuation. In the adult pool, the EAIR was 1.3/100 PY each for "Any secukinumab," secukinumab LD, and secukinumab HD groups, and 1.7/100 PY in the etanercept group (Table 3).

The EAIR for *Candida* infections (HLT) was 2.2/100 PY in the pediatric pool compared with 3.2/100 PY in the adult pool for secukinumab-treated patients. Of the 198 pediatric patients who received secukinumab, one patient reported nail *Candida*, one reported skin *Candida,* and two reported vulvovaginal *Candida* (one patient two episodes) (Table 3). The vulvovaginal and skin *Candida* AEs were mild and did not lead to study treatment discontinuation or interruption. The AE of nail *Candida* was recorded from the day of randomization and was ongoing at time of reporting cut-off; it is of mild intensity with no suspected relationship to study treatment and has been treated intermittently with amorolfine hydrochloride.

The EAIRs for suicidal ideation in the pediatric pool were 0.5/100 PY in the "Any secukinumab" group and 0.0/100 PY in the etanercept group (Table 3).

The EAIRs for inflammatory bowel disease (IBD) (NMQ) in the pediatric pool were 0.5/100 PY in the "Any secukinumab" group and 0.0/100 PY in the etanercept group. In the adult pool, it was 0.4/100 PY in the "Any secukinumab" group and 0.3/100 PY in the etanercept group.

The EAIRs for ISRs in the "Any secukinumab" groups were higher in the pediatric pool (4.5/100 PY) than in the adult pool (1.7/100 PY), but lower than in the etanercept groups (11.5/100 PY in the pediatric pool and 13.0/100 PY in the adult pool). All ISRs in the pediatric pool were mild in severity; most required no treatment (Table 3).

No treatment-emergent anti-drug antibodies were detected in any patient from the secukinumab pediatric treatment groups.

3.3 Safety: Subgroup Analysis of the Pediatric Pool by Age and Bodyweight

Overall, at both weeks 12 and 52, the proportions of patients with infections were similar between the two pediatric age subgroups and the three pediatric bodyweight subgroups (see supplementary appendix for data up to week 12).

3.3.1 Safety Analysis by Age Subgroup in the Pediatric Pool

Up to 52 weeks, the IR of AEs was 167.7/100 PY in the secukinumab-treated patients in the < 12-year subgroup, which was lower than for the etanercept group (212.0/100 PY) and was also lower than the overall IR of AEs in the ≥ 12-year subgroup treated with secukinumab (214.7/100 PY). The EAIR of AEs under the SOC "Infections and infestations" in secukinumab-treated patients was lower in the < 12-year subgroup than in the ≥ 12-year subgroup (88.3/100 PY and 119.0/100 PY, respectively); comparable results were observed with etanercept (82.4/100 PY and 142.9/100 PY, respectively) (Table 4). The most commonly reported AE (by PT) in the < 12-year and ≥ 12-year subgroups was nasopharyngitis in the "Any secukinumab" group (EAIRs: 11.8/100 PY and 42.4/100 PY, respectively) (Table 4). The EAIRs of neutropenia (NMQ, narrow) in the < 12-year and ≥ 12-year groups were 9.8/100 PY and 2.4/100 PY for groups of the pediatric population who received "Any secukinumab," respectively (Table 4).

Table 3 EAIRs for AEs in the pediatric and adult population: Up to week 52 (safety set)

	Pediatric population: EAIR/100 patient-years (95% CI)				Adult population: EAIR/100 patient-years (95% CI)			
	Any SEC LD $N = 98$	Any SEC HD $N = 100$	Any SEC $N = 198$	ETN $N = 41$	Any SEC 150 mg $N = 999$	Any SEC 300 mg $N = 990$	Any SEC $N = 1989$	ETN $N = 323$
Total AEs	190.5 (149.3, 239.5)	207.7 (163.1, 260.8)	198.8 (167.9, 233.6)	266.3 (184.4, 372.2)	255.5 (238.1, 273.9)	256.6 (239.2, 274.9)	256.1 (243.7, 268.9)	248.0 (218.5, 280.4)
SAEs	7.8 (3.1, 16.1)	6.7 (2.5, 14.6)	7.3 (3.9, 12.4)	14.5 (4.7, 33.9)	7.5 (5.8, 9.6)	7.5 (5.8, 9.6)	7.5 (6.3, 9.0)	6.9 (4.2, 10.7)
Discontinued study treatment due to any AE	2.2 (0.3, 7.8)	3.3 (0.7, 9.6)	2.7 (0.9, 6.4)	2.7 (0.1, 14.8)	3.6 (2.4, 5.1)	3.4 (2.3, 4.9)	3.5 (2.7, 4.5)	4.1 (2.1, 7.1)
Most frequent AEs (by SOC)[a]								
Infections and infestation	107.2 (81.4, 138.5)	110.6 (83.8, 143.3)	108.8 (89.9, 130.6)	125.8 (82.9, 183.0)	98.1 (90.0, 106.8)	104.5 (96.1, 113.5)	101.3 (95.4, 107.5)	92.0 (78.7, 106.8)
Skin and subcutaneous tissue disorders	29.5 (18.7, 44.2)	26.2 (16.2, 40.1)	27.8 (20.2, 37.3)	30.0 (14.4, 55.1)	26.7 (23.2, 30.7)	28.9 (25.2, 33.1)	27.8 (25.2, 30.6)	24.3 (18.6, 31.1)
Gastrointestinal disorders	22.2 (13.2, 35.1)	32.9 (21.3, 48.6)	27.4 (19.8, 36.9)	49.6 (27.1, 83.2)	28.7 (25.0, 32.8)	28.7 (25.0, 32.9)	28.7 (26.1, 31.6)	26.9 (20.9, 34.1)
General disorders and administration-site conditions	15.5 (8.3, 26.6)	18.7 (10.4, 30.8)	17.1 (11.3, 24.7)	25.1 (10.8, 49.4)	15.4 (12.8, 18.4)	16.5 (13.8, 19.6)	16.0 (14.1, 18.0)	33.0 (26.1, 41.1)
Respiratory, thoracic, and mediastinal disorders	11.5 (5.5, 21.2)	19.1 (10.9, 31.1)	15.3 (10.0, 22.4)	11.1 (3.0, 28.4)	15.0 (12.5, 18.0)	21.5 (18.4, 25.0)	18.2 (16.2, 20.5)	12.7 (8.9, 17.7)
Most frequent AEs (by PT)[a]								
Nasopharyngitis	29.6 (18.8, 44.5)	34.8 (22.8, 51.0)	32.2 (23.8, 42.5)	33.3 (16.6, 59.6)	29.2 (25.4, 33.3)	30.0 (26.2, 34.2)	29.6 (26.9, 32.5)	36.0 (28.8, 44.4)
Headache	11.4 (5.5, 21.0)	11.6 (5.6, 21.4)	11.5 (7.0, 17.8)	11.2 (3.0, 28.6)	10.3 (8.2, 12.7)	12.6 (10.3, 15.3)	11.5 (9.9, 13.2)	15.0 (10.7, 20.4)
Pharyngitis	9.0 (3.9, 17.7)	8.1 (3.3, 16.7)	8.6 (4.8, 14.1)	8.2 (1.7, 24.0)	2.8 (1.8, 4.2)	2.9 (1.9, 4.3)	2.8 (2.1, 3.8)	2.0 (0.8, 4.5)
URTI	6.7 (2.5, 14.6)	5.6 (1.8, 13.1)	6.2 (3.1, 11.0)	8.4 (1.7, 24.7)	9.9 (7.9, 12.3)	8.3 (6.5, 10.5)	9.1 (7.7, 10.7)	6.3 (3.7, 9.9)
Acne	9.1 (3.9, 17.9)	3.3 (0.7, 9.7)	6.2 (3.1, 11.0)	0.0 (0.0, 9.7)	0.5 (0.1, 1.2)	1.1 (0.6, 2.1)	0.8 (0.4, 1.3)	1.0 (0.2, 3.0)
Diarrhea	4.5 (1.2, 11.4)	7.9 (3.2, 16.3)	6.2 (3.1, 11.1)	2.7 (0.1, 15.0)	6.5 (4.9, 8.5)	7.6 (5.8, 9.7)	7.1 (5.8, 8.4)	7.8 (4.9, 11.8)
AEs of special interest[a]								
Hypersensitivity (SMQ) (narrow)	8.0 (3.2, 16.4)	14.2 (7.3, 24.8)	11.0 (6.6, 17.2)	14.5 (4.7, 33.9)	11.2 (9.0, 13.8)	11.8 (9.6, 14.4)	11.5 (9.9, 13.3)	11.2 (7.6, 15.9)
Neutropenia (NMQ) (narrow)	5.6 (1.8, 13.2)	3.3 (0.7, 9.7)	4.5 (1.9, 8.8)	2.7 (0.1, 14.9)	1.3 (0.6, 2.3)	1.3 (0.6, 2.3)	1.3 (0.8, 1.9)	1.7 (0.6, 4.0)
Neutropenia (PT)	4.5 (1.2, 11.4)	2.2 (0.3, 7.9)	3.3 (1.2, 7.2)	2.7 (0.1, 14.9)	0.7 (0.3, 1.5)	0.7 (0.3, 1.5)	0.7 (0.4, 1.2)	1.4 (0.4, 3.5)
Candida infections (HLT)	2.2 (0.3, 7.9)	2.2 (0.3, 8.0)	2.2 (0.6, 5.6)	0.0 (0.0, 9.7)	2.2 (1.3, 3.4)	4.2 (2.9, 5.8)	3.2 (2.4, 4.2)	1.4 (0.4, 3.5)

Table 3 (continued)

	Pediatric population: EAIR/100 patient-years (95% CI)				Adult population: EAIR/100 patient-years (95% CI)			
	Any SEC LD *N* = 98	Any SEC HD *N* = 100	Any SEC *N* = 198	ETN *N* = 41	Any SEC 150 mg *N* = 999	Any SEC 300 mg *N* = 990	Any SEC *N* = 1989	ETN *N* = 323
Vulvovaginal candidiasis (PT)	1.1 (0.0, 6.1)	1.1 (0.0, 6.1)	1.1 (0.1, 3.9)	0.0 (0.0, 9.7)	0.6 (0.2, 1.3)	0.8 (0.3, 1.7)	0.7 (0.4, 1.2)	0.0 (0.0, 1.2)
Nail *Candida* (PT)	0.0 (0.0, 4.0)	1.1 (0.0, 6.1)	0.5 (0.0, 3.0)	0.0 (0.0, 9.7)	0.0 (0.0, 0.4)	0.0 (0.0, 0.4)	0.0 (0.0, 0.2)	0.0 (0.0, 1.2)
Skin *Candida* (PT)	1.1 (0.0, 6.0)	0.0 (0.0, 4.0)	0.5 (0.0, 3.0)	0.0 (0.0, 9.7)	0.5 (0.1, 1.2)	0.2 (0.0, 0.8)	0.3 (0.1, 0.7)	0.7 (0.1, 2.4)
Suicide/self-injury (SMQ)	2.2 (0.3, 7.8)	0.0 (0.0, 4.0)	1.1 (0.1, 3.9)	0.0 (0.0, 9.7)	0.2 (0.0, 0.8)	0.0 (0.0, 0.4)	0.1 (0.0, 0.4)	0.0 (0.0, 1.2)
Intentional self-injury (PT)	1.1 (0.0, 6.0)	0.0 (0.0, 4.0)	0.5 (0.0, 3.0)	0.0 (0.0, 9.7)	0.0 (0.0, 0.4)	0.0 (0.0, 0.4)	0.0 (0.0, 0.2)	0.0 (0.0, 1.2)
Suicidal ideation (PT)	1.1 (0.0, 6.0)	0.0 (0.0, 4.0)	0.5 (0.0, 3.0)	0.0 (0.0, 9.7)	0.0 (0.0, 0.4)	0.0 (0.0, 0.4)	0.0 (0.0, 0.2)	0.0 (0.0, 1.2)
Suicide attempt (PT)	0.0 (0.0, 4.0)	0.0 (0.0, 4.0)	0.0 (0.0, 2.0)	0.0 (0.0, 9.7)	0.1 (0.0, 0.6)	0.0 (0.0, 0.4)	0.1 (0.0, 0.3)	0.0 (0.0, 1.2)
IBD[b] (NMQ) (narrow)	0.0 (0.0, 4.0)	1.1 (0.0, 6.1)	0.5 (0.0, 3.0)	0.0 (0.0, 9.7)	0.3 (0.1, 1.0)	0.5 (0.1, 1.2)	0.4 (0.2, 0.8)	0.3 (0.0, 1.9)
MACE (MI, Stroke, CV death) (NMQ)	0.0 (0.0, 4.0)	0.0 (0.0, 4.0)	0.0 (0.0, 2.0)	0.0 (0.0, 9.7)	0.7 (0.3, 1.5)	0.5 (0.1, 1.2)	0.6 (0.3, 1.1)	0.3 (0.0, 1.9)
Malignant or unspecified tumors (SMQ)	0.0 (0.0, 4.0)	0.0 (0.0, 4.0)	(0.0 (0.0, 2.0)	0.0 (0.0, 9.7)	1.1 (0.6, 2.1)	0.8 (0.3, 1.7)	1.0 (0.6, 1.6)	0.7 (0.1, 2.4)
ISRs[c]	4.5 (1.2, 11.5)	4.4 (1.2, 11.4)	4.5 (1.9, 8.8)	11.5 (3.1, 29.4)	1.6 (0.9, 2.7)	1.8 (1.1, 3.0)	1.7 (1.2, 2.5)	13.0 (9.1, 18.1)

"Any SEC" for both the treatment groups (LD and HD) includes all patients treated with SEC from the start of the study and those who switched from PBO to SEC at week 12

AE adverse event, *CI* confidence interval, *CV* cardiovascular, *EAIR* exposure-adjusted incidence rate (per 100 patient-years), *ETN* etanercept, *HD* high dose, *HLT* High-Level Term, *IBD* inflammatory bowel disease, *ISR* injection-site reaction, *LD* low dose, *MACE* major adverse cardiovascular event, *MedDRA* Medical Dictionary for Regulatory Activities, *MI* myocardial infarction, *N* total number of patients, *NMQ* Novartis customized MedDRA Query, *PBO* placebo, *PT* preferred term, *SAE* serious AE, *SEC* secukinumab, *SMQ* Standardized MedDRA Query, *SOC* system organ class, *URTI* upper respiratory tract infection

[a]AEs ordered according to the incidence in "Any SEC" group in pediatric population

[b]One patient reported a mild AE of hemorrhagic diarrhea, which was resolved and confirmed not to be IBD

[c]ISRs corresponding to event coded with HLT "Injection-site reaction" and some with HLT "Administration-site reaction" or "Application- and instillation-site reactions"

3.3.2 Safety Analysis by Bodyweight Subgroup in the Pediatric Pool

The EAIR of the most commonly affected SOC of "Infection and infestations" in "Any secukinumab"-treated patients in the < 25 kg, 25 to < 50 kg, and ≥ 50 kg subgroups were 79.3/100 PY, 95.3/100 PY, and 124.4/100 PY, respectively (Table 5, i, ii, and iii). The most commonly reported AE (by PT) in < 25 kg, 25 to < 50 kg, and ≥ 50 kg subgroups was nasopharyngitis in the "Any secukinumab" group (EAIRs: 22.8/100 PY, 19.0/100 PY, and 43.0/100 PY, respectively) (Table 5, i, ii, and iii). The

Table 4 EAIRs for AEs in the pediatric population by age strata: Up to week 52 (safety set)

(i) Age group: <12 years	EAIR/100 patient-years (95% CI)			
	SEC LD *N* = 30	SEC HD *N* = 28	Any SEC *N* = 58	ETN *N* = 10
Total AEs	152.8 (94.6, 233.6)	185.7 (115.0, 283.9)	167.7 (120.8, 226.6)	212.0 (85.2, 436.8)
SAEs	3.5 (0.1, 19.5)	12.2 (2.5, 35.7)	7.5 (2.1, 19.3)	11.6 (0.3, 64.5)
Treatment discontinuation due to AEs	0.0 (0.0, 12.8)	7.9 (1.0, 28.4)	3.7 (0.4, 13.3)	0.0 (0.0, 38.9)
Top five most frequent AEs (by SOC)[a]				
Infections and infestations	63.9 (34.1, 109.4)	121.9 (72.3, 192.7)	88.3 (60.0, 125.4)	82.4 (26.8, 192.4)
Gastrointestinal disorders	20.1 (6.5, 46.9)	22.6 (7.3, 52.8)	21.3 (10.2, 39.2)	26.2 (3.2, 94.6)
Skin and subcutaneous tissue disorders	19.3 (6.3, 45.0)	16.2 (4.4, 41.4)	17.8 (8.1, 33.7)	24.8 (3.0, 89.5)
Blood and lymphatic system disorders	11.2 (2.3, 32.8)	17.5 (4.8, 44.7)	14.1 (5.7, 29.1)	0.0 (0.0, 38.9)
Respiratory, thoracic, and mediastinal disorders	7.3 (0.9, 26.3)	17.1 (4.7, 43.7)	11.8 (4.3, 25.7)	0.0 (0.0, 38.9)
Top five most frequent AEs (by PT)[a]				
Nasopharyngitis	11.1 (2.3, 32.6)	12.5 (2.6, 36.5)	11.8 (4.3, 25.6)	24.5 (3.0, 88.6)
Abdominal pain	7.5 (0.9, 27.0)	8.4 (1.0, 30.3)	7.9 (2.2, 20.2)	11.6 (0.3, 64.5)
Viral upper respiratory tract infection	3.6 (0.1, 19.9)	12.5 (2.6, 36.6)	7.7 (2.1, 19.7)	11.4 (0.3, 63.7)
Cough	3.6 (0.1, 19.9)	8.0 (1.0, 29.0)	5.7 (1.2, 16.6)	0.0 (0.0, 38.9)
Diarrhea	3.6 (0.1, 20.1)	8.2 (1.0, 29.5)	5.7 (1.2, 16.8)	0.0 (0.0, 38.9)
AEs of special interest				
Hypersensitivity (SMQ) (narrow)	3.5 (0.1, 19.7)	8.0 (1.0, 29.0)	5.6 (1.2, 16.5)	44.6 (9.2, 130.3)
Infections and infestations (SOC)	63.9 (34.1, 109.4)	121.9 (72.3, 192.7)	88.3 (60.0, 125.4)	82.4 (26.8, 192.4)
Neutropenia (NMQ) (narrow)	11.2 (2.3, 32.8)	8.2 (1.0, 29.6)	9.8 (3.2, 22.8)	0.0 (0.0, 38.9)
ISRs	7.4 (0.9, 26.7)	0.0 (0.0, 14.3)	3.8 (0.5, 13.7)	11.8 (0.3, 65.5)
(ii) Age group: ≥12 years	EAIR/100 patient-years (95% CI)			
	SEC LD *N* = 68	SEC HD *N* = 72	Any SEC *N* = 140	ETN *N* = 31
Total AEs	211.5 (157.9, 277.3)	217.9 (163.2, 285.1)	214.7 (175.6, 259.9)	285.3 (188.0, 415.1)
SAEs	9.8 (3.6, 21.4)	4.6 (1.0, 13.5)	7.1 (3.3, 13.5)	15.5 (4.2, 39.7)
Treatment discontinuation due to AEs	3.2 (0.4, 11.4)	1.5 (0.0, 8.4)	2.3 (0.5, 6.8)	3.6 (0.1, 19.8)
Top five most frequent AEs (by SOC)[a]				
Infections and infestations	133.2 (97.1, 178.2)	106.1 (75.4, 145.0)	119.0 (94.9, 147.4)	142.9 (89.5, 216.3)

Table 4 (continued)

(ii) Age group: ≥12 years	EAIR/100 patient-years (95% CI)			
	SEC LD *N* = 68	SEC HD *N* = 72	Any SEC *N* = 140	ETN *N* = 31
Skin and subcutaneous tissue disorders	34.5 (20.4, 54.5)	30.7 (17.9, 49.2)	32.6 (22.7, 45.3)	31.6 (13.7, 62.3)
Gastrointestinal disorders	23.1 (12.3, 39.6)	37.2 (22.7, 57.4)	30.0 (20.7, 42.1)	58.2 (30.1, 101.7)
General disorders and administration-site conditions	13.5 (5.8, 26.7)	27.5 (15.4, 45.4)	20.2 (12.8, 30.4)	24.7 (9.1, 53.8)
Nervous system disorders	20.7 (10.7, 36.2)	16.6 (8.0, 30.6)	18.6 (11.7, 28.2)	15.2 (4.1, 38.8)
Top five most frequent AEs (by PT)[a]				
Nasopharyngitis	39.5 (24.1, 60.9)	45.4 (28.8, 68.1)	42.4 (30.7, 57.2)	36.2 (16.5, 68.6)
Headache	17.0 (8.2, 31.3)	16.6 (8.0, 30.6)	16.8 (10.3, 26.0)	15.2 (4.1, 38.8)
Pharyngitis	11.5 (4.6, 23.7)	9.7 (3.6, 21.2)	10.6 (5.6, 18.1)	11.1 (2.3, 32.3)
Acne	11.6 (4.7, 23.9)	4.6 (1.0, 13.6)	8.0 (3.8, 14.7)	0.0 (0.0, 12.9)
Oropharyngeal pain	4.8 (1.0, 14.2)	11.1 (4.5, 23.0)	8.0 (3.8, 14.7)	3.6 (0.1, 20.1)
AEs of special interest				
Hypersensitivity (SMQ) (narrow)	10.1 (3.7, 21.9)	16.8 (8.1, 30.9)	13.4 (7.7, 21.8)	7.2 (0.9, 26.1)
Infections and infestations (SOC)	133.3 (97.3, 178.4)	110.2 (78.7, 150.0)	121.3 (96.9, 150.0)	142.9 (89.5, 216.3)
Neutropenia (NMQ) (narrow)	3.2 (0.4, 11.7)	1.5 (0.0, 8.5)	2.4 (0.5, 6.9)	3.6 (0.1, 19.9)
ISRs	3.2 (0.4, 11.7)	6.2 (1.7, 16.0)	4.8 (1.7, 10.4)	11.4 (2.3, 33.2)

"Any SEC" for both the treatment groups (LD and HD) includes all patients treated with SEC from the start of the study and those who switched from placebo to SEC at week 12

AE adverse event, *CI* confidence interval, *EAIR* exposure-adjusted incidence rate (in 100 patient-years), *ETN* etanercept, *HD* high dose, *ISR* injection-site reaction, *LD* low dose, *MedDRA* Medical Dictionary for Regulatory Activities, *N* total number of patients, *NMQ* Novartis customized MedDRA Query, *PT* preferred term, *SAE* serious AE, *SEC* secukinumab, *SMQ* standardized MedDRA Query, *SOC* system organ class

[a]AEs are sorted in descending order of IR in the "Any SEC" column

Table 5 EAIRs for AEs in the pediatric population by bodyweight strata up to week 52 (safety set)

(i) Bodyweight group: < 25 kg	EAIR/100 patient-years (95% CI)			
	SEC LD *N* = 8	SEC HD *N* = 8	Any SEC *N* = 16	ETN *N* = 4
Total AEs	116.3 (37.8, 271.5)	283.5 (114.0, 584.0)	177.3 (91.6, 309.7)	92.6 (11.2, 334.5)
SAEs	13.6 (0.3, 75.8)	14.3 (0.4, 79.5)	13.9 (1.7, 50.3)	0.0 (0.0, 92.4)
Treatment discontinuation due to AEs	None	None	None	None
Most frequent AEs (by SOC)[a]				
Infections and infestations	34.2 (4.1, 123.6)	141.6 (52.0, 308.1)	79.3 (34.3, 156.3)	30.6 (0.8, 170.3)
Blood and lymphatic system disorders	32.5 (3.9, 117.4)	55.0 (11.3, 160.7)	43.1 (14.0, 100.5)	0.0 (0.0, 92.4)
Cardiac disorders	14.8 (0.4, 82.4)	14.3 (0.4, 79.6)	14.5 (1.8, 52.5)	0.0 (0.0, 92.4)
Skin and subcutaneous tissue disorders	0.0 (0.0, 49.0)	26.9 (3.3, 97.3)	13.4 (1.6, 48.3)	0.0 (0.0, 92.4)
Eye disorders	0.0 (0.0, 49.0)	14.7 (0.4, 82.0)	7.0 (0.2, 38.9)	0.0 (0.0, 92.4)
Most frequent AEs (by PT)[a]				
Nasopharyngitis	15.2 (0.4, 84.8)	30.3 (3.7, 109.4)	22.8 (4.7, 66.5)	0.0 (0.0, 92.4)
Leukopenia	15.0 (0.4, 83.3)	14.4 (0.4, 80.5)	14.7 (1.8, 53.1)	0.0 (0.0, 92.4)
Pharyngotonsillitis	14.7 (0.4, 81.9)	13.2 (0.3, 73.8)	13.9 (1.7, 50.3)	0.0 (0.0, 92.4)
Viral upper respiratory tract infection	0.0 (0.0, 49.0)	29.1 (3.5, 105.0)	13.9 (1.7, 50.2)	30.6 (0.8, 170.3)
Influenza	13.4 (0.3, 74.5)	13.0 (0.3, 72.5)	13.2 (1.6, 47.7)	0.0 (0.0, 92.4)
AEs of special interest				
Hypersensitivity (SMQ) (narrow)	0.0 (0.0, 49.0)	13.3 (0.3, 74.0)	6.6 (0.2, 37.0)	0.0 (0.0, 92.4)
Infections and infestations (SOC)	34.2 (4.1, 123.6)	141.6 (52.0, 308.1)	79.3 (34.3, 156.3)	30.6 (0.8, 170.3)
Neutropenia (NMQ) (narrow)	32.5 (3.9, 117.4)	14.4 (0.4, 80.5)	22.9 (4.7, 67.0)	0.0 (0.0, 92.4)
ISRs	0.0 (0.0, 49.0)	0.0 (0.0, 47.5)	0.0 (0.0, 24.1)	33.1 (0.8, 184.5)
(ii) Bodyweight group: ≥ 25 kg and < 50 kg	EAIR/100 patient-years (95% CI)			
	SEC LD *N* = 37	SEC HD *N* = 34	Any SEC *N* = 71	ETN *N* = 16
Total AEs	185.5 (123.3, 268.2)	200.9 (130.0, 296.5)	192.5 (144.2, 251.8)	319.6 (174.7, 536.2)
SAEs	2.9 (0.1, 16.0)	6.9 (0.8, 25.0)	4.7 (1.0, 13.7)	15.6 (1.9, 56.5)
Treatment discontinuation due to AEs	2.9 (0.1, 16.0)	6.9 (0.8, 24.9)	4.7 (1.0, 13.7)	0.0 (0.0, 25.6)
Most frequent AEs (by SOC)[a]				
Infections and infestations	98.9 (62.0, 149.8)	91.0 (53.0, 145.7)	95.3 (67.8, 130.3)	141.4 (70.6, 253.0)
Gastrointestinal disorders	35.2 (16.9, 64.7)	32.3 (13.9, 63.7)	33.8 (20.1, 53.5)	46.8 (15.2, 109.1)
General disorders and administration-site conditions	27.9 (12.1, 55.1)	19.0 (6.2, 44.3)	23.7 (12.6, 40.5)	34.1 (9.3, 87.2)
Skin and subcutaneous tissue disorders	26.8 (11.6, 52.9)	18.5 (6.0, 43.2)	22.9 (12.2, 39.1)	51.9 (19.1, 113.0)
Respiratory, thoracic, and mediastinal disorders	9.0 (1.9, 26.4)	22.4 (8.2, 48.7)	15.0 (6.9, 28.4)	15.3 (1.9, 55.3)
Most frequent AEs (by PT)[a]				
Nasopharyngitis	15.5 (5.0, 36.2)	23.5 (8.6, 51.2)	19.0 (9.5, 34.1)	23.1 (4.8, 67.6)
Abdominal pain	9.1 (1.9, 26.6)	15.1 (4.1, 38.6)	11.8 (4.7, 24.3)	15.8 (1.9, 57.2)
Cough	5.9 (0.7, 21.4)	14.5 (4.0, 37.1)	9.8 (3.6, 21.3)	7.2 (0.2, 39.9)
Eosinophilia	12.1 (3.3, 31.1)	3.4 (0.1, 19.2)	8.1 (2.6, 18.8)	0.0 (0.0, 25.6)
Headache	0.0 (0.0, 10.5)	18.6 (6.0, 43.3)	8.1 (2.6, 18.8)	15.4 (1.9, 55.7)
AEs of special interest				
Hypersensitivity (SMQ) (narrow)	6.0 (0.7, 21.5)	19.3 (6.3, 45.0)	11.8 (4.7, 24.2)	25.8 (5.3, 75.3)
Infections and infestations (SOC)	98.9 (62.0, 149.8)	91.0 (53.0, 145.7)	95.3 (67.8, 130.3)	141.4 (70.6, 253.0)
Neutropenia (NMQ) (narrow)	2.9 (0.1, 16.2)	3.5 (0.1, 19.3)	3.2 (0.4, 11.4)	0.0 (0.0, 25.6)
ISRs	9.3 (1.9, 27.0)	7.0 (0.8, 25.2)	8.2 (2.7, 19.1)	15.2 (1.8, 54.9)

Table 5 (continued)

(iii) Bodyweight group: ≥ 50 kg	EAIR/100 patient-years (95% CI)			
	SEC LD *N* = 53	SEC HD *N* = 58	Any SEC *N* = 111	ETN *N* = 21
Total AEs	211.2 (150.9, 287.6)	202.8 (146.1, 274.1)	206.8 (164.5, 256.7)	289.1 (171.3, 456.9)
SAEs	10.6 (3.4, 24.6)	5.6 (1.2, 16.3)	7.9 (3.4, 15.6)	17.0 (3.5, 49.6)
Treatment discontinuation due to AEs	2.0 (0.1, 11.2)	1.8 (0.0, 10.2)	1.9 (0.2, 6.9)	5.2 (0.1, 29.0)
Most frequent AEs (by SOC)[a]				
Infections and infestations	130.6 (90.4, 182.4)	118.8 (82.3, 166.0)	124.4 (96.6, 157.7)	144.1 (80.6, 237.6)
Skin and subcutaneous tissue disorders	36.8 (20.6, 60.7)	30.7 (16.8, 51.5)	33.6 (22.5, 48.2)	22.4 (6.1, 57.5)
Gastrointestinal disorders	17.7 (7.7, 34.9)	36.1 (20.6, 58.6)	26.8 (17.2, 39.9)	66.4 (30.4, 126.1)
Nervous system disorders	25.0 (12.5, 44.7)	9.8 (3.2, 22.8)	16.8 (9.6, 27.2)	10.6 (1.3, 38.2)
Respiratory, thoracic, and mediastinal disorders	15.2 (6.1, 31.4)	18.0 (8.2, 34.2)	16.7 (9.5, 27.1)	10.6 (1.3, 38.1)
Most frequent AEs (by PT)[a]				
Nasopharyngitis	43.9 (25.5, 70.2)	42.3 (25.1, 66.9)	43.0 (30.0, 59.9)	49.7 (21.5, 98.0)
Headache	22.3 (10.7, 40.9)	9.8 (3.2, 22.8)	15.6 (8.7, 25.7)	10.6 (1.3, 38.2)
Pharyngitis	17.3 (7.5, 34.0)	9.8 (3.2, 22.9)	13.4 (7.1, 22.9)	16.5 (3.4, 48.1)
Oropharyngeal pain	6.2 (1.3, 18.2)	13.6 (5.5, 28.1)	10.1 (4.8, 18.5)	0.0 (0.0, 18.8)
Rhinitis	6.2 (1.3, 18.1)	11.8 (4.3, 25.6)	9.0 (4.1, 17.2)	5.3 (0.1, 29.7)
AEs of special interest				
Hypersensitivity (SMQ) (narrow)	10.7 (3.5, 25.0)	11.8 (4.3, 25.6)	11.3 (5.6, 20.1)	10.6 (1.3, 38.4)
Infections and infestations (SOC)	130.8 (90.6, 182.8)	124.3 (86.6, 172.8)	127.4 (99.1, 161.2)	144.1 (80.6, 237.6)
Neutropenia (NMQ) (narrow)	4.2 (0.5, 15.0)	1.8 (0.0, 10.3)	2.9 (0.6, 8.6)	5.2 (0.1, 29.1)
ISRs	2.0 (0.1, 11.4)	3.7 (0.5, 13.5)	2.9 (0.6, 8.6)	5.3 (0.1, 29.8)

"Any SEC" for both the treatment groups (LD and HD) includes all patients treated with SEC from the start of the study and those who switched from PBO to SEC at week 12

AE adverse event, *CI* confidence interval, *EAIR* exposure-adjusted incidence rate (per 100 patient-years), *ETN* etanercept, *HD* high dose, *IR* incidence rate (per 100 patient-years), *ISR* injection-site reaction, *LD* low dose, *N* total number of patients, *MedDRA* Medical Dictionary for Regulatory Activities, *NMQ* Novartis customized MedDRA Query, *PBO* placebo, *PT* preferred term, *SAE* serious AE, *SEC* secukinumab, *SMQ* standardized MedDRA Query, *SOC* system organ class

[a]AEs are sorted in descending order of IR in the "Any SEC" column

EAIRs of neutropenia (NMQ, narrow) in the < 25 kg, 25 to < 50 kg, and ≥ 50 kg subgroups were 22.9/100 PY, 3.2/100 PY, and 2.9/100 PY for the pediatric population who received "Any secukinumab," respectively (Table 5, i, ii], and iii). The EAIR of 22.9/100 PY in the < 25 kg subgroup corresponds to three patients: one reported with neutropenia PT and the other two with AEs of leukopenia PT. Neutropenia PT was associated with CTCAE grade 2 neutrophil counts, while the leukopenia PTs were associated with CTCAE grade 1 or grade 2 leukocyte counts. These AEs were all nonserious, resolved, and did not lead to study treatment discontinuation or interruption.

Complementary to the neutropenia AEs reported by the study sites, the laboratory-measured neutrophil counts and their corresponding CTCAE grades represent a more objective measure of neutropenia in a clinical study. The percentage of patients with absolute neutrophil CTCAE grades 1 and 2 (combined) in the < 25 kg, 25 to < 50 kg, and ≥ 50 kg pediatric subgroups was comparable (26.7%, 17.9%, and 20.3%, respectively), indicating no correlation of neutrophil count with bodyweight (Table S9; see the electronic supplementary material). Finally, it must be noted that neutrophil counts are expected to be lower in the pediatric population, with 1.51% of adolescents aged 15–17 years reported to have neutrophil counts < 1.5×10^9/L compared with 0.72% of adults [23].

4 Discussion

In the current study, pooled safety data from two pivotal phase 3 studies in a pediatric population with moderate to severe or severe chronic plaque psoriasis were assessed alongside the pooled safety data from four pivotal studies of secukinumab 150 mg or secukinumab 300 mg in moderate to severe chronic plaque psoriasis in adults. Treatment with secukinumab was associated with a low incidence of AEs. Both dosing regimens of secukinumab (LD and HD) were well tolerated in the pediatric population across the subgroups stratified by age and bodyweight. The overall

safety profile in pediatric patients was consistent with that of adults. In the first 12 weeks of treatment, the overall incidence of AEs was similar among the secukinumab pediatric treatment groups and placebo and slightly lower than in the adult secukinumab group as well as adult and pediatric etanercept treatment group. Consistent with IRs at week 12, AEs up to week 52 were similar across secukinumab treatment groups (LD and HD) and lower than those in the etanercept and adult groups.

The incidence of "Infections and infestations," the most commonly affected SOC, in patients treated with secukinumab was similar in the pediatric and adult populations. In the current analysis, the most commonly reported AE was nasopharyngitis, in agreement with the results reported with ustekinumab in adolescent patients [24]. Similar to previous long-term safety results that reported URTIs as the most frequent AEs associated with secukinumab [25, 26], the present analysis also reports URTI as the most common HLT under "Infections and infestations"; none of these URTI events, however, were serious or resulted in treatment discontinuation. *Candida* infections were reported to be less frequent in pediatric patients compared with adults; they were mild and did not lead to study treatment discontinuation or interruption.

Immune-modulating agents potentially affect counts of peripheral neutrophils, which are important mediators and regulators of innate and adaptive immune responses [27, 28]. However, evidence shows that secukinumab therapy has not been frequently associated with neutropenia or certain mucocutaneous infections [29]. In the present analysis, neutropenia occurred more frequently in the pediatric population. This may be attributed to the lower neutrophil counts in pediatric populations as reported in the literature, with 1.51% of adolescents aged 15–17 years having neutrophil counts $< 1.5 \times 10^9$/L compared with 0.72% of adults [23].

Patients with psoriasis may carry an increased risk of malignancy, cardiovascular events, and IBD (one- to four-fold) [30–32]; however, these cases were not reported for the pediatric pool in the present analysis. One potential case of IBD (0.5%) from the secukinumab HD group, nonserious hemorrhagic diarrhea (mild), resolved and was followed by a noninflammatory diarrhea episode at the end of study visit [16, 17]. Adherence to subcutaneous dosing can be potentially influenced by ISRs in the pediatric population [16–18]; however, ISRs observed in the two secukinumab studies were few, of mild intensity, and resolved without treatment. There were no treatment discontinuations related to ISRs.

The incidence of suicidality-related AEs was very low in the pediatric population, and the potential risk of suicide/self-injury (SMQ) occurred in two patients in the secukinumab LD group. One patient presented suicidal ideation that had been reported previously [18]. The other patient attempted deliberate self-harm that was reported as the SAE of intentional self-injury not suspected to be related to the study treatment. No deaths were reported in the pooled pediatric population.

The overall safety profile of the pooled pediatric population in this analysis was consistent with that of adults in pivotal phase 3 plaque psoriasis trials [33–35]. TEAEs (by SOC and PT) were generally comparable between secukinumab-treated pediatric and adult populations during induction (to week 12) and maintenance (to week 52) periods. No new safety signals were reported.

In summary, the results demonstrated that AEs reported in the subgroups of age and bodyweight were consistent with the overall population, with no clinically meaningful differences between the subgroups. However, the incidence of AEs was lower in the lower age and bodyweight subgroups at both weeks 12 and 52. The most commonly affected SOC in the age and bodyweight subgroups was "Infections and infestations," similar to the safety findings in the overall pediatric population. No new or unexpected safety signals were reported in the age subgroups, and secukinumab was well tolerated in pediatric patients as young as 6 years of age. The AEs were comparable in the bodyweight subgroups; however, it should be noted that patient numbers in some of these subgroups were low, and this should be taken into consideration when interpreting the results. These results are consistent with previous reports from individual pediatric studies involving patients with moderate to severe and severe chronic plaque psoriasis and further confirm the favorable safety profile of secukinumab [16–18].

The strengths of these analyses include the pooling of pediatric data from two pivotal phase 3 studies, allowing analysis by age and bodyweight subgroups, the inclusion of placebo and a positive control (etanercept), and comparisons with similarly collected adult data. These analyses are expected to contribute to more informed treatment decisions for pediatric patients, especially for younger children. Despite the lack of a placebo-controlled period in the A2311 study, and the small sample sizes in some subgroups in both studies (particularly the < 25 kg subgroup), the number of patients who were recruited reflects the prevalence of the disease in this younger and low bodyweight population.

5 Conclusions

This analysis presents, for the first time, pooled safety data from the two secukinumab pivotal pediatric studies by subgroups of age and bodyweight. In addition, pediatric safety data are presented alongside the large adult secukinumab safety data pool. Secukinumab was equally well tolerated in pediatric patients across age and bodyweight subgroups, and

the overall safety profile was consistent with that of adult patients, with no new or unexpected safety signals. The results from this analysis further demonstrate the favorable safety profile of secukinumab in pediatric patients with moderate to severe and severe chronic plaque psoriasis.

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Declarations

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Conflict of interest *Michael Sticherling* is an investigator, speaker, consultant/advisory board member, and participated in clinical trials with the following companies: AbbVie, Amgen, BMS, Celgene, Galderma, GSK, Janssen Cilag, Leo, Lilly, MSD, Mundipharma, Novartis, Regeneron, Pfizer, Sanofi, and UCB. *Arjen F. Nikkels* has nothing to disclosure. *Ashraf M. Hamza* is a principal investigator for Novartis and speaker for Sanofi and Pfizer. *Pearl Kwong* is an investigator, speaker, and/or consultant for Pfizer, Eli Lilly, Regeneron Sanofi Genzyme, Ortho, Verrica, Vyne, Journey, Incyte Almirall, Novartis, Amgen/Celgene, AbbVie, Dermira, Galderma, Castle Creek Biosciences, and Arcutis. *Jacek C. Szepietowski* is an advisory board member of AbbVie, LEO Pharma, Novartis, Pierre-Fabre, Menlo Therapeutics, Sienna Biopharmaceuticals, and Trevi Therapeutics; principal investigator for AbbVie, Novartis, Menlo Therapeutics, Trevi Therapeutics, Janssen, Merck, Regeneron, Amgen, Boehringer Ingelheim, Galapagos, Galderma, InflaRX, Kymab Ltd., Pfizer, UCB, Helm, and Incyte; and a speaker for AbbVie, Novartis, Janssen, Eli Lilly, Sanofi-Genzyme, Sunfarm, and Berlin-Chemie Menarini. *Mahira El Sayed* is a speaker and advisory board member of AbbVie, Novartis, Janssen, Amgen, Sandoz, Sanofi, Pfizer, and Eli Lilly. *Pierre-Dominique Ghislain* is receiving consultancy and fees as speaker, investigator, or grants for Pfizer, MSD, AbbVie, Janssen, Serono, Leo, Novartis, UCB, Amgen, Eli Lilly, Galderma, BMS, Meda, Maruho, Flen, Menarini, Almirall, PellePharm, and Viatris. *Alkes A Khotko* is an investigator in sponsored clinical trials of AbbVie, Novartis, Janssen, Amgen, Sanofi, Eli Lilly, Biocad, Akrikhin, Alfasigma S.p.A., OOO Pharmapark, Argenx BV, and Bristol Myers Squibb. *Manmath Patekar*, *Christine-Elke Ortmann*, *Philemon Papanastasiou*, *Pascal Forrer*, and *Deborah Keefe* are employees of Novartis.

Ethics approval The clinical trials were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) and in compliance with all federal, local, or regional requirements.

Consent to participate An informed consent form approved by a study site's institutional review board was signed by the participants or legal representative and the investigator before enrollment of participants.

Consent to publication Not applicable.

Availability of data and materials The datasets generated and/or analyzed during the current study are not publicly available. 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 on the basis of scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The data may be requested from the corresponding author of the article.

Code availability Not applicable.

Authors' contributions Concept and design: MS, AFN, AMH, PK, JCS, MES, P-DG, AAK, MP, PP, PF, DK. Acquisition, analysis, or interpretation of data: All authors. Drafting of the manuscript: All authors. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: C-EO. Administrative, supervision, technical, or material support: All authors.

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